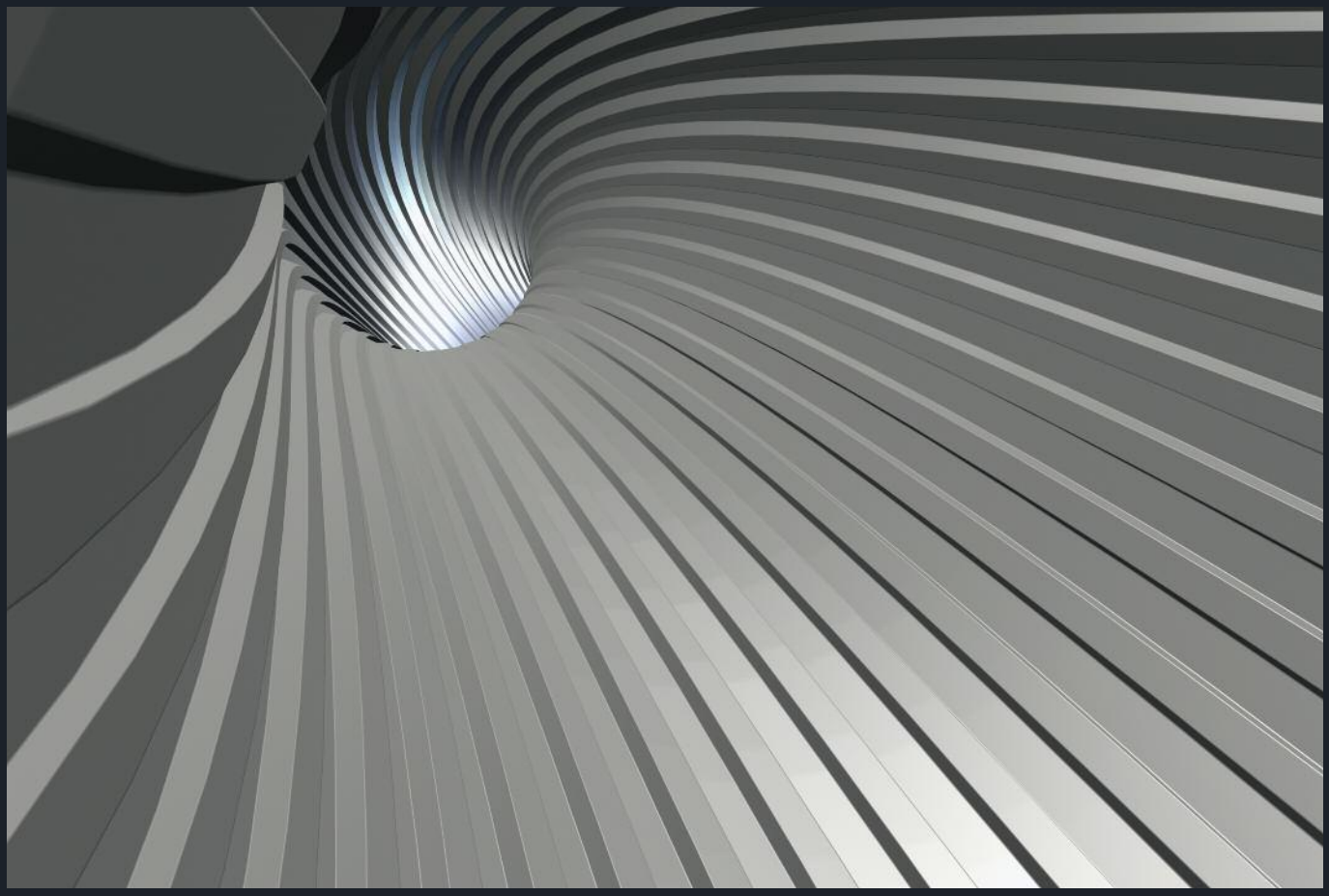

AUTISM

THE NICE GUIDELINE ON THE MANAGEMENT AND SUPPORT OF CHILDREN AND YOUNG PEOPLE ON THE AUTISM SPECTRUM

NATIONAL COLLABORATING CENTRE FOR MENTAL HEALTH

Update information

June 2021: We added new recommendations in the section on interventions for coexisting problems, to highlight the need for assessment and referral for children and young people with feeding problems and restricted diets. We also changed ‘children and young people with autism’ to ‘autistic children and young people’, and ‘symptoms of autism’ to ‘features of autism’ to align with current terminology.

For the current recommendations, see https://www.nice.org.uk/guidance/cg170/chapter/1-Recommendations

Autism

The management and support of children and young people on the autism spectrum

National Clinical Guideline Number 170

National Collaborating Centre for Mental Health

commissioned by the

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1 PREFACE

This guideline has been developed to advise on the management and support of children and young people on the autism spectrum. The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, children and young people with autism, their carers and guideline methodologists after careful consideration of the best available evidence. It is intended that the guideline will be useful to clinicians and service commissioners in providing and planning high-quality care for children and young people with autism while also emphasising the importance of the experience of care for children and young people with autism and their carers (see Appendix 1 for more details on the scope of the guideline).

Although the evidence base is rapidly expanding, there are a number of major gaps. The guideline makes a number of research recommendations specifically to address gaps in the evidence base (for high-priority research recommendations, see Appendix 11). In the meantime, it is hoped that the guideline will assist clinicians, and children and young people with autism and their carers, by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

1.1 NATIONAL CLINICAL GUIDELINES

1.1.1 What are clinical guidelines?

Clinical guidelines are 'systematically developed statements that assist clinicians and service users in making decisions about appropriate treatment for specific conditions' (Mann, 1996). They are derived from the best available research evidence, using predetermined and systematic methods to identify and evaluate the evidence relating to the specific condition in question. Where evidence is lacking, the guidelines include statements and recommendations based upon the consensus statements developed by the Guideline Development Group (GDG).

Clinical guidelines are intended to improve the process and outcomes of healthcare in a number of different ways. They can:

- provide up-to-date evidence-based recommendations for the management of conditions and disorders by healthcare professionals
- be used as the basis to set standards to assess the practice of healthcare professionals
- form the basis for education and training of healthcare professionals
- assist service users and their carers in making informed decisions about their treatment and care
- improve communication between healthcare professionals, service users and their carers
- help identify priority areas for further research.

1.1.2 Uses and limitations of clinical guidelines

Guidelines are not a substitute for professional knowledge and clinical judgement. They can be limited in their usefulness and applicability by a number of different factors: the availability of high-quality research evidence, the quality of the methodology used in the development of the guideline, the generalisability of research findings and the uniqueness of individuals.

Although the quality of research in this field is variable, the methodology used here reflects current international understanding on the appropriate practice for guideline development (Appraisal of Guidelines for Research and Evaluation Instrument [AGREE];www.agreetrust.org; AGREE Collaboration, 2003), ensuring the collection and selection of the best research evidence available and the systematic generation of treatment recommendations applicable to the majority of children and young people with autism. However, there will always be some people and situations where clinical guideline recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual, in consultation with the child or young person with autism or their carer.

In addition to the clinical evidence, cost-effectiveness information, where available, is taken into account in the generation of statements and recommendations in clinical guidelines. While national guidelines are concerned with clinical and cost effectiveness, issues of affordability and implementation costs are to be determined by the National Health Service (NHS).

In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, and of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment programme including a range of activities, the purpose of which may be to help engage the person and provide an appropriate context for the delivery of specific interventions. It is important to maintain and enhance the service context in which these interventions are delivered, otherwise the specific benefits of effective interventions will be lost. Indeed, the importance of organising care in order to support and encourage a good therapeutic relationship is at times as important as the specific treatments offered.

1.1.3 Why develop national guidelines?

The National Institute for Health and Care Excellence (NICE)[1] was established as a Special Health Authority for England and Wales in 1999, with a remit to provide a single source of authoritative and reliable guidance for service users, professionals and the public. NICE guidance aims to improve standards of care, diminish unacceptable variations in the provision and quality of care across the NHS, and

[1] In April 2013 NICE made a revision to its name to reflect new responsibility for developing guidance and quality standards in social care.

ensure that the health service is person-centred. All guidance is developed in a transparent and collaborative manner, using the best available evidence and involving all relevant stakeholders.

NICE generates guidance in a number of different ways, three of which are relevant here. First, national guidance is produced by the Technology Appraisal Committee to give robust advice about a particular treatment, intervention, procedure or other health technology. Second, NICE commissions public health intervention guidance focused on types of activity (interventions) that help to reduce people's risk of developing a disease or condition, or help to promote or maintain a healthy lifestyle. Third, NICE commissions the production of national clinical guidelines focused upon the overall treatment and management of a specific condition. To enable this latter development, NICE has established four National Collaborating Centres in conjunction with a range of professional organisations involved in healthcare.

1.1.4 From national clinical guidelines to local protocols

Once a national guideline has been published and disseminated, local healthcare groups will be expected to produce a plan and identify resources for implementation, along with appropriate timetables. Subsequently, a multidisciplinary group involving commissioners of healthcare, primary care and specialist mental health professionals, service users and carers should undertake the translation of the implementation plan into local protocols, taking into account both the recommendations set out in this guideline and the priorities in the National Service Framework for Mental Health (Department of Health, 1999) and related documentation. The nature and pace of the local plan will reflect local healthcare needs and the nature of existing services; full implementation may take a considerable time, especially where substantial training needs are identified.

1.1.5 Auditing the implementation of clinical guidelines

This guideline identifies key areas of clinical practice and service delivery for local and national audit. Although the generation of audit standards is an important and necessary step in the implementation of this guidance, a more broadly-based implementation strategy will be developed. Nevertheless, it should be noted that the Care Quality Commission in England, and the Healthcare Inspectorate Wales, will monitor the extent to which commissioners and providers of health and social care and Health Authorities have implemented these guidelines.

1.2 THE NATIONAL AUTISM GUIDELINE

1.2.1 Who has developed this guideline?

This guideline has been commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration of the professional organisations involved in the field of mental health, national service user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal

College of Psychiatrists and the British Psychological Society's Centre for Outcomes Research and Effectiveness, based at University College London.

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included carers of children and young people with autism, and professionals from psychiatry, clinical psychology, general practice, nursing, social work, speech and language therapy, occupational therapy and the private and voluntary sectors.

Staff from the NCCMH provided leadership and support throughout the process of guideline development, undertaking systematic searches, information retrieval, appraisal and systematic review of the evidence. Members of the GDG received training in the process of guideline development from NCCMH staff, and the service users and carers received training and support from the NICE Public Involvement Programme. The NICE Guidelines Technical Adviser provided advice and assistance regarding aspects of the guideline development process.

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of 12 times throughout the process of guideline development. It met as a whole, but key topics were led by a national expert in the relevant topic. The GDG was supported by the NCCMH technical team, with additional expert advice from special advisers where needed. The group oversaw the production and synthesis of research evidence before presentation. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

1.2.2 For whom is this guideline intended?

This guideline will be relevant for children and young people with autism and covers the care provided by primary, community, secondary, tertiary and other healthcare professionals who have direct contact with, and make decisions concerning, the care of children and young people with autism.

The guideline will also be relevant to the work, but will not cover the practice, of those in:

- occupational health services
- social services
- the independent sector.

1.2.3 Specific aims of this guideline

The guideline makes recommendations for the management and support of children and young people with autism. It aims to:

- improve access and engagement with treatment and services for children and young people with autism
- evaluate the role of specific psychological, psychosocial and pharmacological interventions in the treatment of autism in children and young people

- evaluate the role of psychological and psychosocial interventions in combination with pharmacological interventions in the treatment of autism in children and young people
- evaluate the role of specific service-level interventions for children and young people with autism
- integrate the above to provide best-practice advice on the care of individuals throughout the course of their treatment
- promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the NHS in England and Wales.

1.2.4 The structure of this guideline

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide a general introduction to guidelines, an introduction to the topic of autism and to the methods used to develop them. Chapter 4 to Chapter 9 provide the evidence that underpins the recommendations about the management and support of children and young people with autism

Each evidence chapter begins with a general introduction to the topic that sets the recommendations in context. Depending on the nature of the evidence, narrative reviews or meta-analyses were conducted, and the structure of the chapters varies accordingly. Where appropriate, details about current practice, the evidence base and any research limitations are provided. Where meta-analyses were conducted, information is given about both the interventions included and the studies considered for review. Clinical summaries are then used to summarise the evidence presented. Finally, recommendations related to each topic are presented at the end of each chapter. In the appendices (available from the NCCMH and NICE websites), full details about the included studies can be found in Appendix 12. Where meta-analyses were conducted, the data are presented using forest plots in Appendix 13 (see Table 1 for details).

Table 1: Appendices

Clinical evidence – study characteristics tables	Appendix 12
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In the event that amendments or minor updates need to be made to the guideline, please check the NCCMH website (nccmh.org.uk), where these will be listed and a corrected PDF file available to download.

2 INTRODUCTION

This guideline is about the management and support of children and young people with autism from birth to 19 years and their parents and carers. It should be read in conjunction with the *Autism Diagnosis in Children and Young People* guideline (NICE, 2011a; National Collaborating Centre for Women's and Children's Health [NCCWCH], 2011). A further guideline (NICE, 2012a; NCCMH, 2012a) describes the recognition, referral, diagnosis, management and support of adults with autism.

2.1 HISTORY

Childhood autism was first described as a specific condition in 1943 by Leo Kanner in the US (Kanner, 1943) and was independently described in Austria in 1944 by Hans Asperger (Asperger, 1944). Both accounts described an overlapping core set of features (that is social difficulties alongside highly repetitive patterns of behaviour) but the people Asperger described were generally of high intelligence and had fluent language skills, while those described by Kanner displayed greater variability in intelligence quotient (IQ) and language development.

In the 1950s and 1960s autism was often attributed to environmental factors (such as unemotional parenting) (Bettelheim, 1967); it was also viewed as an early form of schizophrenia (Kanner, 1944; American Psychiatric Association, 1968). In the 1970s these theories were challenged by Michael Rutter (1978) who argued that associated phenomena such as epilepsy could not be attributed to factors such as poor parenting, but instead indicated abnormalities of brain function. Findings of high concordance rates of autism in identical twins compared with non-identical twins indicated a strong genetic influence in autism (Folstein & Rutter, 1977). It is now evident that autism involves atypical brain development with many different genetic, epigenetic and environmental mechanisms probably being involved (Levy et al., 2009; Hallmayer et al., 2011; Anney et al., 2012).

In the 1950s through to the 1980s, autism was generally considered to be a categorical diagnosis (that is, either present or absent) and as being relatively rare, affecting only around four in 10,000 children (Rutter, 1978). However, a later epidemiological study by Wing and Gould (1979) indicated that autism was much more common than had previously been realised (21 per 10,000). Wing also suggested the term 'autistic spectrum disorder' to reflect the fact that this is a dimensional disorder that presents in various degrees of severity (Wing, 1988).

2.2 DIAGNOSING AUTISM

Diagnosis is the clinical decision-making process that determines whether or not an individual has a disorder. 'Disorder' is not an exact term, but implies the existence of a clinically recognisable set of symptoms or behaviours associated with distress, impairment and interference with personal functioning.

Diagnosis is usually based on accepted diagnostic criteria described in the World Health Organization's *International Classification of Diseases* (ICD) and the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM). Autism was first listed in the ninth revision of ICD (ICD-9; World Health Organisation, 1977) and in the 3rd edition of DSM (DSM-III; American Psychiatric Association, 1980). Later editions, ICD-10 (World Health Organisation, 1992) and DSM-IV-TR (American Psychiatric Association, 2000), use the category 'pervasive developmental disorder' (PDD) to group together diagnoses relating to the autism spectrum. The terms pervasive developmental disorder and 'autism spectrum disorder' or 'ASD' (excluding Rett's syndrome) are regarded as conveying the same meaning; the fifth edition of DSM (DSM-5), published in May 2013, uses the term autism spectrum disorder.

In DSM-IV-TR and ICD-10 diagnosis has been based on deficits in three core domains: (1) social impairments, (2) communication difficulties, and (3) stereotyped and repetitive behaviours. In DSM-5 (and the proposed ICD-11 criteria) diagnosis is based on deficits in two core dimensions: social and communication impairments are collapsed into a single dimension called 'social-communication difficulties', to reflect the fact that they are so intertwined; the second major dimension is repetitive behaviour (incorporating difficulties in adapting to change and unusually narrow interests, as well as sensory sensitivities or interests). Specifiers are used to describe the onset and course of autism and coexisting conditions.

The *Autism Diagnosis in Children and Young People* guideline (NICE, 2011a; NCCWCH, 2011) should be referred to for guidance in relation to the recognition, referral and diagnosis of autism in children and young people.

2.3 TERMINOLOGY USED IN THE GUIDELINE

The GDG recognised that variations in the way that terms to describe autism are used can cause confusion and different individuals and groups have preferences for particular terms, for example, 'autism spectrum disorder' or 'autistic spectrum condition'. Some individuals with autism and their families and carers describe autism as a neurological difference, for which access to support may be necessary, rather than as a 'disorder'. In this guideline, the GDG uses the term 'autism', which is consistent with all NICE guidance on this subject (NICE, 2011a, NICE, 2012a). The term 'autism' encompasses all diagnoses of 'pervasive developmental disorder', 'autism spectrum disorder' and subgroups as in recent Department of Health, National Audit Office and Public Accounts Committee documents.

2.4 CLINICAL FEATURES OF AUTISM

The essential features of a diagnosis of autism are behavioural: a persistent impairment in reciprocal social interaction and social communication and restricted/repetitive patterns of behaviour, interests or activities. These behaviours cause functional impairment and are not better accounted for by any intellectual disability.

Signs and symptoms that should alert the professional to the possibility of autism are described in *Autism Diagnosis in Children and Young People* guideline (NICE, 2011a; NCCWCH, 2011). The manifestations of autism are of delay and/or disorder of typical development and the presence of unusual features of development. Symptoms vary greatly depending on the severity of the autistic condition, developmental level and chronological age and the presence or absence of associated conditions (such as intellectual disability or anxiety), hence the notion of a 'spectrum'. In classic (Kanner's) autism the child is slow to develop language (no single words by age 2 years, no phrase speech by age 3), and usually has additional intellectual impairment (that is, an IQ below 70). In contrast, in Asperger's syndrome, there is no history of delayed language development and IQ is within the average range (that is above 70). While these two subgroups are delineated separately in DSM-IV (American Psychiatric Association, 1994), in DSM-5, they are collapsed into a single category along with all the other subgroups.

2.4.1 Social interaction and communication in autism

Impairments in reciprocal social interaction and social communication in autism can be manifest in many different ways and the profile of difficulties can differ widely from one person to another. No individual feature is either sufficient or necessary for diagnosis. A young child may present with delayed language—a common initial concern—or unusual features of language development. These include excessive echoing, pronoun reversal (for example, when requesting something, the child may ask 'Do you want a biscuit?' rather than 'I want a biscuit') and the use of stereotyped, repetitive and/or made-up phrases (for example, 'hot rain' for steam). Many children fail to respond when their name is called despite having good hearing. There can also be marked difficulty in understanding the underlying meaning behind what people say. This can result in very literal interpretations (for example, a child being told to 'paint the flowers' covering the actual flowers in paint) and an inability to infer meaning in instructions unless each step is made very explicit.

Even among children and young people who have good spoken language there tend to be pragmatic difficulties (understanding and using language in social contexts). They may find it very difficult to understand sarcasm, metaphor or abstract concepts; they frequently have problems recognising the perspective of others or understanding what others are thinking and feeling. Conversational skills, too, are often poor with a tendency to speak in monologues and to talk *at* rather than *with* others. There is frequently a failure to understand the two-way nature of conversation or to respond to verbal or non-verbal cues (for example, that indicate that the listener is bored or wishes to say something). There may be a bluntness and lack of tact, sometimes failure to take into account what other people need to know, or inability to judge whether what they say may be inappropriate or even offensive.

Early social impairment is frequently manifest by limited social interest in others and a difficulty in sharing interests. There may be a lack of 'joint attention', with

little demonstration of gaze switching, pointing and vocalisations between the child, object and adult. Non-verbal communication is also impaired. Problems include: atypical eye contact (prolonged staring at people or barely looking at people's eyes); lack or unusual use of gestures and facial expression; and difficulties recognising others' personal space and body language. Even when these individual aspects of behaviour are relatively well developed there can be difficulty in integrating and regulating all these features in the context of reciprocal social communication.

Other characteristic social problems include: impairments in empathy and in understanding how others feel; poor awareness of appropriate social behaviour; and failure to conform to expected norms. Social naiveté and vulnerability to exploitation are common, as are difficulties in making and keeping friends; and some individuals become obsessed with another person to an intrusive extent. Even children and young people with good cognitive ability and language, who manage well in familiar situations, may struggle in more demanding and unfamiliar social contexts because of a lack of social intuition and this can give rise to significant levels of social anxiety.

Creative imaginative social play is either absent or delayed in development and in later childhood there tends to be limited sharing and reciprocity with some rigidity and insistence on rules. Young people with autism also often have poor skills in negotiation, turn taking, coping with not winning and resolving conflict.

2.4.2 Behaviour, interests and activities in autism

Restricted/repetitive patterns of behaviour, interests or activities may also manifest in many different ways in autism. These include a lack of cognitive and behavioural flexibility and/or unusually intense interests in certain topics. Repetitive behaviours and stereotyped mannerisms, such as spinning or hand flapping, are also common and are often pleasurable for the individual and/or seem to reduce anxiety. There may be a preference for repetition and routine such as watching or doing the same things repeatedly, for example, eating the same restricted range of foods, wearing the same clothes, taking the same routes or going to the same places each day. Most children and young people with autism prefer predictability (knowing exactly what will happen, when and for how long) and they may focus exclusively on detail and have a need for strict order and precision. In those with above average intellectual ability, rigidity of thinking and application of rules may be the most apparent features. There is often difficulty in doing several things at once ('multitasking') although this may not be manifest until secondary school when the demands for organisation become greater. Novelty or unexpected changes to routine can result in tantrums, distress and anxiety.

Sensory sensitivities and interests, such as hypo- and hyper-sensitivities to smell, touch, sound, textures and visual patterns may be marked or subtle. Situations that involve exposure to certain sensory stimuli can be extremely stressful for some individuals with autism, for example crowded and noisy places or bright lights.

Thus autism comprises a range of behaviours, heterogeneous both in causation and manifestation. The concept of continuously distributed traits is now generally accepted leaving no clear diagnostic boundary. This results in a challenge when deciding the 'threshold' for an autistic disorder. Features such as impaired reciprocal social communication skills and rigidity of thinking are now thought to be distributed throughout the general population as traits and are found in approximately 5% of the population (Constantino & Todd, 2003). Such traits are more common in the families of individuals with autism and are referred to as the 'broader autism phenotype' (Bolton et al, 1994). In these individuals, intellectual disability, severe language impairments and motor stereotypies are generally absent. Features of this broader autism phenotype may not always be evident in early childhood but impairment can become more evident over time. Therefore during diagnostic assessment, an individual may be found to have qualitatively similar traits to those of autism but be below threshold ('subthreshold') for a diagnosis of disorder. In such circumstances, the individual and/or family may still find information about autism helpful in order to understand fully the characteristics of the family member (see NICE, 2011a; NCCWCH, 2011).

2.5 THE PREVALENCE OF AUTISM

It is now evident that autism involves atypical brain development with many different genetic, epigenetic and environmental mechanisms probably being involved (Anney et al., 2012; Hallmayer et al., 2011). The factors affecting the rising measured prevalence are not fully known but include changing diagnostic criteria, new ascertainment methods, dependence on existing registers of special needs as well as diagnostic substitution. However, the possibility of an increase in autism cannot be ruled out (Centers for Disease Control and Prevention, 2012). One effect of this rise in prevalence has been to increase demand for all services offering support for people with autism, and their families and carers, which has considerable resource and training implications for the NHS and other agencies, including education and social care.

Autism is far more often diagnosed in males than in females and there is concern that many girls with autism may be unrecognised. In clinic samples, females are more likely to show accompanying intellectual disability (for example, Mandy et al., 2012). There is little known about possible differences in the presentation of autism in males and females, especially in those of high intellectual ability, but clinical reports suggest that girls are better at 'apparent' sociability, and although their interests may be intense and overly focused they are not so unusual in topic.

2.6 THE CAUSES OF AUTISM

Autism is a neurodevelopmental and biologically-based disorder, although the mechanism of causation is unknown. In later brain development there are clear differences in the function and structure of the 'empathy circuit' of the brain (amygdala, ventromedial prefrontal cortex, temporo-parietal junction, orbitofrontal cortex, anterior cingulate and other brain regions) (Lombardo et al., 2011). There are

also differences in connectivity between frontal and parietal lobe functions that are thought to relate to cognitive style, in particular an over-reliance on processing details and a relative under-reliance on processing holistic information. Cognitive theories include a lack of 'central coherence', impaired development of a 'theory of mind', executive dysfunction, poor intersubjectivity and a tendency to 'systematise', but no cognitive explanation is sufficient for all features of autism.

Estimates of the frequency of underlying medical causes vary widely but these probably occur in fewer than 10% of children with autism. A number of medical conditions are associated with increased risk of autism, for example, Fragile X syndrome, tuberous sclerosis complex and PTEN hamartoma tumour syndrome (see the review by State & Levitt, 2011). At least 60 different metabolic and neurological disorders and complex chromosome abnormalities have been reported to be associated with autism. However, there is no specific biomarker or diagnostic test for autism. Diagnosis is made on the basis of the presence of characteristic behaviours.

There is evidence of a substantial genetic basis with strong heritability, but current thinking is of a genetically heterogeneous disorder producing phenotypic heterogeneity (differing physical and behavioural characteristics). Candidate genes are emerging from the advances in molecular-genetic techniques. Rare[2] micro-duplications and micro-deletions (referred to as copy number variants) have been identified in up to 10% of people with so-called idiopathic autism (Miller, 2010). Subgroups of genes have been linked to common underlying mechanisms such as synaptogenesis and cell-to-cell adhesion, as well as converging on different aspects of several common underlying molecular signalling pathways.

For parents of a child with autism the likelihood of having another child with autism is greatly increased. Recent estimates range from 10 to 20%, with higher rates for boys than girls suggesting that awareness and discussion of this is an important part of the diagnostic process (Lauritsen 2005; Constantino 2010; Ozonoff et al., 2011).

The possible contribution of environmental factors, such as maternal infection and exposure to teratogens, has received increasing attention, prompted in part by the dramatic increase in prevalence estimates for autism over the past few decades (Fombonne, 2009). To date, however, no firm links to specific environmental factors have been established. A variety of non-specific risk factors including advanced parental age, maternal infection during pregnancy, prematurity, low birth weight, and early onset epilepsy and brain injury are being strongly considered as contributors to the risk of developing autism. There is also increasing research aimed at identifying neural correlates (as measured by electrophysiology or neuroimaging) that would be able to predict risk or prognosis for autism (Anagnostou & Taylor, 2011).

[2] Occurring in approximately 1 in 1000 affected individuals.

2.7 COEXISTING CONDITIONS

Autism is strongly associated with a number of coexisting conditions that are not part of the diagnostic criteria but have an impact on the wellbeing of the child or young person and their families or carers. Recent studies suggest that approximately 70% of individuals with autism also meet diagnostic criteria for at least one other (often unrecognised) mental and behavioural disorder, and 40 % meet diagnostic criteria for at least two disorders, mainly anxiety, attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD) (Hofvander et al., 2009; Simonoff et al., 2008). Typically, these coexisting mental and behavioural conditions further impair psychosocial functioning. Behaviour that challenges, including harm to others or the self (such as head-banging, hand and wrist biting or skin picking) and surroundings is more common in autism than in other conditions with similar levels of intellectual impairment (Richards et al., 2012).

Intellectual disability (IQ lower than 70) occurs in approximately 50% of young people with autism. Characteristic of autism is the gap between intellectual skills and adaptive skills, the latter being usually more impaired, which has a significant impact on everyday functioning (Charman et al., 2011). Language disorders and specific learning difficulties (literacy, numeracy and other academic skills) are common (Jones et al., 2009). Developmental coordination disorder, manifesting as general clumsiness or an unusual gait, also commonly coexists with autism. Fine motor problems can affect self-help skills and include slow, laboured handwriting, which can lead to frustration and problems at school.

Epilepsy coexists with increased frequency in autism strongly linked to intellectual disability (Bolton et al., 2011). Functional problems are common and have a major impact on the child and family such as sleeping problems and eating difficulties (restricted and rigid food choices), which may be the presenting feature of autism in early childhood. Gastrointestinal problems are frequently reported, particularly diarrhoea, abdominal pain and constipation. These and other common medical problems can further impair psychosocial functioning and cause or increase behaviour that challenges (Kohane et al., 2012).

Mortality rates are higher in autism than in the general population, in association with comorbid medical health issues (Gillberg et al., 2010).

2.8 ONSET AND COURSE OF AUTISM

Core autistic behaviours are typically present in early childhood, although features may not always be manifest until social demands increase, for example when starting at nursery or school or moving to secondary school. Some parents notice that their child is different from birth, others in the second year or later. Regression and/or stasis of language and social behaviour are reported in between one fifth and one third of children, usually but not exclusively in the second year of life; the reasons for this are unknown. Later regression after a period of 3 years of apparently normal development is rare (1.7 per 100,000) (Fombonne, 2002) and has been termed

'childhood disintegrative disorder'; self-care, continence and mood may all be affected during regression.

Commonly, the first symptoms noticed by parents are language delay, lack of social interest and/or unusual, repetitive interests in the second or third year of life, together with behavioural challenges possibly related to sensory sensitivities, for example, dislike of certain foods or change. Features of autism vary at different ages and most individuals change with maturity. For example, early language delays may improve at around age 4 to 6 years; sensory sensitivities often wane over time and children who are initially socially very withdrawn or aloof may become much more socially interactive as they get older. On the other hand, motor mannerisms can become more obvious with age and although special interests can change, the repetitive or intense quality remains. A profile of marked strengths and weaknesses of skills is common in autism and symptoms vary with the demands of the environment and the presence of any coexisting conditions, as well as the severity of the core impairments. Puberty, as with all children, can bring more challenging behaviour and increased awareness of difference from the peer group, which may be a factor in low mood and self-esteem. Motivation to use academic potential and skills in a conventional way may also be a significant problem for some young people (and their teachers). Nevertheless, follow-up studies indicate that many problem behaviours and the severity of autism symptoms decrease with age, with improvements often being most evident in adolescence or early adulthood.

Intellectual ability and language skills remain the best predictors of outcome and around 25 to 30% of individuals with good intellectual skills are able to perform well academically and find employment as adults (Howlin et al., in press). In familiar and supportive settings such individuals may be able to function relatively well, but 'autistic' features may again become apparent in stressful situations, and support for planning, organisation and social participation is often required. Research indicates that only a small proportion of young people lose skills as they grow older, but mental health problems, particularly anxiety and depression, may develop in adolescence or early adulthood (Hutton et al., 2008). Some people also develop catatonia (Dhossche et al., 2006), which is a marked disturbance in the voluntary control of movement characterised by extreme slowing of motor activity, problems with initiation of motor actions, 'freezing' mid-action leading to the assumption and maintenance of rigid, unusual or bizarre postures and requiring external prompts to complete even simple tasks such as self-feeding and walking.

2.9 THE IMPACT OF AUTISM

The impact of autism goes well beyond the 'core' symptoms described above. Research consistently shows that people with autism are significantly impaired in their adaptive functioning, that is, the ability to have fulfilling relationships with peers, family members and more widely, to achieve expected levels in schools, gain skills for some degree of independent living and take part in community activities (Charman et al 2011). Outcomes in adult life, with respect to employment, relationships, independent living and community participation, are often poor

(Eaves & Ho, 2008; Howlin et al, 2004). Furthermore, having a child or sibling with autism has a significant, often deleterious, impact on other family members. Parents report high stress levels (Davis & Carter, 2008; Estes, 2009) and poor physical health (Smith et al, 2012).

It is the experience of parents and children/young people that while professionals in all agencies may understand the seriousness of a diagnosis of autism, they struggle to recognise what this actually means for an individual and their family. In some people, professionals and the public will witness what appear to be extreme reactions to everyday experiences; and families may be subjected to negative and judgmental views, for example that the problem would be much better if the parent 'didn't let them get away with it'. For others, seemingly idiosyncratic ideas or routines can seem irritating and irrational; teachers and other staff may dismiss the behaviour as within the child's control. For those children with autism who have no friends, some professionals may assume that if they spent more time in a social context (for example, in the playground or a social club) then the problem would be resolved. It is common for professionals to consider that after a period of using strategies such as visual support systems or augmentative communication, the individual with autism should attempt to manage without them; some practitioners who work with people with autism equate this to saying that 'after reading with glasses for a while, a child with poor sight ought to try to read without them'.

In summary, autism can impact significantly upon the child or young person and their family members. While it is important to recognise that some people with autism will have highly productive and fruitful lives, for those with more severe autism, particularly with associated and coexisting conditions, it is a lifelong, significantly impairing disorder with profound effects, not only for the individual, but on family members who may require ongoing assistance from health, education and social care. However, it is often argued (Ambitious About Autism, 2011; Howlin & Moss, 2012; National Autistic Society [NAS], 2011) that appropriate intervention and supportive social and economic conditions can have a significant impact on outcomes and functioning for individuals across the spectrum, and on the extent to which their families can adapt and flourish.

2.10 SERVICES FOR PEOPLE WITH AUTISM, PREVIOUS GUIDELINES AND THE NATIONAL CONTEXT

The first direct services for children with autism in England and Wales were specialist schools, established in the 1960s by parents. The need for such schools was based on a recognition that teachers needed to adapt their approach to teaching to enable children with autism to make progress. Until these schools were established, there was no recognised treatment or pedagogy available.

Psychiatry was the dominant profession within which to identify and diagnose 'childhood schizophrenia' (the category that once contained autism), but specialist health and social care did not exist. Diagnosis did not lead to practical strategies for helping children or their families. Many children with autism who had an

accompanying learning disability were placed in long-stay residential establishments from a young age.

The need for health and social care sectors, in addition to the educational sector, to respond more proactively to the distinct needs of children and young people with autism was only formally recognised at a policy level in the late 1990s. The Department for Education and Employment and the Department of Health Autism Working Group was established in 1998 and this led to the publication of *Autism Good Practice Guidance* (published 2002, now withdrawn). While clinical guidance on autism exists in documents such as the practice parameter from the US (Johnson and Myers, 2007; Myers and Johnson, 2007), national plans from the UK (NAS, 2003), the Welsh strategic action plan (Welsh Assembly Government, 2009) and guidelines from Scotland (Scottish Intercollegiate Guidelines Network, 2007) and New Zealand (Ministries of Health and Education, 2008), there remains wide variation in access to and quality of diagnostic and intervention services. Since the National Autism Plan for Children (National Initiative for Autism Screening and Assessment, 2003), there has been an increase in the number of district teams in the UK who have a formal autism assessment protocol (32% in 2001 rising to 54% in 2007); more services are using a multidisciplinary/multi-agency team approach (48% in 2001 rising to 93% in 2007), and more teams have joint clinics with child mental health services (34% in 2001 rising to 57% in 2007) (Palmer et al, 2011). However, the current estimated prevalence rates of autism have major resource implications and continue to place a considerable strain on local diagnostic services.

As part of the Early Support Programme (established 2004), the Department for Education and Skills and the Department of Health produced professional and parent guides on autism. More recently, in England and in Wales in 2007 the government supported the establishment of the Autism Education Trust, under whose auspices work has commenced to identify good practice and appropriate outcomes and to develop formal competencies and training for educational practitioners. While focused on education, these initiatives share an emphasis on the importance of multi-agency and multiprofessional working.

The Autism Act 2009 (Her Majesty's Stationery Office [HMSO], 2009) put a duty on the Secretary of State for Health to develop a strategy for adults with autism regardless of their level of intellectual ability or disability. The Act sets out several legal requirements for local authorities and/or NHS bodies (including foundation trusts) to take forward. These include: specialist training for key professionals as well as autism awareness training for all staff working in health and social care; a requirement for a clear diagnostic pathway; identification of lead professionals for diagnosis and assessment; clear transition plans; a named joint senior commissioner; and local commissioning plans. Statutory guidance was published in December 2010; this also asserts the requirement for services to recognise that individuals with autism with an IQ of 70 or over may require their support, not just those with intellectual disability.

2.11 THE NEED FOR A GUIDELINE ON MANAGEMENT AND SUPPORT FOR CHILDREN AND YOUNG PEOPLE WITH AUTISM AND THEIR FAMILIES

The NHS (primary, secondary and tertiary services) has a crucial role in the lifelong management and care of people with autism and their families or carers, both directly and through coordination with other key services, such as education, social care and the voluntary sector. Many parents have found it difficult to get the support and access to autism expertise they require for their child with autism. Importantly it is the experience of parents and carers that both health and social care services regularly fail to recognise the impact that autism has on both the young person and their families and carers. This shortfall relates not only to autism-specific interventions, but also to medical treatment and healthcare more generally. All services, including general practitioners (GPs) and community health teams, need to be mindful of the need to recognise that many presenting symptoms in children and young people with autism may signify additional medical needs that are in danger of being under-treated where professionals and services have not made necessary adaptations to their practice.

Primary care encompasses general practice as well as the wider community-based services that have an important role in delivering healthcare to children and young people with autism. Secondary care varies from region to region. In some areas, specialist services for children with a neurodisability are provided in generic services, community paediatrics or hospital-based secondary care services. In addition there are child and adolescent mental health services (CAMHS) teams that often work in isolation delivering mental health services, and, as identified by the NAS (Madders, 2010), they often struggle to meet the distinct needs of children and young people with autism. It is therefore often difficult for parents, carers and primary care services to know which pathway to follow for appropriate help. Tertiary care has an important role in supporting local services in ongoing management.

Managing and supporting children, young people and their families and carers needs a lifespan approach, which can be considered in three stages:

1. *The initial phase encompassing recognition, referral, diagnosis and post-diagnosis*: the *Autism Diagnosis in Children and Young People* guideline (NICE, 2011a) proposed a clear pathway following concerns being raised about the child or young person with possible autism, which included a single point of entry to diagnosis and a case coordinator appointed for every family going through a diagnostic assessment for autism.

2. *The review phase(s),* which may have particular crisis points (for example, changing schools): children's needs and the impact of their autism on them and those around them, may change substantially as they progress through childhood and adolescence, such that each 'phase' of

development may require a review of the support and services that are necessary. Regular follow-up rarely happens in the NHS but those with a special educational need (SEN) statement will have an annual review in school.

3. *The transition phase to adulthood*: it is likely that the views of parents about the focus of intervention changes over time. For example, the parents of a child aged 2 to 3 years newly diagnosed with autism may be looking for both the causation of autism and a 'cure' for their child. This is particularly likely following regression when parents have seen often dramatic losses of developmental function and the absence of a medical reason seems counterintuitive. As the child gets older and their strengths and weaknesses become more clear and stable, the focus of need often changes to that of function, participation in life, management of social and sexual relationships, leisure and work, quality of life, and good mental and physical health within what is possible for a person with autism. Also, as the child or young person gets older, it is increasingly important to ask about and take into account their views on their current and future aims and feelings in assessing their needs for support and treatment, including managing coexisting physical and mental health problems.

2.12TRANSITION TO ADULT LIFE

What we know about young people with autism is that their aspirations for their future are much the same as those of their peers: good quality of life, personal wellbeing, help to understand and cope with their condition, access to appropriate work and leisure activities and social contact with others as desired (which may be very variable). But they also need support to develop the skills needed for independent living (or what is realistic and appropriate), and autonomy of choice and decision-making whenever this can be achieved (Wittemeyer et al, 2011). Removing the barriers to achievement of these goals is the broad aim of intervention and multi-agency planning.

There are comprehensive guidelines and advice available from a number of organisations that cover transition for young people with an underlying disorder, although most do not specifically cover autism. These organisations include the Royal College of Nursing, the Social Care Institute for Excellence, and the Joint Commissioning Panel for Mental Health, which is made up of representation from the Royal College of General Practitioners and the Royal College of Psychiatrists. The exception is the Autism Education Trust, which has extensive advice available on its website.[3]

The Joint Commissioning Panel for Mental Health identifies two major factors in the failure of a successful transition to adult care in mental health services, namely:

[3] http://www.autismeducationtrust.org.uk/

- young people with mental health problems whose needs have been met primarily by paediatric services, education or social care may find that there is no equivalent service for adults, for example there is no adult equivalent of the neurodisability specialist or community paediatrician
- the way mental health services are currently structured creates gaps through which young people may fall as they undergo transition from CAMHS to adult mental health services (AMHS) (Singh et al., 2009, 2010).

The Joint Commissioning Panel and the Children and Young People's Outcomes Forum (Department of Health, 2012) recommend that there should be formal joint working arrangements to address the interface of children and young people and adult services, specifically CAMHS and AMHS and the differences in approach arising from cultural differences between the two services. The Joint Commissioning Panel's guidance for commissioners on transition[4] gives examples of good practice found around the country, with models of care such as dedicated transition services and extending CAMHS services from age 18 to 25. It also lists measures to evaluate the outcomes of these services, which include a reduction in the number of young people placed out of area because of a lack of local transition services.

Adolescent transition care planning from the Royal College of Nursing (www.rcn.org.uk) advocates a keyworker, with an extensive care plan starting at 12 years. It recommends an interdisciplinary planning checklist that encompasses self-advocacy, sexual health, psychosocial support (including for parents and carers) and educational and vocational planning. Young people themselves or, where appropriate, their parents and carers need to have information on changing benefits entitlements once they move from childhood to adulthood, including their entitlement to access education after school-leaving age. The Autism Education Trust[5] has a transition toolkit that advocates transition teams who are advised to learn about the individual and offer visual easy-read information.

The young person and their family may find local pathways for transition within learning disability services that are more comprehensive than for the population without an intellectual disability. Transition planning within special education is usually more comprehensive and includes health and social care collaboration. However even then there can be confusing differences between personnel and their roles that can be very difficult to negotiate. For example, AMHS will frequently not offer a service to the person with autism as a matter of routine. The comprehensive school nursing service at a special school that addresses all aspects of healthcare will be replaced by not only adult community learning disability nurses but other nurses in the community such as district, respiratory and epilepsy nurses. Allied health professionals such as speech and language therapists, occupational therapists and physiotherapists that have been accessed through school will now be community based.

[4] https://www.rcpsych.ac.uk/pdf/JCP-MH%20CAMHS%20transitions%20 (March%202012).pdf
[5] www.autismeducationtrust.org.uk

Because there is no equivalent adult service to the community pediatrician, ongoing healthcare will be accessed through general practice. Likewise adult neurology services will not usually offer routine support for those with autism and no other neurological problems. Young people looked after by hospital services for coexisting conditions need good transition plans to adult care. What is clear is that no one organisation is responsible for ensuring a successful transition into adulthood for a young person with autism (Department of Health, 2006).

2.13CONCEPTUAL FRAMEWORKS FOR INTERVENTION

This guideline is based on the current diagnostic criteria, which focus exclusively on specific areas of impairment. Intervention is aimed at ameliorating impairments, improving function and minimising behaviours that impact negatively on function, activities and participation following the social model of disability (World Health Organisation, 2001). However, it should be noted that there is a growing field of research into areas of autistic strengths (for example, Mottron, 2011) and that many autism advocates are therefore critical of the traditional emphasis placed on impairment. It is important for all who are involved in the support and management of autism in children and young people that their strengths and potential are recognised.

An alternative conceptual framework arising from activism on the part of people with autism and their supporters is that of neurodiversity (Mackenzie, 2011). From a neurodiversity perspective, it may be appropriate to treat certain aspects of autism when these are experienced as impairments, such as developing skills needed to read social cues, but to refrain from intervening in those behaviours that are atypical, but not experienced as impairments, such as intense focus on single activities, insistence on routines, placing objects in patterned arrangements and self-stimulating (sometimes called 'stimming') or repetitive movements. Support and management of children and young people with autism may thus involve implementing strategies to alleviate disadvantage using autism-specific strategies (Chapter 6) and modifying the environment while respecting difference. This perspective chimes with the social model of disability, in which the emphasis is placed on how appropriately the wider physical and social environment adapts to individual difference, rather than viewing the differences of individuals as solely medical problems to be 'treated'.

Appropriate adaptation of the environment (psychological, sensory, physical and even economic) to the particular needs of the developing child recognises that children and young people with autism may react to the environment in unique and unusual ways, often with enhanced sensitivity. Appropriate adaptation brings about an improved 'goodness of fit' of child to environment; this in turn helps prevent a negative cycle of adverse responses and actively promotes positive responses, leading to good outcomes. This applies to all environments and all processes of care including access to routine healthcare and encompasses the idea of 'reasonable adjustments' legally mandated in Sections 20 to 22 of the Equality Act 2010 (HMSO, 2010).

An example would be in relation to adverse behavioural outcomes. If appropriate adaptations are made, for instance to a specialised schooling environment or for healthcare, then behavioural difficulties may be reduced. In the health sector, this may include timing of appointments, whether rehearsal of procedures may help, what sensory needs if any can impact on access to healthcare, and potential triggers for behaviour that challenges. Modifications to procedures can then be put in place. A further example would be in relation to the extreme vulnerability of children with autism, both verbal and non-verbal, to violations in terms of child protection. Difficulties in communication and social understanding will make it even harder for these children to recognise or articulate when abuse is happening.

Adaptations to the environment will not be solely in terms of physical adaptations, but will also require those people around the child to adapt their communication style, attitudes, assumptions, expectations and behaviour towards the child, including the need for skill and sensitivity in judging when and if to apply physical restraint – something that should only be used to protect individuals and not to control them. Provision of a 'health passport' detailing the special needs of the individual and a plan for managing crisis and emergency care, including in hospital, would take away much of the anxiety felt by the young person and their carers; this may include how effective communication can best happen (Pratt et al., 2012).

Generic principles for developing an adapted environment to maximise 'goodness of fit' ideally may include: initial assessment and specific understanding of the child's profile of needs; engagement of the child and family and services to identify a shared understanding of need; an intelligent and individualised adaptation of different aspects of the environment in the light of those difficulties; implementation; and measuring progress and feedback to further implementation.

Applied behaviour analysis (ABA) is a general approach to intervention that can involve a wide range of behavioural strategies and can be used to change behaviours across multiple domains. It derives from theories of reinforcement and operant conditioning that stem from work by BF Skinner, Edward Thorndike and others in the 1930s and 1940s. Behavioural approaches to intervention (also called behaviour modification or behaviour therapy) can take many different forms and include strategies such as discrete trial learning, pivotal response training, shaping, modelling and prompting of behaviours, backward and forward chaining, time out and extinction. The essential principle, however, is that all behaviours are affected by their consequences (which may be negative or positive). While behavioural principles affect everyone's daily activities, ABA involves a systematic study of the factors that may be causing problem behaviours ('who', 'where', 'when' triggers) or limiting skill acquisition, detailed assessment of the behaviour (s) and assessment of potential rewards and maintaining factors. This analysis is then used to formulate hypotheses about the behaviour, its antecedents, triggers, causes and maintaining factors, and then modifying any or all of these in order to effect behavioural change. Behavioural approaches can be used either to build up skills in areas of deficit or to

reduce behaviours that result in difficulties either for the individual or those living with, working with or caring for them. There are many interventions used in autism (such as the Picture Exchange Communication System [PECS], the Early Start Denver Model [ESDM], Parent-mediated Communication-focused Treatment [PACT], Learning Experiences – an Alternative Program for Preschoolers and Parents [LEAP], Treatment and Education of Autistic and Communication-Handicapped Children [TEACCH], joint attention training, and Responsive Education and Prelinguistic Milieu Training [RPMT]) in which behavioural strategies are an essential component combined with the specific strategies that are the focus of these interventions. However, the term 'applied behaviour analysis' is also sometimes used to refer to specific comprehensive, multi-component programmes, and early intensive behavioural intervention (EIBI) programmes (such as the Lovaas Young Autism Project, see Chapter 6). Behavioural strategies are also important in managing behaviour that challenges (see Chapter 7).

2.14 MULTIPROFESSIONAL AND MULTI-AGENCY COLLABORATION

This guideline provides the evidence base for the management and support of children and young people with autism, and their families and carers, provided by primary, community, secondary, tertiary and other health and social care services. At the time of writing, NICE has a remit to issue guidelines for the health and social care services only, not education. However, the information in this guideline is relevant to all settings and to all professionals who come into contact with children and young people with autism and their families and carers.

The needs of a child or young person with autism are likely to span a number of professionals and agencies, such that for many parents and carers the demarcation between what is education and what is health and social care support can appear both arbitrary and confusing. For the child or young person with a learning disability, not only access to the school curriculum, but also most or all aspects of day-to-day functioning, may require specific teaching and learning, including activities that fall within the expertise and responsibility of healthcare professionals such as speech and language therapists, occupational therapists and behavioural psychologists. These interventions may be educational in essence but delivered by healthcare professionals. Likewise teachers may need support from specialist speech and language therapists and occupational therapists, as well as behavioural input, in order to help their pupils build up appropriate communication skills and overcome behavioural difficulties in order to make educational progress[6]. The need for integrated services was a main recommendation of the Children and Young Person's Outcomes Forum (Department of Health, 2013), which is fully endorsed by the GDG. The Children and Families Bill (HMSO, 2013) makes clear that integration of services around the child or young person and family is a key aim of the legislation. SEN statements are to be replaced by an education, health and care plan to which all agencies contribute to provide a holistic package of care.

[6] For further support see the Autism Education Trust (http://www.autismeducationtrust.org.uk/).

2.15 EVALUATING THE EVIDENCE OF THE EFFECTIVENESS OF INTERVENTIONS FOR CHILDREN AND YOUNG PEOPLE WITH AUTISM

Despite the significance of environmental change as the focus for interventions for autism, in the context of the social model of disability the bulk of research that has taken place has focused on individual change. It is possible, nonetheless, to concentrate on individual change within a social model. For example, intervention may be targeted at individuals to improve their access to society and to minimise behaviours that impact negatively on participation, but not to address core features of autism *per se*, even though the outcome measures used may relate to the core features.

Although the overall quality of the research into interventions for autism has improved considerably over the past decade, as demonstrated particularly by the growth in randomised control trials (RCTs), there continue to be many limitations in study design and methodology. Unlike pharmacological trials, in which it is possible to recruit very large samples and it is relatively easy to design placebo interventions so that both participants and researchers are blind to treatment, the costs of psychosocial interventions limit sample size and 'blinding' raises sometimes insurmountable difficulties. Thus, if the intervention is teacher- or parent-mediated it is not possible to keep them unaware of whether they are receiving treatment or not. Although bias can be reduced by ensuring that pre- and post-intervention measures are as objective and well standardised as possible, and are collected by researchers who themselves are blind to treatment, many of the most appropriate and relevant outcome measures are based on parental or teacher reports. Hence, they can never be considered bias free. Even if objective measures of child behaviour are used by assessors blind to treatment (such as standardised measures of overall autism symptomatology, IQ or language), these may not correlate with improvements in the child's behaviour at home or school. For example, if the study stipulates two primary outcome measures (for example, the child's autism score and problem behaviours at home), which should be considered most important? What if the standardised score improves significantly while parents continue to report major difficulties at home? The opposite may also be the case, with parental reports being positive but objective measures showing no change.

There are many other issues that limit the conclusions that can be drawn concerning the effectiveness of psychosocial interventions for children with autism. The lack of evidence to show that treatments affect functioning in 'real life' is a particular problem. For example, several studies with a focus on improving social skills or anxiety report significant effects on standardised questionnaires or analogue measures, but none to date has documented improvements in the child's ability to function in the playground or to control their anxiety in stressful situations. It is well established that children with autism have marked problems in generalising learning from one situation to another and this remains a major challenge in intervention research.

A further problem relates to the complexity of psychosocial interventions. In contrast to pharmacological trials the content of the both the treatment and the non-treatment programmes is far more complicated and less controllable. All psychosocial interventions include components related to behavioural, social and communication skills although the emphasis on one or other of these areas varies from programme to programme. The PECS programme (Bondy & Frost, 1998), for example, has a focus on picture communication, but whether it is the PECS symbols, the emphasis on social initiation, the reinforcement contingencies involved, or many other factors that are crucial to treatment success remains unexplored. Similarly, 'treatment as usual' may vary widely, with some children receiving very high quality care and others little or none.

Yet another important issue that limits conclusions about treatment effectiveness is the wide variability of measures used in different studies. This makes it very difficult to compare results across studies or to combine findings in ways that provide consistent evidence about the success or otherwise of particular treatments.

Finally there are many unanswered questions concerning the long-term impact of an intervention. Although more studies now include some follow-up measures, these rarely extend beyond 6 months or 1 year post-treatment. Even within this short time period the findings are inconsistent. Some studies suggest improvements can be maintained or even increase, at least in the first few months after intervention ceases; others indicate a rapid decrease in treatment effects. How to achieve long-term treatment effects is yet a further challenge to research in this area.

2.16 THE ECONOMIC COST OF AUTISM

Autism has a considerable economic impact on individuals with the condition, their family members and carers, health and social care services, and the wider society. In a recent study conducted in the UK, Knapp and colleagues (2009) estimated that the annual cost of supporting children and young people with autism reaches £2.7 billion, while the respective cost for adults with autism amounts to £25 billion (2006 prices). These estimates are based on 1% prevalence of autism across all ages and have taken into account costs associated with provision of health and social care, respite care, special education and day services, accommodation, voluntary organisation support, as well as productivity losses (lost employment) of parents and adults with autism, but do not include cost estimates on benefit payments or informal care.

The presence of intellectual disability appears to be an important driver of these costs, as the costs incurred by children and adults with autism and intellectual disability account for approximately 63% of the total costs associated with autism in the UK. The largest part of the total national cost for children (95%) is accounted for by services funded by the state, while the remaining 5% is attributed to family expenses. The high cost elements for children and young people (irrespective of presence of intellectual disability) are special education, health and social care and

respite care. Placement costs are also substantial for children and young people not living with their families. For adults, 59% of the total national cost is attributable to publicly funded services, 36% to lost employment for people with autism, and the remaining 5% to family expenses. For adults with autism without intellectual disability who live in private households, the largest proportion of the associated total cost relates to productivity losses of the individual, while for adults with or without intellectual disability in supported accommodation or care homes, a sizeable part of the total cost is incurred by accommodation costs, including costs of staff employed in, or attached to, those settings.

Taking into account all cost elements, the mean annual total cost per child or young person with autism in the UK reaches £25,400, ranging from roughly £600 for very young children (aged up to 3 years) with autism with intellectual disability living with their families, up to approximately £62,500 for young people (aged 12 to 17 years) with intellectual disability living in residential/foster care. For adults with autism, the mean annual total cost per person ranges from £32,500 for adults with autism without intellectual disability living in private accommodation, to £98,000 for adults with autism with intellectual disability living in hospital. Using these estimates and an annual discount rate of 3.5%, Knapp and colleagues (2009) estimated that in the UK the lifetime cost of a person with autism without intellectual disability reaches £0.8 million (undiscounted £3.1 million), while the lifetime cost of a person with autism with intellectual disability approximates to £1.23 million (undiscounted £4.6 million).

A more recent study by Barrett and colleagues (2012) assessed the service and wider societal costs of young children (aged 2 to 5 years) with autism in the UK. The study considered health and social care services provided in primary, secondary and community settings including medication and services provided by non-statutory organisations, specialist accommodation such as foster and respite care, education and day care facilities used by the children, parents' expenditure resulting directly from their child's autism such as specialist equipment costs, costs associated with home adaptations, conference or training attendance, as well as parents' productivity losses (time off work) attributable to their child's autism. The study was conducted in 152 children with autism over a 6-month period. The mean total service cost over this period was £2,581 (range £317 to £6,698), equivalent to £450 per month and over £5,000 per year. Almost half the costs (45%) were for education and childcare, 41% were for community health and social services and 12% for hospital services. The mean total societal cost over 6 months, which included family costs and productivity losses, was £3,083 (range £556 to £9,611), equivalent to £500 per month and £6,000 per year.

The economic cost of autism is considerable worldwide: Ganz (2007) estimated that the annual societal cost of caring for and treating all people with autism in the US reaches $35 billion (2003 prices, range from £13 billion to $76 billion, depending on the underlying assumptions used to estimate the cost figure). This cost includes direct medical costs (visits to healthcare professionals, prescription medications,

dental care, complementary and alternative therapies, behavioural therapies, hospital and emergency services, allied health, equipment and supplies, home health and medically related travel), direct non-medical costs (child care and adult care, respite and family care, home and care modifications, special education, supported employment and other costs) as well as productivity losses of families, carers and adults with autism. The lifetime societal cost per person with autism in the US, using an annual discount rate of 3%, is estimated at $3.2 million; the largest component of this cost comprises lost productivity and adult care.

In Sweden, Järbrink (2007b) estimated the mean annual service cost per child with autism at €43,000 (2005 prices). This cost included healthcare services (inpatient and outpatient care, medication), community support (such as home placement, respite care, support workers, and so on) and special education. When relatives' expenses, informal care and productivity losses were considered, the annual societal cost reached €50,000 per child with autism.

A large part of the cost associated with autism relates to productivity losses, both of adults with autism, but also of families of children and adults with the condition. It has been reported that, on average, mothers of children with autism earn 35% less than the mothers of children with another health problem and 56% less than the mothers of children with no health problem (Cidav et al., 2012).

The substantial societal cost of autism emphasises the need for provision of effective interventions that will improve the quality of life of people with autism, their family and carers, and will reduce the costs borne to health and social services, people with autism and their families, and the wider society.

3 METHODS USED TO DEVELOP THIS GUIDELINE

3.1 OVERVIEW

The development of this guideline drew upon methods outlined by NICE (*The Guidelines Manual* [NICE, 2009])[7]. A team of health and social care professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the NCCMH staff, undertook the development of a person-centred, evidence-based guideline. There are seven basic steps in the process of developing a guideline:

1. Define the scope, which lays out exactly what will be included (and excluded) in the guidance.
2. Define review questions that cover all areas specified in the scope.
3. Develop a review protocol for the systematic review that specifies the search strategy and method of evidence synthesis for each review question.
4. Synthesise and (meta-) analyse data retrieved, guided by the review protocols.
5. Produce Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles and summaries.
6. Consider the implications of the research findings for clinical practice and reach consensus decisions on areas where evidence is not found.
7. Answer review questions with evidence-based recommendations for clinical practice.

The clinical practice recommendations made by the GDG are therefore derived from the most up-to-date and robust evidence for the clinical and cost effectiveness of the treatments and services used in the treatment and management of autism. Where evidence was not found or was inconclusive, the GDG discussed and attempted to reach consensus on what should be recommended, factoring in any relevant issues. In addition, to ensure a service user and carer focus, the concerns of service users and carers regarding health and social care have been highlighted and addressed by recommendations agreed by the whole GDG.

3.2 THE SCOPE

Topics are referred by the Secretary of State and the letter of referral defines the remit which defines the main areas to be covered (see *The Guidelines Manual* [NICE, 2012c] for further information). The NCCMH developed a scope for the guideline based on the remit (see Appendix 1). The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude

[7] At the time of publication, a revised version of *The Guidelines Manual* had been published (NICE, 2012).

- identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the National Collaborating Centre, and the remit from the Department of Health/Welsh Assembly Government
- inform the development of the review questions and search strategy
- inform professionals and the public about expected content of the guideline
- keep the guideline to a reasonable size to ensure that its development can be carried out within the allocated period.

An initial draft of the scope was sent to registered stakeholders who had agreed to attend a scoping workshop. The workshop was used to:

- obtain feedback on the selected key clinical issues
- identify which population subgroups should be specified (if any)
- seek views on the composition of the GDG
- encourage applications for GDG membership.

The draft scope was subject to consultation with registered stakeholders over a 4-week period. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from stakeholder organisations The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by NICE.

3.3 THE GUIDELINE DEVELOPMENT GROUP

During the consultation phase, members of the GDG were appointed by an open recruitment process. GDG membership consisted of: professionals in psychiatry, clinical psychology, nursing, social work and general practice; academic experts in psychiatry and psychology; and carers. The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economic literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

3.3.1 Guideline Development Group meetings

Twelve GDG meetings were held between 9 December 2011 and 31 May 2013. During each day-long GDG meeting, in a plenary session, review questions and clinical and economic evidence were reviewed and assessed, and recommendations formulated. At each meeting, all GDG members declared any potential conflicts of interest, and service user and carer concerns were routinely discussed as a standing agenda item.

3.3.2 Service users and carers

Individuals with direct experience of services gave an integral service-user focus to the GDG and the guideline. The GDG included three carers. They contributed as full GDG members to writing the review questions, providing advice on outcomes most

relevant to service users and carers, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service user research to the attention of the GDG. In drafting the guideline, they contributed to writing the guideline's introduction and identified recommendations from the perspective of service users and carers.

3.3.3 National and international experts

National and international experts in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to identify unpublished or soon-to-be published studies, to ensure that up-to-date evidence was included in the development of the guideline. They informed the GDG about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 4 lists researchers who were contacted.

3.4 REVIEW QUESTIONS

Review (clinical) questions were used to guide the identification and interrogation of the evidence base relevant to the topic of the guideline. Before the first GDG meeting, an analytic framework (see Appendix 5) was prepared by NCCMH staff based on the scope (and an overview of existing guidelines), and discussed with the guideline Chair. The framework was used to provide a structure from which the review questions were drafted. Both the analytic framework and the draft review questions were then discussed by the GDG at the first few meetings and amended as necessary. Where appropriate, the framework and questions were refined once the evidence had been searched and, where necessary, subquestions were generated. The final list of review questions can be found in Appendix 6.

For questions about interventions, the PICO (population, intervention, comparison and outcome) framework was used (see Table 2).

Table 2: Features of a well-formulated question on intervention effectiveness – the PICO guide

Population	Which population of service users are we interested in? How can they be best described? Are there subgroups that need to be considered?
Intervention	Which intervention, treatment or approach should be used?
Comparison	What is/are the main alternative/s to compare with the intervention?
Outcome	What is really important for the service user? Which outcomes should be considered: intermediate or short-term measures; mortality; morbidity and treatment complications; rates of relapse; late morbidity and readmission; return to work, physical and social functioning and other measures such as quality of life; general health status?

Although service user experience is a component of all review questions, specific questions concerning what the experience of care is like for children and young

people with autism, and where appropriate, their families/carers, were developed by the GDG.

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of review question of relevance to NICE guidelines. These are listed in Table 3. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'.

However, in all cases, a well-conducted systematic review (of the appropriate type of study) is likely to always yield a better answer than a single study.

The use of evidence from inferior study designs may be necessary and usually depends on the availability of high-quality evidence (further information can be found in each evidence chapter).

Table 3: Best study design to answer each type of question

Type of question	*Best primary study design*
Effectiveness or other impact of an intervention	RCT; other studies that may be considered in the absence of RCTs are the following: internally/externally controlled before and after trial, interrupted time-series.
Accuracy of information (for example, risk factor, test, prediction rule)	Comparing the information against a valid gold standard in a RCT or inception cohort study.
Rates (of disease, service user experience, rare side effects)	Prospective cohort, registry, cross-sectional study.
Experience of care	Qualitative research (for example, grounded theory, ethnographic research).

3.5 SYSTEMATIC CLINICAL LITERATURE REVIEW

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific review questions developed by the GDG. Thus, clinical practice recommendations are evidence-based, where possible, and, if evidence is not available, informal consensus methods are used to try and reach general agreement (see Section**Error! Reference source not found.** and the need for future research is specified.

3.5.1 The review process

Scoping searches

A broad preliminary search of the literature was undertaken in May 2011 to obtain an overview of the issues likely to be covered by the scope, and to help define key areas. Searches were restricted to clinical guidelines, Health Technology Assessment

(HTA) reports, key systematic reviews and RCTs and conducted in the following databases and websites:

- Agency for Healthcare Research and Quality [United States]
- *BMJ* Clinical Evidence
- Canadian Medical Association Infobase [Canadian guidelines]
- Clinical Policy and Practice Program of the New South Wales Department of Health [Australia]
- Clinical Practice Guidelines [Australian Guidelines]
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews (CDSR)
- Excerpta Medica Database (Embase)
- Guidelines International Network
- Health Evidence Bulletin Wales
- Health Management Information Consortium (HMIC)
- HTA database (technology assessments)
- Medical Literature Analysis and Retrieval System Online (MEDLINE/MEDLINE In-Process)
- National Health and Medical Research Council
- National Library for Health Guidelines Finder
- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination
- Organizing Medical Networked Information Medical Search
- Scottish Intercollegiate Guidelines Network
- Turning Research Into Practice
- Websites of NICE (including NHS Evidence) and the National Institute for Health Research HTA Programme for guidelines and HTAs in development.

Further information about this process can be found in *The Guidelines Manual* (NICE, 2012c).

Systematic literature searches

After the scope was finalised, a systematic search strategy was developed to locate as much relevant evidence as possible. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise a broad approach to searching to maximise retrieval of evidence to all parts of the guideline. Searches were restricted to systematic reviews, RCTs, qualitative and survey research and conducted in the following databases:

- Applied Social Services Index and Abstracts (ASSIA)
- Australian Education Index (AEI)
- British Education Index (BEI)
- CDSR

- CENTRAL
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- DARE
- Education Resources in Curriculum (ERIC)
- Embase
- HMIC
- HTA database
- International Bibliography of Social Science (IBSS)
- MEDLINE/MEDLINE In-Process
- PsycEXTRA
- Psychological Information Database (PsycINFO)
- Social Policy and Practice
- Social Sciences Citation Index (SSCI)
- Social Services Abstracts (SSA).

The search strategies were initially developed for MEDLINE before being translated for use in other databases or interfaces. Strategies were built up through a number of trial searches and discussions of the results of the searches with the review team and GDG to ensure that all possible relevant search terms were covered. In order to assure comprehensive coverage, search terms for autism were kept purposely broad to help counter dissimilarities in database indexing practices and thesaurus terms, and imprecise reporting of study populations by authors in the titles and abstracts of records. The search terms for each search are set out in full in Appendix 7.

EndNote

Citations from each search were downloaded into EndNote (a software product for managing references and formatting bibliographies) and duplicates removed. Records were then screened against the eligibility criteria of the reviews before being quality appraised (see below). The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

Search filters

To aid retrieval of relevant and sound studies, filters were used to limit a number of searches to systematic reviews, RCTs, qualitative and survey research. The search filters for systematic reviews and RCTs are adaptations of filters designed by the Health Information Research Unit of McMaster University. The qualitative research filter was developed in-house. Each filter comprises index terms relating to the study type(s) and associated text words for the methodological description of the design(s).

Date and language restrictions

Systematic database searches were initially conducted in May 2011 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in January 2013 ahead of the guideline consultation.

After this point, studies were only included if they were judged by the GDG to be exceptional (for example, if the evidence was likely to change a recommendation).

Although no language restrictions were applied at the searching stage, foreign language papers were not requested or reviewed, unless they were of particular importance to a review question.

Date restrictions were not applied, except for searches for systematic reviews, and experience of care, which were limited to research published from 1995 onwards, since older research was thought to be less useful.

Other search methods

Other search methods involved: (a) scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence and included studies) for more published reports and citations of unpublished research; (b) checking the tables of contents of key journals for studies that might have been missed by the database and reference list searches; (c) tracking key papers in the Science Citation Index (prospectively) over time for further useful references; (d) conducting searches of the 'Research Autism', International Standard Randomized Controlled Trial Number (ISRCTN) Register and ClinicalTrials.gov websites for unpublished trial reports; (e) contacting included study authors for unpublished or incomplete datasets. Searches conducted for existing NICE guidelines were updated where necessary. Other relevant guidelines were assessed for quality using the AGREE instrument (AGREE Collaboration, 2003). The evidence base underlying high-quality existing guidelines was utilised and updated as appropriate.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 7.

Study selection and quality assessment

All primary-level studies included after the first scan of citations were acquired in full and re-evaluated for eligibility at the time they were being entered into the study information database. More specific eligibility criteria were developed for each review question and are described in the relevant clinical evidence chapters. Eligible systematic reviews and primary-level studies were critically appraised for risk of bias (see *The Guidelines Manual* [NICE, 2012c]) for the methodology checklist templates). The eligibility of each study was confirmed by at least one member of the GDG.

Unpublished evidence

Authors and principal investigators were approached for unpublished evidence (see Appendix 4). The GDG used a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must have been accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must have been submitted with the understanding that data from the study and a summary of the study's characteristics would be published in the full

guideline. Therefore, the GDG did not accept evidence submitted as commercial in confidence. However, the GDG recognised that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.

3.5.2 Data extraction

Quantitative analysis

Study characteristics, methodological quality, and outcome data were extracted from all eligible studies that met the minimum quality criteria, using Review Manager 5.1 (The Cochrane Collaboration, 2011) and Excel-based forms (see Appendix 12).

In most circumstances, for a given outcome (continuous and dichotomous), where more than 50% of the number randomised to any group were missing or incomplete, the study results were excluded from the analysis (except for the outcome 'leaving the study early', in which case, the denominator was the number randomised). Where there were limited data for a particular review, the 50% rule was not applied. In these circumstances the evidence was downgraded due to the risk of bias.

Where possible, outcome data were used from an intention-to-treat analysis (ITT) (that is, a 'once-randomised-always-analyse' basis). Adverse effects were entered into Review Manager as reported by the study authors because it is usually not possible to determine whether early withdrawals had an unfavourable outcome.

Consultation with another reviewer or members of the GDG was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing dataset. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer were checked by the second reviewer. Disagreements were resolved through discussion. Where consensus could not be reached, a third reviewer or GDG members resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad et al., 1996; Berlin, 2001).

Qualitative analysis

After transcripts or reviews of service user experience were identified (see Section 3.5.1), each was read and re-read and sections of the text were collected under different headings using an Excel-based form. Initially the text from the transcripts/reviews was organised using a matrix of service user experience (see Table 4).

A matrix was formed by creating a table with the eight dimensions of patient-centred care developed by the Picker Institute Europe[8] (see Table 4 for further information), down the vertical axis, and the key points on a pathway of care (as specified by the GDG before data extraction) across the horizontal axis. With regard to terminology, the GDG preferred the term 'person-centred' rather than 'patient-centred', therefore the former is used in the matrix. The Picker Institute's dimensions of patient-centred care were chosen because they are well established, comprehensive, and based on research. In addition, a variation of these dimensions has been adopted by the US Institute of Medicine (Institute of Medicine, 2001).

Table 4: Matrix of service user experience

Experience of the disorder		*Key points on the pathway of care*		*Themes that apply to all points on the pathway*
The relationship between individual service users and professionals	Involvement in decisions and respect for preferences			
	Clear, comprehensible information and support for self-care			
	Emotional support, empathy and respect			
The way that services and systems work	Fast access to reliable health advice			
	Effective treatment delivered by trusted professionals			
	Attention to physical and environmental needs			
	Involvement of, and support for, family and carers			
	Continuity of care and smooth transitions			

Under the broad headings in the matrix, specific emergent themes were identified and coded by two researchers working independently. Overlapping themes and themes with the highest frequency count across all testimonies were extracted and regrouped using the matrix. The findings from this qualitative analysis can be found in Chapter 4.

[8] http://www.pickereurope.org/patientcentred

Expert advisory group validation for the qualitative evidence review

It was not possible to have a child or young person service user as a regular GDG member partly because of the demands it would make on their time and partly because of problems associated with the group-based environment and format of GDG meetings. Instead the NAS presented the results of the qualitative analysis to an expert advisory group of children and young people with autism recruited from a number of different settings to validate the conclusions of the analysis.

Material from these focus groups or individual interviews was used to supplement the literature review of service user and carer experience of care and organisation and delivery of care. This enabled a triangulation of the service user and carer experience findings – that is, it was possible to compensate for possible weaknesses in one data collection or analysis method by using additional methods, in this case, material from a systematic qualitative literature review was combined with that from focus groups and individual sessions conducted by the NAS.

3.5.3 Synthesising the evidence for intervention effectiveness

Meta-analysis

Where possible, meta-analysis was used to synthesise evidence for the effectiveness of interventions using Review Manager. If necessary, re-analyses of the data or sub-analyses were used to answer review questions not addressed in the original studies or reviews.

Dichotomous outcomes were analysed as relative risks (RRs) or odds ratios (ORs) with the associated 95% confidence interval (CI) (see Figure 1 for an example of a forest plot displaying dichotomous data). A relative risk (also called a risk ratio) is the ratio of the treatment event rate to the control event rate. A RR of 1 indicates no difference between treatment and control. The overall RR in Figure 1 of 0.73 indicates that the event rate (that is, non-remission rate) associated with intervention A is about three-quarters of that of the control intervention or, in other words, the RR reduction is 27%.

The CI shows a range of values within which we are 95% confident that the true effect will lie. If the effect size has a CI that does not cross the 'line of no effect', then the effect is commonly interpreted as being statistically significant.

Continuous outcomes were analysed using the mean difference (MD) or standardised mean difference (SMD) when different measures were used in different studies to estimate the same underlying effect (see Figure 2 for an example of a forest plot displaying continuous data). If reported by study authors, ITT data, using a valid method for imputation of missing data, were preferred over data only from people who completed the study.

Figure 1: Example of a forest plot displaying dichotomous data

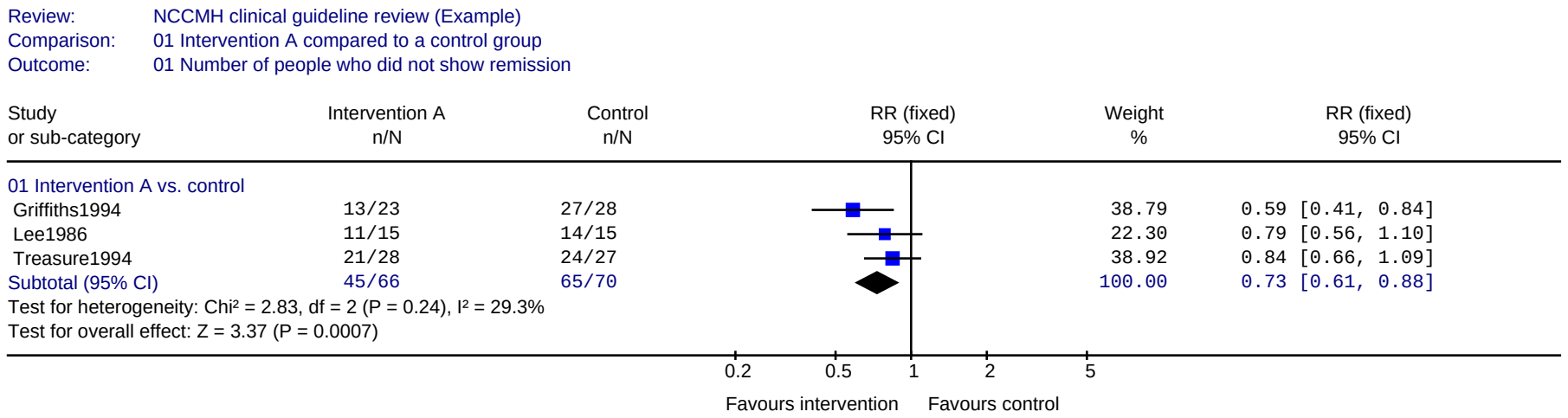
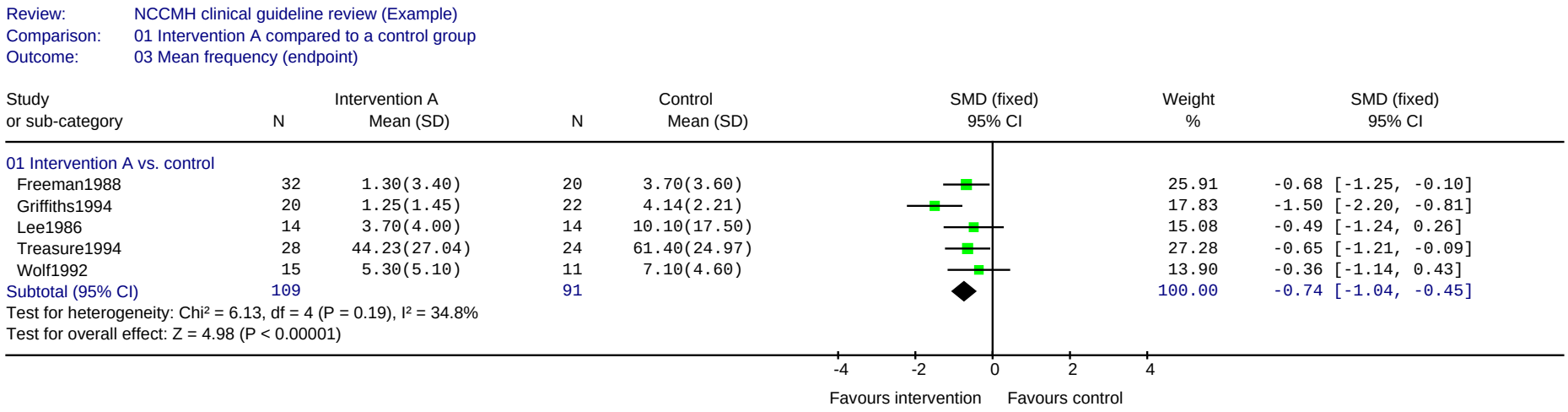


Figure 2: Example of a forest plot displaying continuous data



Heterogeneity

To check for consistency of effects among studies, both the I^2 statistic and the chi-squared test of heterogeneity, as well as a visual inspection of the forest plots were used. The I^2 statistic describes the proportion of total variation in study estimates that is as a result of heterogeneity (Higgins & Thompson, 2002). For a meta-analysis of comparative effectiveness studies, the I^2 statistic was interpreted in the following way based on Higgins and Green (2011):

- 0 to 40%: might not be important
- 30 to 60%: may represent moderate heterogeneity
- 50 to 90%: may represent substantial heterogeneity
- 75 to 100%: considerable heterogeneity.

The Cochrane Collaboration advice suggests that overlapping categories are less misleading than simple thresholds since the importance of inconsistency depends on (a) the magnitude and direction of effects, and (b) the strength of evidence for heterogeneity (for example, *p* value from the chi-squared test, or a CI for I^2).

Publication bias

Where there were sufficient data, funnel plots were used to explore the possibility of publication bias. Asymmetry of the plot would be taken to indicate possible publication bias and investigated further.

Where necessary, an estimate of the proportion of eligible data that were missing (because some studies did not include all relevant outcomes) was calculated for each analysis.

3.5.4 Grading the quality of evidence

For questions about interventions, the GRADE approach[9] was used to grade the quality of evidence for each outcome. For questions about the experience of care and the organisation and delivery of care, methodology checklists were used to assess the risk of bias, and this information was taken into account when interpreting the evidence. The technical team produced GRADE evidence profiles (see below) using GRADEprofiler (GRADEpro) software (Version 3.6), following advice set out in the GRADE handbook (Schünemann et al., 2009).

Evidence profiles

A GRADE evidence profile was used to summarise both the quality of the evidence and the results of the evidence synthesis for each 'critical' outcome (see Table 5 for an example of an evidence profile). The GRADE approach is based on a sequential assessment of the quality of evidence, followed by judgment about the balance between desirable and undesirable effects, and subsequent decision about the strength of a recommendation.

[9] For further information about GRADE, see www.gradeworkinggroup.org

Within the GRADE approach to grading the quality of evidence, the following is used as a starting point:

- randomised trials without important limitations provide high-quality evidence
- observational studies without special strengths or important limitations provide low-quality evidence.

For each outcome, quality may be reduced depending on five factors: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision and (5) publication bias. For the purposes of the guideline, each factor was evaluated using criteria provided in Table 6.

For observational studies without any reasons for downgrading, the quality may be upgraded if there is a large effect, all plausible confounding would reduce the demonstrated effect (or increase the effect if no effect was observed), or there is evidence of a dose-response gradient (details would be provided under the 'Other' column).

Each evidence profile includes a summary of findings: number of participants included in each group, an estimate of the magnitude of the effect, and the overall quality of the evidence for each outcome. Under the GRADE approach, the overall quality for each outcome is categorised into one of four groups (high, moderate, low or very low).

3.5.5 Presenting evidence to the Guideline Development Group

Study characteristics tables and, where appropriate, forest plots generated with Review Manager and GRADE summary of findings tables were presented to the GDG.

Where meta-analysis was not appropriate and/or possible, the reported results from each primary-level study were included in the study characteristics table. The range of effect estimates were included in the GRADE profile, and where appropriate, described narratively.

Table 5: Example of a GRADE evidence profile

Quality assessment							Summary of Findings				
Participant (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With treatment as usual	**With behavioural intervention**		**Risk with treatment as usual**	**Risk difference with behavioural intervention** (95% CI)
Outcome 1 (measured with: any valid method; better indicated by lower values)											
45 (1 study) 104 weeks	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	Undetected	⊕⊕⊖⊖ **LOW**[1] due to imprecision	21	24	Not applicable (N/A)	N/A	Intervention group was **0.16 standard deviations lower** (0.75 lower to 0.43 higher)
Outcome 2 (assessed with: any valid method)											
45 (1 study) 104 weeks	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	Undetected	⊕⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	1/21 (4.8%)	7/24 (29.2%)	**RR 8.24** (0.92 to 73.79)	**Study population**	
										48 per 1000	**345 more per 1000** (from 4 fewer to 1000 more)
										Moderate	
										N/A	N/A

[1] N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2] High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as blinding of outcome assessment is unclear.
[3] Events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 6: Factors that decrease quality of evidence

Factor	Description	Criteria
Risk of bias	Methodological quality/ risk of bias.	In the studies that reported a particular outcome, serious risks across most studies (that reported a particular outcome). The evaluation of risk of bias was made for each study using NICE methodology checklists (see Section 3.5.1).
Inconsistency	Unexplained heterogeneity of results.	Moderate or greater heterogeneity (see Section 3.5.3 for further information about how this was evaluated).
Indirectness	How closely the outcome measures, interventions and participants match those of interest.	If the comparison was indirect, or if the question being addressed by the GDG was substantially different from the available evidence regarding the population, intervention, comparator or outcome.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide CIs around the estimate of the effect.	If either of the following two situations were met: • the optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) was not achieved • the 95% CI around the pooled or best estimate of effect included both (a) no effect and (b) appreciable benefit or appreciable harm
Publication bias	Systematic underestimate or an overestimate of the underlying beneficial or harmful effect as a result of the selective publication of studies.	If there was evidence of selective publication. This may be detected during the search for evidence, or through statistical analysis of the available evidence.

3.5.6 Structure of the guideline

The GDG decided that it was more clinically useful to structure the guideline chapters according to critical outcomes rather than intervention type because service users present with target behaviours that the interventions seek to address and this is how the data are meta-analysed. Critical outcomes were divided into impact on core features of autism (Chapter 6) and additional outcomes (Chapters 7 to 9). According to a neurodiversity and social model perspective, impact on core features may be seen as a less critical outcome than impact in others areas. By structuring the guideline according to critical outcomes rather than intervention type, the GDG also recognised that many interventions cannot be strictly divided along professional lines (for example, speech therapy, occupational therapy, behaviour analysis) since many or most can be multidisciplinary or pan specialist in delivery.

Where trials have reported on a number of outcomes, the data from all relevant outcomes have been included, but have been split across the appropriate chapters

and cross-referenced. The study characteristics tables in Appendix 12 are organised according to the direct outcome (target) of the intervention.

3.6 HEALTH ECONOMICS METHODS

The aim of the health economics was to contribute to the guideline's development by providing evidence on the cost effectiveness of interventions for the management and support of children and young people with autism and their families and covered in the guideline. This was achieved by:

- systematic literature reviews of existing economic evidence
- decision-analytic economic modelling.

Systematic reviews of economic literature were conducted in all areas covered in the guideline. Economic modelling was undertaken in areas with likely major resource implications, where the current extent of uncertainty over cost effectiveness was significant and economic analysis was expected to reduce this uncertainty, in accordance with *The Guidelines Manual* (NICE, 2012c). Prioritisation of areas for economic modelling was a joint decision between the health economist and the GDG. The rationale for prioritising review questions for economic modelling was set out in an economic plan agreed between NICE, the GDG, the health economist and the other members of the technical team. The following economic questions were selected as key issues that were addressed by economic modelling:

- cost effectiveness of interventions aimed at behaviour that challenges (focusing on antipsychotic medication)
- cost effectiveness of interventions aimed at coexisting problems or disorders (focusing on cognitive behavioural therapy [CBT] for the management of anxiety).

In addition, literature on the health-related quality of life of children and young people with autism was systematically searched to identify studies reporting appropriate utility scores that could be utilised in a cost-utility analysis.

The rest of this section describes the methods adopted in the systematic literature review of economic studies. Methods employed in economic modelling are described in the respective sections of the guideline.

3.6.1 Search strategy for economic evidence

Scoping searches

A broad preliminary search of the literature was undertaken in October 2011 to obtain an overview of the issues likely to be covered by the scope, and help define key areas. Searches were restricted to economic studies and HTA reports, and conducted in the following databases:

- Embase
- MEDLINE/ MEDLINE In-Process
- HTA database (technology assessments)
- NHS Economic Evaluation Database (NHS EED).

Any relevant economic evidence arising from the clinical scoping searches was also made available to the health economist during the same period.

Systematic literature searches

After the scope was finalised, a systematic search strategy was developed to locate all the relevant evidence. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies from the results) was carefully considered, and a decision made to utilise a broad approach to searching to maximise retrieval of evidence to all parts of the guideline. Searches were restricted to economic studies and HTA reports, and conducted in the following databases:

- Embase
- HTA database
- MEDLINE/ MEDLINE In-Process
- NHS EED
- PsycINFO.

Any relevant economic evidence arising from the clinical searches was also made available to the health economist during the same period.

The search strategies were initially developed for MEDLINE before being translated for use in other databases or interfaces. Strategies were built up through a number of trial searches, and discussions of the results of the searches with the review team and GDG to ensure that all possible relevant search terms were covered. In order to assure comprehensive coverage, search terms for autism were kept purposely broad to help counter dissimilarities in database indexing practices and thesaurus terms, and imprecise reporting of study populations by authors in the titles and abstracts of records.

For standard mainstream bibliographic databases (CINAHL, Embase, MEDLINE and PsycINFO) search terms for autism combined with a search filter for health economic studies. For searches generated in topic-specific databases (EconLit[10], HTA, NHS EED) search terms for autism were used without a filter. The sensitivity of this approach was aimed at minimising the risk of overlooking relevant publications, because of potential weaknesses resulting from more focused search strategies. The search terms are set out in full in Appendix 9.

[10] The American Economic Association's electronic bibliography.

EndNote

Citations from each search were downloaded into EndNote and duplicates removed. Records were then screened against the inclusion criteria of the reviews before being quality appraised. The unfiltered search results were saved and retained for future potential reanalysis to help keep the process both replicable and transparent.

Search filters

The search filter for health economics is an adaptation of a pre-tested strategy designed by the Centre for Reviews and Dissemination (2007). The search filter is designed to retrieve records of economic evidence (including full and partial economic evaluations) from the vast amount of literature indexed to major medical databases such as MEDLINE. The filter, which comprises a combination of controlled vocabulary and free-text retrieval methods, maximises sensitivity (or recall) to ensure that as many potentially relevant records as possible are retrieved from a search. A full description of the filter is provided in Appendix 9.

Date and language restrictions

Systematic database searches were initially conducted in May 2011 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in January 2013. After this point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

Although no language restrictions were applied at the searching stage, foreign language papers were not requested or reviewed, unless they were of particular importance to an area under review. All the searches were restricted to research published from 1995 onwards in order to obtain data relevant to current healthcare settings and costs.

Other search methods

Other search methods involved scanning the reference lists of all eligible publications (systematic reviews, stakeholder evidence and included studies from the economic and clinical reviews) to identify further studies for consideration.

Full details of the search strategies and filter used for the systematic review of health economic evidence are provided in Appendix 9.

3.6.2 Inclusion criteria for economic studies

The following inclusion criteria were applied to select studies identified by the economic searches for further consideration:

- Only studies from Organisation for Economic Co-operation and Development countries were included, as the aim of the review was to identify economic information transferable to the UK context.

- Selection criteria based on types of clinical conditions and service users as well as interventions assessed were identical to the clinical literature review.
- Studies were included provided that sufficient details regarding methods and results were available to enable the methodological quality of the study to be assessed, and provided that the study's data and results were extractable. Conference abstracts or poster presentations were excluded.
- Full economic evaluations that compared two or more relevant options and considered both costs and consequences as well as costing analyses that compared only costs between two or more interventions were included in the review.
- Economic studies were included if they used clinical effectiveness data either from a single study (a clinical trial, a cohort study, a study with a mirror-image design etc) or from a literature review of primary studies.
- Non-UK studies that reported exclusively intervention costs, without any other cost implications, were excluded from consideration as this information was deemed not useful or relevant to the UK setting.

3.6.3 Applicability and quality criteria for economic studies

All economic papers eligible for inclusion were appraised for their applicability and quality using the methodology checklist for economic evaluations recommended by NICE (NICE, 2012c), which is shown in Appendix 10 of this guideline. The methodology checklist for economic evaluations was also applied to the economic models developed specifically for this guideline. All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered during the guideline development process, along with the results of the economic modelling conducted specifically for this guideline. The completed methodology checklists for all economic evaluations considered in the guideline are provided in Appendix 15.

3.6.4 Presentation of economic evidence

The economic evidence considered in the guideline is provided in the respective evidence chapters, following presentation of the relevant clinical evidence. The references to included studies and the respective evidence tables with the study characteristics and results are provided in Appendix 16. Methods and results of economic modelling undertaken alongside the guideline development process are presented in the relevant evidence chapters. Characteristics and results of all economic studies considered during the guideline development process (including modelling studies conducted for this guideline) are summarised in economic evidence profiles accompanying respective GRADE clinical evidence profiles in Appendix 17.

3.6.5 Results of the systematic search of economic literature

The titles of all studies identified by the systematic search of the literature were screened for their relevance to the topic (that is, economic issues and information on the health-related quality of life in children and young people with autism).

References that were clearly not relevant were excluded first. The abstracts of all potentially relevant studies (116 references) were then assessed against the inclusion criteria for economic evaluations by the health economist. Full texts of the studies potentially meeting the inclusion criteria (including those for which eligibility was not clear from the abstract) were obtained. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications of one study, or had been updated in more recent publications were subsequently excluded. Economic evaluations eligible for inclusion (six references) were then appraised for their applicability and quality using the methodology checklist for economic evaluations. Three economic studies identified by the systematic literature search, as well as one study that was unpublished at the time of the guideline development and was identified through consultation with the GDG, met fully or partially the applicability and quality criteria for economic studies, and were thus considered at formulation of the guideline recommendations.

3.7 FROM EVIDENCE TO RECOMMENDATIONS

Once the clinical and health economic evidence was summarised, the GDG drafted the recommendations. In making recommendations, the GDG took into account the trade-off between the benefits and harms of the intervention or instrument, as well as other important factors, such as economic considerations, values of the development group and society, the requirements to prevent discrimination and to promote equality[11], and the GDG's awareness of practical issues (Eccles et al., 1998; NICE, 2009).

The GDG agreed a set of criteria between themselves for interpreting the clinical evidence and deciding on recommendations for interventions. The criteria for positive recommendations that the GDG considered appropriate were that there was data from more than one study (meta-analysis was possible), outcome assessment was blinded and the outcome was a direct outcome (target) of the intervention. For negative treatment recommendations the criteria threshold was lower as is appropriate for the clinical priority to first do no harm. 'Do not do' recommendations were based on evidence of significant adverse events and/or evidence of significant negative/placebo treatment effects.

Finally, to show clearly how the GDG moved from the evidence to the recommendations, each chapter has a section called 'from evidence to recommendations'. Underpinning this section is the concept of the 'strength' of a recommendation (Schunemann et al., 2003). This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare professionals and service users would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some service users

[11]See NICE's equality scheme: www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp

would not choose an intervention whereas others would. This may happen, for example, if some service users are particularly averse to some side effects and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of service users. The strength of each recommendation is reflected in the wording of the recommendation, rather than by using ratings, labels or symbols.

Where the GDG identified areas in which there are uncertainties or where robust evidence was lacking, they developed research recommendations. Those that were identified as 'high priority' were developed further in the NICE version of the guideline, and presented in Appendix 11.

3.8 STAKEHOLDER CONTRIBUTIONS

Professionals, service users, and companies have contributed to and commented on the guideline at key stages in its development. Stakeholders for this guideline include:

- service user and carer stakeholders (national service user and carer organisations that represent the interests of people whose care will be covered by the guideline)
- local service user and carer organisations (but only if there is no relevant national organisation)
- professional stakeholders' national organisations that represent the healthcare professionals who provide the services described in the guideline
- commercial stakeholders (companies that manufacture drugs or devices used in treatment of the condition covered by the guideline and whose interests may be significantly affected by the guideline)
- providers and commissioners of health services in England and Wales
- statutory organisations (including the Department of Health, the Welsh Assembly Government, NHS Quality Improvement Scotland, the Care Quality Commission and the National Patient Safety Agency)
- research organisations that have carried out nationally recognised research in the area.

NICE clinical guidelines are produced for the NHS in England and Wales, so a 'national' organisation is defined as one that represents England and/or Wales, or has a commercial interest in England and/or Wales.

Stakeholders have been involved in the guideline's development at the following points:

- commenting on the initial scope of the guideline and attending a scoping workshop held by NICE
- contributing possible review questions and lists of evidence to the GDG
- commenting on the draft of the guideline.

3.9 VALIDATION OF THE GUIDELINE

Registered stakeholders had an opportunity to comment on the draft guideline, which was posted on the NICE website during the consultation period. Following the consultation, all comments from stakeholders and experts (see Appendix 3) were responded to, and the guideline revised as appropriate. NICE also reviewed the guideline and checked that stakeholders' comments had been addressed.

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE for a quality assurance check. Any errors were corrected by the NCCMH, then the guideline was formally approved by NICE and issued as guidance to the NHS in England and Wales.

4 EXPERIENCE OF CARE AND THE ORGANISATION AND DELIVERY OF CARE

4.1 INTRODUCTION

The experience of care of children and young people with autism and their families and carers is integral to the guideline, for both directly and indirectly informing recommendations. While there is no doubt that guidance on improving service user and carer experience and the development and organisation of care for children and young people with autism is needed, it is nonetheless challenging to develop. In significant part this relates to the very limited evidence base on the organisation and delivery of healthcare. The wide range of problems in children and young people with autism, the different nature of the presentation of these problems and the needs for care that arise from them, add considerably to the challenge. Guidance on improving service user and carer experience and the organisation and delivery of care has to encompass the needs of children and young people with autism with a moderate or severe learning disability (cared for mainly in learning disability services), those with a milder learning disability (IQ ranging from 50 to 69) and those with intellectual ability in the normal range (IQ of 70 and above). These latter two groups may not have their problems recognised, and even if they are they may find it difficult to access services because no specialist diagnostic or treatment service is available, or because staff in existing mental health and related services have limited knowledge of, and expertise in, autism. In addition, there are different conceptual frameworks about what constitutes impairment in autism and what should be 'treated' (see Chapter 2). Transition to adult care is a particularly challenging time for young people and families.

This chapter centres on a thematic analysis of the qualitative literature, which was undertaken in order to identify themes relevant to the experience of care for children and young people with autism and their families and carers. This analysis will directly inform the development of recommendations aimed to improve the experience of care for children and young people with autism and their families and carers.

It was not possible to have a child or young person service user as a regular GDG member; the results of the qualitative analysis were instead presented by the NAS to an expert advisory group of children and young people with autism recruited from a number of different settings to validate the conclusions of the analysis.

The analysis of the experience of care will also be used to help provide a framework to inform the organisation and delivery of services so as to maximise the impact of all the recommendations in this guideline. To do this, the GDG have also used the current policy context, including the legal framework provided by the Autism Act

2009 (HMSO, 2009), the service structures set out in *Autism Diagnosis in Children and Young People* guideline (NICE, 2011a) and *Autism: Recognition, Referral, Diagnosis and Management of Adults on the Autism Spectrum* (NICE, 2012a), and the GDG's opinion and experience of services and their current limitations. However, at the heart of this chapter remains the experience of care of children and young people with autism and the GDG's attempts to improve that experience.

4.2 REVIEW OF THE PRIMARY EVIDENCE

4.2.1 Review protocol – experience of care and organisation and delivery of care

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 7 (further information about the search strategy can be found in Appendix 7). A systematic search for published reviews of relevant qualitative studies of children and young people with autism and their families and carers was undertaken using standard NCCMH procedures as described in Chapter 3. Reviews were sought of qualitative studies that used relevant first-hand experiences of children and young people with autism and their families and carers. The GDG did not specify a particular outcome. Instead the review was concerned with any narrative data that highlighted the experience of care. Where a significant body of systematic reviews was not identified, the GDG looked for primary studies of experiences of children and young people with autism and their families and carers and adopted the method described in Chapter 3, Section 3.5.2, for the analysis of the studies.

Table 7: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s) (RQs)	**RQ 1.1:** What services and treatments are effective in providing a positive experience of care for children and young people with autism and their families and carers? **RQ 1.2**: What are the key problems associated with the experience of care for children and young people with autism and their families and carers? **RQ 1.3**: For children and young people with autism, and their families and carers, what would help improve the experience of care? **RQ 2.1**: What information and day-to-day support is effective in supporting children and young people with autism and their families and carers: • in the post-diagnosis period (including genetic advice and advice about investigation for possible causes of autism including regression) • when treatment and care is provided (including case coordination or case management) • at intervention/management plan reviews • during periods of crisis • at key transitions (for example, school transitions and transition to

	adult services)? **RQ 2.2:** What information and day-to-day support do children and young people with autism and their families and carers want: • in the post-diagnosis period • when treatment and care is provided • at intervention/management plan reviews • during periods of crisis • at key transitions (for example, school transitions and transition to adult services)? **RQ 3.1:** What are the essential elements that allow integration across services/ agencies for the optimal organisation and delivery of care to children and young people with autism and their families and carers? **RQ 3.2**: What are the essential elements that assist in the transition into adulthood services for young people with autism? **RQ 3.3:** What are the effective ways of monitoring progress in children and young people with autism? **RQ 3.4:** What alterations need to be made to routine and acute healthcare for children and young people with autism to ensure access for those with autism?
Sub-question(s)	For children and young people with autism, and their families and carers, is the experience of care and the organisation and delivery of care different for: • looked-after children • immigrant groups • children with regression in skills?
Objectives	To evaluate the experience of care, and the organisation and delivery of care for children and young people with autism and their families and carers.
Criteria for considering studies for the review	
Population	Children and young people (from birth until their 19th birthday) with autism, (across the full range of intellectual ability) and their families and carers. If some, but not all, of a study's participants are eligible for our review, we will ask the study authors for disaggregated data. If we are unable to obtain the appropriate disaggregated data, then we will include a study if the majority (at least 51%) of its participants are eligible for our review. If we are unable to determine the exact proportion of a study's participants who are eligible, then we will include the study if its participants are eligible on average (for example, the mean participant age is less than 19 years). Adults giving retrospective reports will also be included but results will be analysed separately. Consideration will be given to the particular management and support needs of: • looked-after children • immigrant groups • children with regression in skills. Excluded groups include: • adults (19 years and older).
Intervention	The review will include: experience of care received by service users and

	carers; experience of access to care; experience of and/or views on care planning, delivery and/or management; service user experience reported indirectly (for example, where the service user has been facilitated/supported to provide feedback)*; experience of health, housing, education and social care services; experiences of living with autism where there are explicit implications for management, planning and/or delivery of care; experience of diagnosis; and qualitative reports of perceived intervention effectiveness where a qualitative approach is the most appropriate methodology. This review will exclude: experiences of autism with no explicit implications for management, planning and/or delivery of care; case studies; autobiographical accounts; and qualitative measures of perceived intervention effectiveness where a quantitative approach would have been more appropriate.
Comparison	None.
Critical outcomes	Service user and carer experience – emerging themes.
Time points	Not applicable.
Study design	Systematic reviews of qualitative studies, primary qualitative studies, surveys. Books, dissertation abstracts, trade magazines, policy and guidance, non-English language papers, and non-empirical research will be excluded.
Include unpublished data?	Yes, but only where: • the evidence was accompanied by a report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	Date of publication post-1992.
Minimum sample size	No minimum sample size.
Study setting	• Setting is in a country operating a developed service infrastructure. • Primary, secondary and tertiary health and social care. This guideline will also be relevant to other health and social care settings (including forensic services and youth justice settings) although they are not explicitly covered. • The guideline will also address interventions relevant to early years services and educational settings.
Electronic databases	AEI, ASSIA, BEI, CINAHL, Embase, ERIC, IBSS, MEDLINE, PreMEDLINE, PsycINFO, Sociological Abstracts, SSA, SSCI.
Date searched	1995 up to January 2013.
Searching other resources	Hand-reference searching and citation searches of included studies, hand-searching of the 'Research Autism' website, and searching the ISRCTN and ClinicalTrials.gov website using the term 'autism'.
The review strategy	The review strategy will be a thematic analysis of primary qualitative studies, the results of which will be validated through the expert advisory group of service users
Note. *This will be highlighted in analysis/reporting.	

4.2.2 Introduction

In line with the method normally adopted for this type of review a search for systematic reviews of the experience of care for children and young people with autism and their families and carers was conducted. However, no relevant systematic reviews could be included. Consequently, a second search was conducted to identify relevant primary qualitative studies and survey data for children and young people with autism and their families and carers. The literature review supported a thematic analysis of the qualitative and quantitative data reported in the primary studies and identified emergent themes relevant to the experience of care.

4.2.3 Method

The method used in this section is set out in Chapter 3. In summary, the included primary qualitative studies and survey data (see Table 7 for details of inclusion criteria) were reviewed using data extraction techniques consistent with the methodology used in the *Service User Experience in Adult Mental Health* guidance (NICE, 2011b; NCCMH, 2012b). Each included study was reviewed by members of the review team and broad themes were identified and coded using the matrix detailed in *Service User Experience in Adult Mental Health*. This matrix was formed by creating a table with the eight dimensions of person-centred care developed by the Picker Institute Europe[12], down the vertical axis, and the key points on a pathway of care (as specified by the GDG) across the horizontal axis (see Table 9). The Picker Institute's dimensions of patient-centred care were chosen because they are well established, comprehensive, and based on research. In addition, a variation of these dimensions has been adopted by the US Institute of Medicine (Institute of Medicine, 2001).

Consultation with another reviewer or members of the GDG was used to overcome difficulties with coding. Data from studies was extracted independently by two reviewers. Disagreements were resolved through discussion. Where consensus could not be reached, a third reviewer or GDG member resolved the disagreement. Masked assessment (that is, blind to the journal from which the article comes, the authors, the institution and the magnitude of the effect) was not used since it is unclear that doing so reduces bias (Jadad et al., 1996; Berlin, 2001).

4.2.4 Qualitative studies considered for service user experience

Eighty-seven studies from the search met the eligibility criteria for full-text retrieval. Of these, 24 provided relevant clinical evidence and were included in the review. Seven studies examined service user experience only (BERESFORD2007 [Beresford et al., 2007], BREWSTER2010 [Brewster & Coleyshaw, 2010], CARRINGTON2003 [Carrington et al., 2003], CONNOR2000 [Connor, 2000], ECOTEC2010 [ECOTEC, 2010], PREECE2009 [Preece & Jordan, 2009], WELSHASSEMBLY2006 [Welsh Assembly Government New Ideas Research Fund, 2006]), 16 examined service user and carer experience (ALLARD2009 [Allard, 2009], BERESFORD2013 [Beresford et

[12]http://www.pickereurope.org/patientcentred

al., 2013], CAMARENA2009 [Camarena & Sarigiani, 2009], CARTER2004 [Carter et al., 2004], DANN2011 [Dann, 2011], HAY2005 [Hay & Winn, 2005], HUMPHREY2008A [one study reported across two papers: Humphrey & Lewis, 2008a, 2008b], JINDALSNAPE2005 [one study reported across two papers: Jindal-Snape et al., 2005, 2006], NASUNPUBLISHED (NAS, unpublished), PRUNTY2011 [Prunty, 2011], REID2011 [Reid, 2011], ROSE2009 [Rose & Anketell, 2009], TIPPETT2004 [Tippett, 2004], TOBIAS2009 [Tobias, 2009], WEIDLE2006 [Weidle et al., 2006], WITTEMEYER2011 [Wittemeyer et al., 2011]), and one study examined service user, carer and sibling experience of care (DITTRICH2011 [Dittrich et al., 2011]. All studies were published in peer-reviewed journals or online between 2003 and 2013 except one study provided by NAS, which was unpublished. Sixty-three studies were excluded from the analysis. The most common reasons for exclusion were age of the participants (participants were over 19 years old and the paper was not concerned with recollections of childhood experience), quantitative case study methodology, the paper was concerned with the experience of autism with no explicit implications for management, planning and/or delivery of care, mixed autism and developmental disabilities population and not possible to extract disaggregated autism data, or the paper was a non-systematic review. Further information about both included and excluded studies can be found in Appendix 12a.

The characteristics of the included primary qualitative studies for service user experience of care have been summarised in Table 8 and the studies from which data was extracted categorised according to the key themes are summarised in the experience of care matrix in Table 9 and Table 10.

Table 8: Study information table for included primary qualitative studies of the experience of care of children and young people with autism

	Primary qualitative studies of the experience of care of children and young people with autism
Included studies	K = 24
Sample size	3-43 (mean: 15)
Autism population (Axis I/II disorders)	100% autism spectrum disorder (K = 10) Autism spectrum disorder with coexisting mental health disorder (K = 1) Autism spectrum disorder or ADHD (K = 1) 60% autism and 40% Asperger's syndrome (K = 1) 33% autism and 67% Asperger's syndrome (K = 1) 30% autism, 44% Asperger's syndrome and 7% high-functioning autism (4% waiting for diagnosis and 15% other) (K = 1) 20% autism and 80% Asperger's syndrome (K = 2) 91% Asperger's syndrome (K = 1) 100% Asperger's syndrome (K = 5) Not reported (K = 1)
Mean age (years)	5-25 (mean: 12.7)
Sex (percent female)	0-33 (mean: 15)
Focus of study	46% experience of education/school 12.5% experience of information/support 12.5% experience of specific intervention (social skills group/friendship club/support group) 4% experience of CAMHS 4% experience of residential care (short breaks) 8% unmet needs (social skills/criminal justice system) 8% barriers to access (services/leisure activities) 4% experience of transition
Data collection method	50% face-to-face interview 12.5% focus group 8% face-to-face interview and/or focus group 12.5% focus group and survey (open-ended) 8% survey (open-ended) 4% oral and written evidence submitted to a parliamentary inquiry 4% interview (format not reported) and student diaries
Setting	67% not reported 21% school 12.5% home
Country	71% UK 8% US 8% Australia 4% New Zealand 4% Ireland 4% Norway

Table 9: Matrix of qualitative evidence for service user experience (part 1)

Dimensions of person-centred care	Key points on a pathway of care							
	Access	**Information and support**	**Assessment and referral in crisis**	**CAMHS**	**Transition (CAMHS to AMHS)**	**Community services (for example, leisure programmes)**	**Therapeutic intervention**	**Primary care**
Involvement in decisions and respect for preferences	-	-	-	-	-	-	-	-
Clear, comprehensible information and support for self-care	-	DITTRICH2011 WELSHASSEMBLY2006	-	-	-	-	-	-
Emotional support, empathy and respect	-	-	-	-	-	-	-	-
Fast access to reliable health advice	-	-	-	-	-	-	-	-
Effective treatment delivered by trusted professionals	ECOTEC2010	-	-	DITTRICH2011 NASUNPUBLISHED	-	BERESFORD2007 BERESFORD2013 BREWSTER2010 DITTRICH2011	ALLARD2009 BERESFORD2007 BERESFORD2013 CARTER2004 DITTRICH2011 ECOTEC2010 ROSE2009 WEIDLE2006	-
Attention to physical and environmental needs	-	-	-	NASUNPUBLISHED	-	-	CARTER2004	-

Involvement of, and support for, family and carers	-	-	-	-	-	-	-	-
Continuity of care and smooth transitions	ALLARD2009 ECOTEC2010	-	-	-	BERESFORD2013 NASUNPUBLISHED	-	-	-

Table 10: Matrix of qualitative evidence for service user experience (part 2)

Dimensions of person-centred care	**Key points on a pathway of care**							
	Secondary care	**Social care**	**Residential care: short breaks**	**Residential care: long term**	**Educational setting: mainstream**	**Educational setting: specialist**	**Educational setting: home education**	**Themes that apply to all points on the pathway**
Involvement in decisions and respect for preferences	-	-	-	-	CARRINGTON2003 DANN2011 HUMPHREY2008A REID2011 TIPPETT2004 WITTEMEYER2011	-	-	-
Clear, comprehensible information and support for self-care	-	DITTRICH2011	-	-	DITTRICH2011 TOBIAS2009 WITTEMEYER2011	-	-	-
Emotional support, empathy and respect	-	-	-	-	DITTRICH2011 PREECE2009 REID2011 TIPPETT2004 WITTEMEYER2011	-	-	-
Fast access to reliable health	-	-	-	-		-	-	-

advice								
Effective treatment delivered by trusted professionals	-	DITTRICH2011 PREECE2009	PREECE2009	-	CARRINGTON2003 DITTRICH2011 ECOTEC2010 TOBIAS2009 WITTEMEYER2011	-	-	-
Attention to physical and environmental needs	-	-	PREECE2009	-	CONNOR2000 DITTRICH2011 HAY2005 HUMPHREY2008A REID2011 TIPPETT2004 WITTEMEYER2011	-	-	
Involvement of, and support for, family and carers	-	-	-	-	PRUNTY2011 REID2011	-	-	-
Continuity of care and smooth transitions	-	ECOTEC2010	-	-	BERESFORD2013 CAMARENA2009 DANN2011 DITTRICH2011 ECOTEC2010 HAY2005 JINDALSNAPE2005	BERESFORD2013	-	-

4.2.5 Summary of themes from the qualitative analysis of service user experience

Access

Effective treatment delivered by trusted professionals

Service users discussed how the names of services can impact on access (ECOTEC2010), for instance, young people may be put off accessing services that are labelled as 'autism services'. It was suggested that services might be more appropriately labelled based on the targeted behaviour, such as 'people needing help with communication' or 'people who find communication difficult':

> *The over-association with Aspergers and other disorders can be useful in some respects, but also counter-productive in others, so it would be more useful to have groups focused towards the activity than having a label applied, in respect to getting more people interested and not drawing up boundaries between groups of people.* (ECOTEC2010, p. 35)

Continuity of care and smooth transitions

Service users discussed problems with accessing help and support for individuals with autism who do not have a coexisting learning disability (IQ higher than 70). This was highlighted as a particular problem during and after transition:

> *Not having a statement means that young people will struggle more in adulthood because they did not get adequate support early on.* (ALLARD2009, p. 13)

Service users expressed a desire for one point of contact during transition, even if support was only needed at a low level or as a preventative measure (ECOTEC2010).

Information and support

Clear, comprehensible information and support for self-care

A number of service users expressed negative experiences when coming into contact with the police and criminal justice system or expressed a need for autism-specific support when dealing with the criminal justice system (DITTRICH2011, WELSHASSEMBLY2006). For instance, in response to questions about interactions with the police and opinions about carrying an 'attention card' (which alerts people working within the criminal justice system that the person has autism), children and young people with autism perceived a number of potential benefits including:

> *Could use it if you got lost.*
>
> *In case police start asking me questions. I have been in trouble. They thought I was being cheeky but I was just being honest.*

I'd use the card in tricky situations or when I am too traumatised to speak.

In case I get apprehended wrongly and get stressed. (WELSHASSEMBLY2006, p. 15-16)

Service users also expressed a desire for autism-specific information about available services (for instance, employment, benefits, education, housing, support services, therapeutic interventions and activities for people with autism) and a named contact person (DITTRICH2011).

CAMHS

Effective treatment delivered by trusted professionals

Service users emphasised the importance of professional understanding of autism in terms of modifications that professionals may need to make to their communication:

> *Well I go to two, one of them I like, but there's one I really don't like. The one I like [the occupational therapist] plays games with me, and ask me questions, but not many of them. The type of questions that I will answer… the other one I don't like because it's not very interesting. It's just that, well that's the thing, I don't know how to explain problems… I never like to go, it's terrible. (8-year-old child)* (NASUNPUBLISHED, p. 41)

Individuals with autism also spoke about experiences where inadequate professional understanding had led to inappropriate treatment and very negative experiences of CAMHS:

> *It was all about letting Mum and Dad get to sleep and not about making me feel better. There was never any talk of, 'Let's find out why K is so miserable. Let's find out why she doesn't want to go to bed. Then we can make it better, then it will be better for everyone.' It was just, 'She's a badly behaved child, let's lock her in her room and make things easier for the parents.' Of course, it didn't make things easier for them, because they had to listen to me screaming and screaming and screaming. I was terrified of nightmares. I was hallucinating. I was seeing demons coming out of my walls and everything. He was saying, 'Oh no, never mind about that. Just turn the light off and lock her in there.' Mum and Dad weren't allowed to let me out no matter how much I screamed and screamed and cried and begged them. I never really even talked to the psychologist myself. Like I say, he introduced himself, said something about my cold hands, but he didn't try to get to know me or find out anything. There was never any mention of autism or anything else. It was just, 'She's misbehaving.'… It had just traumatised me so much and made things worse. I mean, when I went in to the meeting I was miserable and depressed. When I came out I was suicidal. I was trying to throw myself out of my windows and hang myself. You know, I was nine years' old. It was that bad. It took me several years to recover and I didn't ever want anything to do with them. (18-year-old young woman talking of her experiences as a 9-year-old)* (NASUNPUBLISHED, p. 45)

A lack of professional understanding of autism also impacted upon access to services with the individual not being considered eligible (DITTRICH2011).

The complex three-way relationship between service user, professional and carer, particularly for young people approaching transition, was also highlighted by 16 to 18 year olds in the NASUNPUBLISHED study where the need for greater autonomy was discussed:

> *I prefer somebody who tries to get to know me, so that they know how to help me in the best way they possibly can. My Mum thinks CAMHS are crap. They always just seem to talk more to my mum. They always seem to go for the adult, they don't really seem to ever trust a child, 'Oh it's a child, they don't know what they're talking about.' They need to listen to me and what I'm telling them. If I need help with something, they should help me with it, and not just give me medication. They should like give me strategies to help it, or something like that. She never comes to meetings either. We're always asking her to come to meetings about school, and she never turns up. (16-year-old young woman)* (NASUNPUBLISHED, p. 44)

Children and young people with autism wanted to be listened to and actively involved in treatment decisions and were sometimes frustrated at the feeling that routine appointments were concerned only with discussing medication rather than other therapeutic interventions that might be helpful:

> *She's friendly but doesn't really try and find out much how I've been. Then when I try and explain things to her, she'll try and guess what it's like. She'll be like, 'Oh, so did this happen or did that happen, or did this happen?' I'll ask her if she can help, and she'll just go, 'Well you're on medication and I can't change it,' but she doesn't offer me any like different solutions other than just medication. Now they've got to take me off it because it's ruining my internal organs. (16-year-old young woman)* (NASUNPUBLISHED, p. 44)

Attention to physical and environmental needs

Children and young people with autism discussed how environmental considerations are important, particularly for waiting areas, and the impact the environment may have on calming any nerves:

> *I like to make sure the room smells alright. Just fresh air and a clean smell. That the walls are not too bare and what's within the place. Just a bit of space. (15-year-old girl)* (NASUNPUBLISHED, p. 43)

Transition (CAMHS to AMHS)

Continuity of care and smooth transitions

Service users highlighted a lack of inter-agency transition planning (BERESFORD2013, NASUNPUBLISHED) and described how this lack of planning often meant that there was a delayed transfer to AMHS:

> *I was supposed to have been passed, been passed over to adult services.... so like adult mental health. Dr Jones [child psychologist] was supposed to have done it. He said, he promised me that before I turned 18 I'd be able to go, go back to him and he'd get an adult psychologist with him and therefore, I'd be able to meet the adult psychologist and all that sort of stuff… it didn't happen and I seem to have fallen through the net a bit. …He's [Dr Jones], he's left it to my GP to sort out and my GP, my GP's been brilliant. He's managed to get me the social worker. …So I'm being passed from pillar to post basically.* (BERESFORD2013, p. 119-120)

Young people with autism described how this uncertainty surrounding transition created anxiety and worry, particularly given difficulties with opening up to new people (BERESFORD2013). Many service users also acknowledged that a lack of adequate transition planning placed strain on their carers (BERESFORD2013). Service users attributed some of problems with transition to lack of professional communication across services:

> *There needs to be a better transition period. They don't really provide any links between. Apparently the two services don't even communicate with each other or anything. They have a completely different way of doing things. They don't really know how the other one works at all. (18-year-old young woman)*
> (NASUNPUBLISHED, p. 64)

Children and young people with autism also expressed an unmet need for psychological support during the transition period and for professionals to allow carer involvement where appropriate:

> *It's all very strange. For a long time, I was treated as a child. You know, they give you these questionnaires and you have to circle how true this statement is about you. They say things, like, to do with school and sharing toys with other kids. I'm like, 'I'm seventeen,' you know. 'I haven't been to school in years.' Just completely inappropriate. Then I moved up to adult services and suddenly I was supposed to be an adult. I don't feel like that either. I feel like I'm, kind of, stuck because I'm expected to go in without my mum and talk all myself. At the moment, I just can't. Some days I can't talk. Some days, especially because I'm so scared of those sorts of places, I find it incredibly difficult. When I get there, I close up. So I go in and, you know, the last time I went I was having real difficulties speaking. I looked at mum and said, 'Can't find words.' Mum started to try and help me and the doctor goes, 'Oh no, no no. Mum's not allowed to say anything. I want to hear it from you.' Don't you understand that I'm autistic? (18-year-old young woman)* (NASUNPUBLISHED, p. 64)

One service user discussed a positive experience of transition as a result of her carer suggesting that the child psychiatrist attended the first meeting with adult services:

> *Then when I went up to adult services, the first meeting I went to, she (psychiatrist) actually came with us to help the changeover. That was not something they suggested. Mum actually asked if they could do that sort of thing. They said 'No one's ever*

suggested that before!' So we had this great big discussion about how we could make it easier for me moving up, because obviously all this history with people, it's just terrifying for me to meet another doctor. We wanted to make it simple, it was helpful, I think. (18-year-old young woman) (NASUNPUBLISHED, p. 64)

Community services

Effective treatment delivered by trusted professionals

A number of children and young people with autism discussed the desire to take part in leisure activities and for extra groups to be available such as a computer group for children (DITTRICH2011). However, barriers to accessing leisure activities were also discussed, such as the need for predictability and routine among individuals with autism and the generally less structured nature of leisure activities. Thus, planning was highlighted as an important component for facilitating access to leisure activities:

> *Yeh – plenty of information on whatever I'm thinking of doing. I like to gather information before I do anything… I never make a move with anything without gaining as much information about it first, so I can make the best choice possible… you don't always know what's round the corner.* (BREWSTER2010, p. 289)

Those service users who had taken part in planned leisure activities described positive experiences:

> *Art group, cooking group and cinema have all been positive.* (DITTRICH2011, p. 49)

Some service users expressed a preference for specialist leisure activity programmes designed for individuals with autism with perceived benefits including improved understanding of autism among staff and a greater scope to form supportive relationships with peers:

> *I now go to a youth group called 'Getting on'… it's mostly people with, I've recently discovered that it's mostly people with ASD, or with some form of it, so it makes us feel normal if you like.* (BERESFORD2013, p. 143)

Therapeutic intervention

Effective treatment delivered by trusted professionals

Unmet needs in terms of interventions aimed at social skills

A number of service users expressed the desire to make new friends but felt unable to do so and wanted to learn how to do this (BERESFORD2007, BREWSTER2010). Times of transition were specifically highlighted as periods where help with social skills was an unmet need, for instance, participants in BERESFORD2007 wanted to feel able to cope with new social situations such as starting a new school and in

ECOTEC2010 concerns were raised about social isolation post-16 years of age as service users left the structured social environment of school:

> *Socially it was hard for me at university. It was hard to make friends; I have acquaintances but not friends. Finding a girlfriend is a real challenge. I find it hard to meet girls. I was lonely. I had no-one to give me moral support.* (ECOTEC2010, p. 21)

Interestingly, participants who expressed an unmet need for help with social skills and making friends often suggested a more informal setting including group activities and opportunities to meet other children and young people with autism, rather than formal social skills groups with an emphasis on didactic instruction:

> *My suggestion on money to be spent would be on socialising. As some ASD people struggle with socialising who want to socialise, if the money is there to help, it would be good getting them involved in a group and making friends.* (ECOTEC2010, p. 31)

> *I think it is nice to touch base with people who are similar to you, it would be great if this included social events too, like a BBQ.* (DITTRICH2011, p. 49)

Other children and young people with autism suggested that a mentoring system might be useful in order to facilitate access to social groups:

> *I find groups difficult as I don't always understand the rules and I don't like big groups of people or noisy places, it would be good to have someone to go to the group with me to help me understand what is going on.* (DITTRICH2011, p. 50)

> *A buddy system where I could go out socially with support to gain more social skills.* (DITTRICH2011, p. 50)

Younger participants (aged 6 to 15 years) who had attended a social skills group (ROSE2009) or friendship club (CARTER2004) generally reported positive experiences, including providing more socialisation opportunities for service users, the content of the intervention (such as enjoying learning about strategies for social interaction and communication), and discussing things with each other (CARTER2004, ROSE2009). Negative aspects of a social skills group were varied and may highlight the importance of interventions being individualised to participants because service users expressed frustration at learning about things that they already knew or about the format of the intervention (ROSE2009). The need to consider the physical and social environment was also emphasised, with some participants disliking the mess, noise or lack of direction associated with a friendship club (CARTER2004).

Unmet needs in terms of interventions aimed at daily living skills

A number of service users expressed problems they experienced with daily living skills, such as cooking and using public transport (ECOTEC2010). Barriers to

accessing public transport, including problems with the noise, smells, proximity of other people and unreliability, contributed to feelings of social isolation, and children and young people with autism expressed a need for coping strategies:

> *…don't know how to ask for a ticket on a bus, obviously I can use a train, but I don't know how to get a ticket on a bus.* (ECOTEC2010, p. 27)

Those who had experienced an intervention to help them to access public transport were positive about the experience:

> *I use trains the most out of public transport and after help from child and adolescent mental health services (CAMHS) I feel I can handle it and manage to go almost everywhere. Changing trains worries me but if I plan it well it is okay.* (ECOTEC2010, p. 27)

A few service users who had accessed a money management course were also very positive about the training and, in particular, appreciated that the intervention was individualised, appropriately paced and delivered by professionals who had an understanding of autism (BERESFORD2013).

Unmet needs in terms of interventions aimed at vocational skills

Many young people with autism, particularly those without a learning disability, want to work and want support in order to find and maintain employment:

> *If you are not in work, being in work will make the biggest difference to [our] lives, to help people with autism help themselves.* (ECOTEC2010, p. 16)

Service users specifically mentioned vocational skills such as preparing CVs and attending job interviews as areas where they would like help, and where this help had been received perceptions were positive (BERESFORD2013). However, this support was predominantly not available and one young person in ECOTEC2010 described how they had spent a large proportion of their working life in temporary or agency work in order to avoid having to participate in a formal interview. In addition to support finding a job, the need for ongoing support in order to maintain the job was also emphasised by service users:

> *As much as I have developed my skills, I will always need support from other people.* (ALLARD2009, p. 7)

The need for employers to understand what autism is and about strategies to be used in managing young people with autism was also highlighted as necessary support for finding and maintaining employment:

> *I resigned from 2 posts because my employers did not understand me and made no attempt to understand me.* (DITTRICH2011, p. 45)

Service users described frustrations at what they felt was generic and inappropriate support for finding a job that they had been able to access through the job centre (BERESFORD2013). Conversely, participants who had accessed Prospects, an employment and training service delivered by NAS, were very positive about it but barriers to access included non-nationwide service and long waiting lists (ECOTEC2010).

Unmet needs for therapeutic interventions in general

Service users expressed the concern that children and young people with autism who have intellectual ability within the normal range often fall through the gaps in terms of accessing therapeutic interventions (ECOTEC2010). The need for individualised treatment was also emphasised with a request to move away from a 'one size fits all' approach and towards person-centred intervention:

> *Some people seem to think there is one answer to deal with these problems and that it is a formula. Different people need different strategies.* (ECOTEC2010, p. 34)

Social care

Clear, comprehensible information and support for self-care

Service users described a lack of support from social services:

> *[Social Services (Children and SEN), health visitors and information services] Moved and had no support or understanding of the situation, passed from one department to another, gave up and Mum went on Prozac.* (DITTRICH2011, p. 54)

Specifically, a need and desire were expressed for housing support, including information and advice about entitlements, help with neighbours and organising their living space, support so they were not as reliant on their parents and assisted living help (DITTRICH2011).

Effective treatment delivered by trusted professionals

Some service users expressed a lack of understanding about the role of the social worker in their lives (PREECE2009). Problems with a lack of professional understanding of autism were also highlighted as resulting in inadequate support being offered:

> *Care managers not understanding autism and being 'assessed' wrongly as a lazy person…. Resulted in my withdrawal from life as I could not cope alone.* (DITTRICH2011, p. 54)

Continuity of care and smooth transitions

Children and young people with autism talked about unmet needs in relation to making the transition from living in the family home to independent living. Many service users expressed a desire to live independently in the future but were unaware how they would achieve this or worried that this might never be possible:

> *I am worried about never being able to move out from home and survive. I don't understand all about house payments, mortgages and insurance for houses.* (ECOTEC2010, p. 25)

Residential care: short breaks

Effective treatment delivered by trusted professionals

Children who had accessed short break services had positive experiences. In particular, children spoke about enjoying being taken out:

> *The best thing is that you get… if it's a nice day then you get to go out.* (PREECE2009, p. 15)

Attention to physical and environmental needs

A number of modifications to short-term residential care environments were identified by service users as being positive, including sensory rooms and visual schedules:

> *[The sensory room is] very relaxing and pretty, 'cos it's got all sorts of pretty lights.* (PREECE2009, p. 15)

> *[talking about visual schedules] Yeah, yeah… 'cos then I don't forget what I'm supposed to do.* (PREECE2009, p. 15)

However, experiences of the environment for short breaks were not universally positive, for instance, one service user discussed problems with noise:

> *Sometimes the radiators are a bit noisy. You know, how they make a noise sometimes...Bang bang bang!* (PREECE2009, p. 15)

Educational setting: mainstream

Involvement in decisions and respect for preferences

Children and young people described exclusion from educational planning and wanted teachers to listen to them, and to use their knowledge and consult with them in order to inform teaching strategies:

> *I try to tell them but no, they won't listen to me.* (TIPPETT2004, p. 16)

Children and young people with autism also expressed frustrations at being excluded from school activities:

> *I only go to school in the mornings. I need somebody to help me all the time but teachers just ignore me and the other kids pick on me. I don't get enough help and they always ring my mummy and I have to go home. I just want to be like the other kids but they are better than me. I'm not allowed to stay for lunch breaks and if I have*

> *a meltdown I can't go on school trips – but when I panic that I'll miss out I have a meltdown and then I miss out anyway. The teachers don't listen to me, they always blame stuff on me and then I get angry because no-one is listening. I hate school.* (REID2011, p. 9)

Where children and young people were allowed some autonomy in school, for instance, in terms of lunchtime decisions the opportunity to exercise choice was valued:

> *We get more free time and we can buy cookies and drinks and stuff.* (DANN2011, p. 302)

A recurring theme in the service user evidence was a desire for an inclusive focus to interventions delivered in educational settings so that additional support did not exacerbate differences between children and young people with autism and their typically-developing peers:

> *I don't want people to know that I'm special. I just want them to know I'm an ordinary person.* (CARRINGTON2003, p. 19)

> *If they were following me then the other students know that there's something different about me and I don't like it at all.* (HUMPHREY2008A, p. 38)

> *It's annoying – they are constantly asking 'are you doing this?'...It'd be better to just help everybody ... I don't like too much attention on me.* (WITTEMEYER2011, p. 42)

Clear, comprehensible information and support for self-care

Children and young people with autism were positive about their experiences with keyworkers who delivered material at an appropriate pace, helped in understanding the material (particularly metaphorical meanings in subjects like English), and helped with organisation and coping strategies (WITTEMEYER2011). Service users also appreciated academic support which was individualised to specific strengths and weaknesses (TOBIAS2009). Children and young people with autism suggested that more attention from teachers and having a named contact to go to for support would have made things easier in primary and secondary education (DITTRICH2011).

Emotional support, empathy and respect

The importance of having access to professionals who understand autism within a mainstream school environment was emphasised (WITTEMEYER2011) as service users described negative experiences that stemmed from not having access to professionals who understand autism in school:

> *I am leaving my present school as they do not understand autism at all. I get treated pretty much the same as other children although I don't think I act like them. I am different but they don't take much notice of me at my school. My mum has found me a*

> *much better school that has a unit for children with Asperger's. Although I won't be in there, my mum says that the teachers and teaching assistants have more knowledge and a better understanding of my problems. I hope I will finally find a school I am happy in.* (REID2011, p. 18)
>
> *Poor attention, isolation and bluntness was just seen as brash and poor behaviour.* (DITTRICH2011, p. 30)
>
> *People think I use autism as an excuse ... I hate it when people say that. (11-year-old girl)* (WITTEMEYER2011, p. 42)

The need for teachers to make autism-specific modifications to communication was discussed (PREECE2009, WITTEMEYER2011) and emphasised as important because misinterpretations of instructions can cause frustration on both sides and further exacerbate difficulties in the relationship (TIPPETT2004):

> *I don't do the theory in Food tech[nology] anymore as the teacher talks too fast. He likes to get a move on.* (WITTEMEYER2011, p. 41)
>
> *There is a teacher who talks really quickly, and I find it hard to understand… She goes ba-ba-ba-ba-ba-ba-baba-ba-ba, and I don't know what on earth they're talking about.* (PREECE2009, p. 14)

Effective treatment delivered by trusted professionals

Interventions in school: social skills training

A need for help with social skills was identified by a number of children and young people with autism in terms of being able to have conversations with peers and understanding social norms in school:

> *Conversations are difficult because you mightn't know what to say in the conversation with no words in your head or you get stuck in a conversation and you say to yourself: 'Oh! I've got to get out of this one!' or something. And these people might think you're weird, walking away or something. I don't want it to happen but I don't know how to react.* (CARRINGTON2003, p. 18)
>
> *…bullied in my first schools for not understanding social norms.* (WITTEMEYER2011, p. 41)

Service users who had experience of a mentoring system were positive about it (TOBIAS2009).

Academic support and transitions

Service users talked about their unmet need for academic support, particularly during and immediately following the primary to secondary school transition (WITTEMEYER2011). One pupil noted that the worst thing about secondary school was:

> *The assumption that I would have independent study skills.* (WITTEMEYER2011, p. 41)

The need for ongoing support, particularly in the context of helping young people with autism to cope with increasing stressors in further education, was highlighted:

> *I need help with staying in college. Every time there is a problem I seem to press the self-destruct button… I fear one time I will capitulate and have life changing consequences.* (ECOTEC2010, p. 24)

Service users pointed to the lack of autism-specific support as a barrier to accessing support in further education (DITTRICH2011, ECOTEC2010):

> *The college mainly focused on dyslexia and other special needs, so I did not reach out to any support services that the college had.* (DITTRICH2011, p. 34)

Attention to physical and environmental needs

Children and young people with autism raised problems with noisy classroom environments (HAY2005, TIPPETT2004), particularly where lessons were streamed:

> *[Diary of student] Thursday, 22 June 2006: In English [lessons] there was so much noise. I just wanted the class to be quiet and I can get on with my work.* (HUMPHREY2008A, p. 138)

Anxiety about performing in front of other students and a preference for individual work were also discussed:

> *I don't like talking in front of a whole group.* (CONNOR2000, p. 291)

> *I like working on my own in a big class where you can be spaced out.* (CONNOR2000, p. 291)

Children and young people with autism described problems they had experienced in dealing with the crowded school environment:

> *It does bother me because sometimes there can be a lot of pushing and shoving including the corridors because they are small.* (HUMPHREY2008A, p. 137)

Helpful concessions that were mentioned included pre-school activities to reduce the amount of time spent in the playground:

> *Some teachers were understanding and allowed me helpful concessions, for instance I could come straight into the classroom in the morning (with the 'job' of putting out the chairs) instead of waiting and lining up in the playground. This was useful as the*

> *busy, noisy playground full of parents and children was a very anxiety-provoking place for me.* (REID2011, p. 39)

Conversely, lack of lunchtime or break-time activities were discussed as a cause of anxiety for children and young people with autism:

> *I don't really play with anyone or play games or anything: when I'm doing nothing lunchtime seems a long time.* (CONNOR2000, p. 290)

> *It's worse than in class because in class you are busy – I try to stay away from other people.* (CONNOR2000, p. 290)

A quiet space was suggested by children and young people with autism as something that would be very beneficial (DITTRICH2011, REID2011):

> *I think all schools should have a room to go to for quiet time and for kids like me to be able to concentrate away from the noise and clutter and just chill out or work in peace. Sometimes I have panic attacks at school in the cookery room; it's too smelly and there's not enough time to finish the food I'm cooking. My head needs time off from the noise and amount of people. Regular breaks in the day would be good.* (REID2011, p. 38)

Visual schedules that meet the autistic need for predictability in routines were also mentioned by children and young people with autism as an extra source of support for coping with the school environment (DITTRICH2011, TIPPETT2004).

The differences in the school environment between primary and secondary school, and the generally more positive experiences in the former, imply that support for environmental change might be an important aspect of transition planning:

> *[In primary school] I stayed with my class all the time and I was used to it.* (WITTEMEYER2011, p. 41)

Involvement of, and support for, family and carers

Children and young people with autism expressed a desire for their carers to be involved in their education:

> *His Mum and Dad really need to have a say about this Learning Plan. If they don't, they won't know that he's gonna be put into, you know, a different classroom and she might not even see him for a while and she might not even see him come out the door. And he might be learning the wrong things.* (PRUNTY2011, p. 31)

> *Q: What else could make school better?*
> *A: If they believed my parents more... I can't show my true feelings at school, only home, and so they just don't believe I have a problem.* (REID2011, p. 13)

Continuity of care and smooth transitions

Children discussed the more complex social environment in secondary school, and suggested that help with making friends may be an unmet need for the primary to secondary school transition for children with autism (HAY2005, JINDALSNAPE2005):

> *In the primary school I knew what I was doing. In high school it is more confusing. Everything keeps changing and I do not like change. I had more friends in primary school. I would like to have more friends now but I cannot help it if I am unpopular.* (HAY2005, p. 148)

The importance of pre-visits and orientation opportunities were discussed as a crucial element in adjusting to the transition from primary to secondary school:

> *Mrs H, she knows me enough because I went to visit [name of secondary school] ... she's very nice to me, she understands.* (DANN2011, p. 299)

Positive experiences of pre-visits and orientation in aiding the secondary school to further education transition were also discussed by young people with autism (BERESFORD2013, ECOTEC2010):

> *I think the biggest transition for me was from spending three hours out of home, to going to college when I was 17. I think most transitions are made a lot easier by forward planning. For example my transition to university was really smooth because I had [my] student support advisor coming and emailing me, phoning me up and just making sure he knew everything about me.* (ECOTEC2010, p. 23)

Where pre-visits and orientation had not been offered they were identified as a significant unmet need, with suggested improvements to transition planning including pre-meetings with professors, attending practice classes, and career planning (CAMARENA2009).

The need for support in the less structured environment of further education was also highlighted:

> *Self paced structure very difficult to adhere to, lack of support in this area, just left to mill along.* (DITTRICH2011, p. 34)

Young people with autism also stressed the importance of preparing for the social as well as the educational aspects of transition to further education (BERESFORD2013). For instance, some talked about perceived benefits of a mentoring system:

> *Having a mentor would have helped in the Sixth Form and/or the opportunity to have joined a group of similar individuals.* (DITTRICH2011, p. 34)

Service users spoke positively about proactive and early initiated transition planning, and the provision of clear and easy to understand information, in helping to prepare them for the transition from secondary school to further education (BERESFORD2013). Young people also talked about appreciating the help with college applications and interviews that they had received:

> *They [Connexions] helped fill in the college application forms. They helped me with the interview, they just generally helped me.* (BERESFORD2013, p. 77)

However, some service users expressed frustration with being promised transition support that never materialised, and some young people described the formal support they had received as a 'one-off form filling' exercise rather than useful ongoing support and/or guidance (BERESFORD2013). Young people also described how this lack of support placed additional strain on their carers:

> *Int: Who do you think was the most helpful [transferring to college]?*
> *YP: I think it was definitely Mum and Dad. But it must be pretty hard on…, I know how hard it is on my parents to have to keep chasing these people up because of bureaucracy and their stupidity.* (BERESFORD2013, p. 81)

Educational setting: specialist

Continuity of care and smooth transitions

Similarly to experiences of transition between mainstream educational settings, advice on CVs and application forms and the opportunity for pre-visits to further education were also described as beneficial by young people in a specialist educational setting. This was particularly important to one service user when considering a residential college:

> *Int: You had a look for three days, so you stayed down there?*
> *YP: I stayed down there for three days and the first day wasn't great but then I…*
> *Int: Why wasn't it great?*
> *YP: Cos I was homesick and I just didn't like it and then after the two, the other two days I got used, I got used to it, made some friends and wanted to stay there, didn't want to come out.* (BERESFORD2013, p. 75-76)

4.2.6 Qualitative studies considered for family and carer experience

Two hundred and nineteen studies from the search met the eligibility criteria for full-text retrieval. Of these, 120 studies provided relevant clinical evidence and were included in the review. As outlined in Section 4.2.4, 16 of these studies examined service user and carer experience, and one study examined service user, carer and sibling experience of care[13]. One hundred of these studies examined carer experience

[13] ALLARD2009, BENDERIX2007B, BERESFORD2013, CAMARENA2009, CARTER2004, DANN2011, DITTRICH2011, HAY2005, HUMPHREY2008A, JINDALSNAPE2005, NASUNPUBLISHED, PRUNTY2011, REID2011, ROSE2009, TIPPETT2004, TOBIAS2009, WEIDLE2006, WITTEMEYER2011.

only (ALLGOOD2005 [Allgood, 2005], ALTIERE2009 [Altiere & von Kluhe, 2009], AUERT2012 [Auert et al., 2012], BEATSON2002 [Beatson & Prelock, 2002], BENDERIX2007A [Benderix et al., 2007], BERESFORD2012 [Beresford et al., 2012], BEVANBROWN2010 [Bevan-Brown, 2010], BIRKIN2008 [Birkin et al., 2008], BRAIDEN2010 [Braiden et al., 2010], BREWIN2008 [Brewin et al., 2008], BROOKMANFRAZEE2012 [Brookman-Frazee et al., 2012], BROWN2012 [Brown et al., 2012], BUNDY2009 [Bundy & Kunce, 2009], BURROWS2008 [Burrows & Adams, 2008], BURROWS2010 [Burrows, 2010], CARBONE2010 [Carbone et al., 2010], CASSIDY2008 [Cassidy et al., 2008], CHELL2006 [Chell, 2006], CULLEN2002A [one study reported across three papers: Cullen & Barlow, 2002a, 2002b, Cullen et al., 2005], DILLENBURGER2004 [Dillenburger et al., 2004], DILLENBURGER2010 [Dillenburger et al., 2010], DILLENBURGER2012 [Dillenburger et al., 2012], DILLON2012 [Dillon & Underwood, 2012], DONALDSON2011 [Donaldson et al., 2011], DYMOND2007 [Dymond et al., 2007], FISH2006 [Fish, 2006], FLYNN2010 [Flynn et al., 2010], GLAZZARD2012 [Glazzard & Overall, 2012], GRANGER2012 [Granger et al., 2012], GREEN2007 [Green, 2007], GREY2010 [Grey et al., 2010], GRINDLE2009 [Grindle et al., 2009], HACKETT2009 [Hackett et al., 2009], HALL2010 [Hall & Graff, 2010], HARE2004 [Hare et al., 2004], HURLBUTT2011 [Hurlbutt, 2011], HUTTON2005 [Hutton & Caron, 2005], JEGATHEESAN2010 [one study reported across two papers: Jegatheesan et al., 2010; Jegatheesan, 2011], JOHNSON2002 [Johnson & Hastings, 2002], JONES2008A [Jones & Hack, 2008], JONES2008C [Jones et al., 2008], KEANE2012 [Keane et al., 2012], KEENAN2010 [Keenan et al., 2010], KERRELL2001 [Kerrell, 2001], KIDD2010 [Kidd & Kaczmarek, 2010], KIMURA2010 [Kimura et al., 2010], KOYDEMIROZDEN2010 [Koydemir-Özden & Tosun, 2010], KUHANECK2010 [Kuhaneck et al., 2010], LARSON2010 [Larson, 2010], LILLY2004 [Lilly et al., 2004], LILLEY2011 [Lilley, 2011], LIN2008 [Lin et al., 2008], LUONG2009 [Luong et al., 2009], MACKINTOSH2012 [Mackintosh et al., 2012], MANSELL2004 [Mansell & Morris, 2004], MCCABE2008A [McCabe, 2008a], MCCABE2008B [McCabe, 2008b], MCCONKEY2011 [McConkey et al., 2011], MEIRSSCHAUT2010 [Meirsschaut et al., 2010], MIDENCE1999 [Midence & O'Neill, 1999], MINNES2009 [Minnes & Steiner, 2009], MORRISON2009 [Morrison et al., 2009], MULLIGAN2010 [Mulligan et al., 2010], MYERS2009 [Myers et al., 2009], NASUNO2003 [Nasuno et al., 2003], NICHOLS2010 [Nichols & Blakeley-Smith, 2010], NISSENBAUM2002 [Nissenbaum et al., 2002], OLIVIER2009 [Olivier & Hing, 2009], OSBORNE2008 [Osborne & Reed, 2008], PARSONS2009A [Parsons et al., 2009a], PATTERSON2011 [Patterson & Smith, 2011], PHELPS2009 [Phelps et al., 2009], PICKERING2005 [Pickering & Goode, 2005], RENTY2006A [Renty & Roeyers, 2006], RYAN2009 [Ryan & Cole, 2009], SANSOSTI2012 [Sansosti et al., 2012], SELKIRK2009 [Selkirk et al., 2009], SERPENTINE2011 [Serpentine et al., 2011], SHYU2010 [Shyu et al., 2010], SMYTH2010 [Smyth & Slevin, 2010], SPANN2003 [Spann et al., 2003], SPERRY1999 [Sperry et al., 1999], STARR2001 [Starr et al., 2001], STARR2012 [Starr & Foy, 2012], STEIN2012 [Stein et al., 2012], STIRLING1999 [Stirling & Prior, 1999], STONER2005 [one study reported across three papers: Stoner et al., 2005, 2006, 2007], STUART2006 [Stuart et al., 2006], TISSOT2006 [one study reported across two papers: Tissot, 2011; Tissot & Evans, 2006], TRUDGEON2007 [Trudgeon & Carr, 2007], VALENTINE2010 [Valentine, 2010], WADDINGTON2006

[Waddington & Reed, 2006], WEBSTER2003 [one study reported across two papers: Webster et al., 2003, 2004], WHITAKER2002 [Whitaker, 2002], WHITAKER2007 [Whitaker, 2007], WHITTINGHAM2006 [Whittingham et al., 2006], WHITTINGHAM2009 [Whittingham et al., 2009], WILLIAMS2003 [Williams & Wishart, 2003], WOODGATE2008 [Woodgate et al., 2008], WRIGHT2011 [Wright et al., 2011]). Three studies examined sibling experience of care only (BENDERIX2007B [Benderix & Sivberg, 2008], MOYSON2011 [Moyson & Roeyers, 2011], PETALAS2009 [Petalas et al., 2009]). One unpublished study provided by NAS was included in the review. All other studies were published in peer-reviewed journals or online between 1999 and 2012. In addition, 99 studies were excluded from the analysis. The most common reasons for exclusion were: the age of the family's/carer's child with autism (over 19 years old and the paper was not concerned with recollections of childhood experience); case study methodology; the paper was concerned with the experience of autism with no explicit implications for management, planning and/or delivery of care; the focus was on family/carer experience of perceived effectiveness of interventions for child outcomes where an RCT approach would have been more appropriate; the healthcare system was not comparable to the UK; mixed autism and developmental disabilities population and it was not possible to extract disaggregated autism data; or the paper was a non-systematic literature review. Further information about both included and excluded studies can be found in Appendix 12a.

The characteristics of the included primary qualitative studies for family and carer experience of care have been summarised in Table 11 and the studies from which data was extracted categorised according to the key themes are summarised in the experience of care matrix in Table 12 and Table 13.

Table 11: Study information table for included primary qualitative studies of the experience of care for families and carers of children and young people with autism

	Primary qualitative studies of the experience of care for the families and carers of children and young people with autism
Included studies	K = 120
Sample size	2-783 (mean: 57)
Age of children and young people (years)	0-35 (mean: 8.7)
Sex of children and young people (percent female)	0-89 (mean: 15)
Age of family/carer (years)	5-72 (mean: 37)
Sex of family/carer (percent female)	0-100 (mean: 78)
Focus of study	27% experience of education/school 25% experience of information/support 29% experience of specific intervention (music therapy/support group/parent training/speech and language therapy/service dog/social skills group/touch

	therapy/ABA/EIBI) 1% experience of CAMHS 1% experience of community mental health teams (US) 2% experience of residential care (group homes) 2% experience of primary care 2% experience of transition 9% experience of accessing services 3% experience of unmet needs
Data collection method	33% face-to-face interview 5% face-to-face and/or telephone interview 3% telephone interview 4% interview (format not reported) 18% focus group 5% face-to-face interview and/or focus group 3% focus group and survey (open-ended) 23% survey (open-ended) 3% survey and face-to-face interview 1% survey and interview (format not reported) 1% oral and written evidence submitted to a parliamentary inquiry 1% interview (format not reported) and student diaries
Setting	62% not reported 18% home 3% school 2% location familiar to carer 1% hospital 3% university 12% other
Country	37% UK 27.5% US 7% Australia 5% Ireland 7.5% Canada 2.5% New Zealand 2.5% Belgium 2% Sweden 2% Taiwan 2% China 6% other 1% not reported

Table 12: Matrix of qualitative evidence for family and carer experience (part 1)

Dimensions of person-centred care	Key points on a pathway of care							
	Access	**Information and support**	**Assessment and referral in crisis**	**CAMHS**	**Transition (CAMHS to AMHS)**	**Community services (for example, leisure programmes)**	**Therapeutic intervention**	**Primary care**
Involvement in decisions and respect for preferences	-	-	-	-	-	-	-	-
Clear, comprehensible information and support for self-care	-	-	-	-	-	BERESFORD2013 DITTRICH2011 DYMOND2007 SPANN2003	-	-
Emotional support, empathy and respect	-	CHELL2006 MORRISON2009 TOBIAS2009 WITTEMEYER2011	-	-	-	-	-	-
Fast access to reliable health advice	-	-	-	-	-	-	-	BERESFORD2007 BEVANBROWN2010 CARBONE2010 DITTRICH2011 STEIN2012
Effective treatment delivered by trusted professionals	ALLARD2009 BERESFORD2012 BROOKMANFRAZEE2012 BROWN2012 BURROWS2010 DILLENBURGER2004 DILLENBURGER2010 DILLENBURGER2012 DITTRICH2011 DYMOND2007 GLAZZARD2012 GREY2010 HALL2010 HURLBUTT2011 HUTTON2005 JONES2008A	-	-	BROOKMAN-FRAZEE2012 DITTRICH2011 NAS UNPUBLISHED	-	-	ALLARD2009 ALLGOOD2005 AUERT2012 BERESFORD2007 BERESFORD2013 BREWIN2008 BROWN2012 BUNDY2009 BURROWS2010 CARTER2004 CASSIDY2008 CHELL2006 CULLEN2002ADITTRICH2011 DYMOND2007 FISH2006	CARBONE2010 CHELL2006 DITTRICH2011 DYMOND2007 OSBORNE2008 VALENTINE2010

	JONES2008C LILLY2004 MACKINTOSH2012 MCCABE2008A MEIRSSCHAUT2010 MYERS2009 NISSENBAUM2002 PHELPS2009 REID2011 RENTY2006A SANSOSTI2012 SERPENTINE2011 SHYU2010 SPERRY1999 STUART2006 TRUDGEON2007 VALENTINE2010 WADDINGTON2006						GLAZZARD2012 GREEN2007 GRINDLE2009 HURLBUTT2011 JEGATHEESAN2010 LUONG2009 MACKINTOSH2012 MANSELL2004 NICHOLS2010 OLIVIER2009 OSBORNE2008 PATTERSON2011 REID2011 ROSE2009 SERPENTINE2011 SPANN2003 SPERRY1999 STARR2001 STUART2006 TOBIAS2009 WADDINGTON2006 WEBSTER2003 WEIDLE2006 WHITAKER2002 WHITTINGHAM2006 WITTEMEYER2011 WRIGHT2011	
Attention to physical and environmental needs	-	-	-	-	-	-	-	-
Involvement of, and support for, family and carers	BERESFORD2012 BEVANBROWN2010 BIRKIN2008 BROOKMANFRAZEE2012 BURROWS2008 BURROWS2010 CAMARENA2009 CARBONE2010 DILLENBURGER2004 DITTRICH2011 DYMOND2007 GREY2010 GRINDLE2009 HALL2010 HUTTON2005 JEGATHEESAN2010	ALTIERE2009 BERESFORD2012 BRAIDEN2010 BROWN2012 BURROWS2010 CARBONE2010 CASSIDY2008 CHELL2006 CULLEN2002A DILLENBURGER2010 DITTRICH2011 DYMOND2007 FLYNN2010 GLAZZARD2012 GREY2010 HACKETT2009	NAS UNPUBLISHED OSBORNE2008	NAS UNPUBLISHED	-	HAY2005 JEGATHEESAN 2010	ALLGOOD2005 AUERT2012 BERESFORD2012 BURROWS2010 CULLEN2002A DILLENBURGER2004 DONALDSON2011 DYMOND2007 GLAZZARD2012 GRANGER2012 GRINDLE2009 JEGATHEESAN2010 MACKINTOSH2012 MCCABE2008B NASUNO2003 NICHOLS2010	CARBONE2010

	JOHNSON2002 JONES2008A LUONG2009 MACKINTOSH2012 MANSELL2004 MCCABE2008A MINNES2009 NASUNO2003 PARSONS2009A PATTERSON2011 REID2011 SMYTH2010 SPERRY1999 STONER2005 TISSOT2006 TRUDGEON2007 VALENTINE2010 WEBSTER2003 WOODGATE2008	HALL2010 HURLBUTT2011 HUTTON2005 JEGATHEESAN2010 JONES2008C KERRELL2001 KIMURA2010 KUHANECK2010 LILLEY2011 LIN2008 LUONG2009 MANSELL2004 MCCABE2008A MCCONKEY2011 MEIRSSCHAUT2010 MIDENCE1999 MOYSON2011 MULLIGAN2010 MYERS2009 NASUNO2003 NISSENBAUM2002 OLIVIER2009 OSBORNE2008 PATTERSON2011 PETALAS2009 PHELPS2009 PICKERING2005 REID2011 RENTY2006A RYAN2009 SANSOSTI2012 SELKIRK2009 SPERRY1999 STIRLING1999 STARR2001 TRUDGEON2007 VALENTINE2010 WADDINGTON2006 WEBSTER2003 WEIDLE2006 WHITAKER2002 WITTEMEYER2011					PATTERSON2011 SHYU2010 SMYTH2010 SPERRY1999 STONER2005 TRUDGEON2007 WEBSTER2003 WHITAKER2002 WHITTINGHAM2006 WHITTINGHAM2009 WILLIAMS2003 WOODGATE2008 WRIGHT2011	
Continuity of care and smooth transitions	ALLARD2009 BROWN2012 CARBONE2010 DITTRICH2011 DYMOND2007 GREY2010	ALLARD2009 BERESFORD2013 BEVANBROWN2010 BREWIN2008 CAMARENA2009 DANN2011		BROOKMAN-FRAZEE2012 DITTRICH2011 NAS UNPUBLISHED	BERESFORD2013 DYMOND2007 NAS UNPUBLISHED RENTY2006A		BERESFORD2012 DITTRICH2011 GRANGER2012 WEBSTER2003 WHITAKER2002 WHITTINGHAM2006	

	HUTTON2005 JONES2008C MINNES2009 OSBORNE2008 REID2011 WEBSTER2003	DILLENBURGER2010 DITTRICH2011 GLAZZARD2012 HALL2010 HARE2004 JINDALSNAPE2005 JONES2008C PICKERING2005 REID2011 STONER2005 STUART2006 TOBIAS2009 TRUDGEON2007 WEBSTER2003 WITTEMEYER2011						

Table 13: Matrix of qualitative evidence for family and carer experience (part 2)

Dimensions of person-centred care	Key points on a pathway of care							
	Secondary care	**Social care**	**Residential care: short breaks**	**Residential care: long term**	**Educational setting: mainstream**	**Educational setting: specialist**	**Educational setting: home education**	**Themes that apply to all points on the pathway**
Involvement in decisions and respect for preferences	DITTRICH2011	-	-	-	-	-	-	-
Clear, comprehensible information and support for self-care	-	DITTRICH2011	-	-	-	-	-	-
Emotional support, empathy and respect	-	-	-	-	JONES2008C KIDD2010 REID2011	-	-	-
Fast access to reliable health advice	-	-	-	-	-	-	-	-
Effective treatment delivered by trusted professionals	-	-	-	BENDERIX2007A DITTRICH2011	BEATSON2002 BERESFORD2013 BEVANBROWN2010 BREWIN2008 BROOKMANFRAZEE2012 BROWN2012 BUNDY2009 CAMARENA2009 CASSIDY2008 DILLENBURGER2012 DILLON2012 DITTRICH2011 DYMOND2007	BERESFORD2013 CASSIDY2008 DITTRICH2011 GREY2010 JINDALSNAPE2005 JONES2008C KOYDEMIROZDEN2010 MOYSON2011 PRUNTY2011 REID2011 RENTY2006A STUART2006 WADDINGTON2006	KIDD2010	CASSIDY2008 DITTRICH2011 PHELPS2009

					FISH2006 GLAZZARD2012 GREY2010 HALL2010 HAY2005 HUMPHREY2008A JINDALSNAPE2005 JONES2008C KEANE2012 KEENAN2010 KIDD2010 MACKINTOSH2012 OSBORNE2008 PARSONS2009A PHELPS2009 REID2011 RENTY2006A SPANN2003 STARR2001 STARR2012 STONER2005 TIPPETT2004 TISSOT2006 TOBIAS2009 WADDINGTON2006 WEBSTER2003 WHITAKER2007 WHITTINGHAM2006 WITTEMEYER2011			
Attention to physical and environmental needs	DITTRICH2011	BERESFORD2013	-	DITTRICH2011	BERESFORD2013 BEVANBROWN2010 BREWIN2008 DILLON2012 HAY2005 PARSONS2009A STARR2001 STONER2005 TOBIAS2009 WEBSTER2003	-	-	-
Involvement of, and support for, family and carers	-	DITTRICH2011	BROWN2012 BURROWS2010 CASSIDY2008 DITTRICH2011 DYMOND2007 HALL2010 HUTTON2005 LARSON2010 MEIRSSCHAUT2010	BENDERIX2007A BENDERIX2007B DYMOND2007	BEATSON2002 BEVANBROWN2010 BUNDY2009 DANN2011 DILLON2012 DITTRICH2011 FISH2006 GREY2010 HAY2005	GREY2010 JONES2008C KOYDEMIROZDEN2010 PRUNTY2011 REID2011 STUART2006 WITTEMEYER2011	CASSIDY2008 KIDD2010 NASUNPUBLISHED REID2011	CARBONE2010 CHELL2006 DILLENBURGER2010 DITTRICH2011 HUTTON2005 JEGATHEESAN2010 KEENAN2010 OSBORNE2008 TISSOT2006

			OSBORNE2008 PETALAS2009 PHELPS2009 WITTEMEYER2011		JINDALSNAPE2005 JONES2008C KEENAN2010 KIDD2010 LILLY2004 PHELPS2009 REID2011 RENTY2006A SANSOSTI2012 SPANN2003 STARR2001 STARR2012 STONER2005 TIPPETT2004 TISSOT2006 TOBIAS2009 WHITAKER2007 WITTEMEYER2011			
Continuity of care and smooth transitions	BERESFORD2013	ALLARD2009 BERESFORD2013 DITTRICH2011	-	BENDERIX2007A	BERESFORD2013 DILLON2012 KEANE2012 RENTY2006A STONER2005	BERESFORD2013 GREY2010	-	-

4.2.7 Summary of themes from the qualitative analysis for family and carer experience

Access

Effective treatment delivered by trusted professionals

Parents and carers spoke negatively about the limited availability of intervention or services, for example, interventions not being available in school (HUTTON2005, LILLY2004, MYERS2009). This was most often raised in relation to the ABA intervention (DILLENBURGER2010, DILLENBURGER2012, DYMOND2007, HURLBUTT2011):

> *We wouldn't need multi-disciplinary support if our child was getting ABA in school.* (DILLENBURGER2010, p. 18)

Parents and carers talked about their unmet needs for support out-of-school hours (DYMOND2007, JONES2008A, STUART2006) and locally (MYERS2009), and discussed their frustration with limited choice (NISSENBAUM2002, SPERRY1999, VALENTINE2010), travel and paperwork (DILLENBURGER2010, DITTRICH2011, DYMOND2007, HUTTON2005, JONES2008A, MEIRSSCHAUT2010, RENTY2006A) and long waiting lists (BROWN2012, HURLBUTT2011, MCCABE2008A, MACKINTOSH2012, MEIRSSCHAUT2010, RENTY2006A):

> *[One mother wanted her son to have ABA but after] waiting for 4 years, was told he was a year too old.* (HURLBUTT2011, p. 245)

Parents and carers felt that problems with securing funding were a major barrier to accessing intervention, services and education (BERESFORD2012, BROWN2012, BURROWS2010, DILLENBURGER2004, DILLENBURGER2010, DYMOND2007, GLAZZARD2012, GREY2010, HALL2010, MACKINTOSH2012, MCCABE2008A, MYERS2009, PHELPS2009, SANSOSTI2012, SERPENTINE2011, SHYU2010, SPERRY1999, TRUDGEON2007, VALENTINE2010, WADDINGTON2006):

> *I have called around for like an ABA program and [.] the price is outrageous and we could not afford it. So for a little while, for about 6 months [child's name] was not on any program at all. (mother of 6-year-old boy with autism)* (VALENTINE2010, p. 955)

Importantly, access to direct payments did not appear to completely address funding concerns:

> *We understand that because of his exceptional needs and the need for a high staffing ratio – we would need to make up the financial shortfall in funding – Could we find staff willing to put up with his behaviour for £7 an hour?* (JONES2008A, p. 172)

However, direct payments were welcomed by some carers as a perceived improvement:

> *Would really welcome [a personal budget] as it would enable parents to buy services that the children really need.* (REID2011, p. 32)

A recurring theme in the family and carer experience was a gap in services for children and young people with autism without a coexisting learning disability (IQ higher than 70) and this was particularly emphasised as a barrier to accessing services, support and education (ALLARD2009, BROOKMANFRAZEE2012, BROWN2012, DILLENBURGER2010, DYMOND2007, JONES2008C, RENTY2006A):

> *Despite considerable social difficulties at school (which resulted in school phobia), my daughter was refused a statement. Because of this, she had no access to trained support (or any support). She was, and still is, not eligible for a raft of services which those with a statement or learning difficulty have access to as their right, like independent living skills training, anger management, money management and budgeting, supported housing, specialist housing options, supported employment, Direct Payments, social care, befriending schemes, specialist social activities and more.* (ALLARD2009, p. 6)

Problems with varying eligibility thresholds across services were also discussed as a barrier to access by carers (ALLARD2009, BROOKMANFRAZEE2012, BROWN2012, MACKINTOSH2012, RENTY2006A), particularly during periods of transition (ALLARD2009, DITTRICH2011):

> *Being told at every turn that my son does not meet the team criteria.* (ALLARD2009, p. 11)

Families and carers were also frustrated that they could not access services unless they were in crisis (DITTRICH2011). Conversely, services that did not have eligibility criteria and otherwise facilitated access (by being easy to contact, acting quickly and making services affordable) were rated positively by families and carers (DITTRICH2011).

Involvement of, and support for, family and carers

Parents and carers talked about having to fight 'the system' in order to access interventions, services or support for the child or young person (CAMARENA2009, DYMOND2007, GREY2010, GRINDLE2009, LILLY2004, PARSONS2009A, REID2011, SPERRY1999, STONER2005, TRUDGEON2007, WOODGATE2008) and discussed how the time and effort required to access services was stressful for them, had a negative impact upon the family (including siblings) and caused considerable financial strain (BROOKMANFRAZEE2012):

> *They said it would be 6 months to a year to get into speech therapy. And I said, 'That is not acceptable.' I said, 'Get us in as soon as possible, and what is your earliest you*

> *can get us in?' And he told me that they occasionally phone parents if someone is sick or does not show up for an appointment. I said, 'Okay, you give me a 30-minute notice, 5-minute notice, I will be there.' And we got in, in 3 weeks.* (WOODGATE2008, p. 1079)

Lack of access to therapeutic interventions often forced parents and carers into the role of teacher or clinician (DYMOND2007, MCCABE2008A, TISSOT2006, VALENTINE2010):

> *I think it's a lot, it's up to the parents. So we've been working with them, my husband's done the More Than Words program [.] I've done an ABA course. I've been to [state peak body] and done two courses there and we went to the global, the conference as well. So we have been doing quite a bit of training. (mother of 2-year-old girl with autism)* (VALENTINE2010, p. 954)

Responsibility for the administration of intervention programmes (such as ABA or EIBI), including therapist recruitment and management, completing paperwork and preparing teaching resources, and arranging funding, placed additional strain on parents and carers (DILLENBURGER2004, GRINDLE2009, JOHNSON2002, MACKINTOSH2012, NASUNO2003, TRUDGEON2007, WEBSTER2003).

Parents and carers talked about the need for support for themselves and suggested that access to support groups or parent training could be facilitated by considering the location and timing of intervention sessions, having information about the aims and content of the intervention, and about the intervention administrator, and the administrators being approachable and friendly (BERESFORD2012, BIRKIN2008, DITTRICH2011, HUTTON2005, LUONG2009, MANSELL2004, PATTERSON2011).

Cultural differences were also perceived as creating barriers to accessing support groups or parent training (BIRKIN2008, JEGATHEESAN2010, LUONG2009), and parents and carers suggested that careful consideration should be given to the group format and language of any intervention or support for them:

> *The shyness thing. Pacific Islanders are shy. It's understandable we are a minority culture in a different system and the way things work. The EarlyBird program seems very Western. (Pasifika Parent)* (BIRKIN2008, p. 113)

> *Yeah, most people can't speak the language. Language is a problem. (Korean Parent)* (BIRKIN2008, p. 113)

Continuity of care and smooth transitions

Carers who had been able to access case management described the experience as positive:

> *The services were really easy to obtain. My case manager put everything together for us right away.* (HUTTON2005, p. 185)

However, case management was not always available (DITTRICH2011, DYMOND2007, HUTTON2005, WEBSTER2003), and lack of care coordination support placed considerable strain on parents and carers who had to fill this role (CARBONE2010, HUTTON2005, WEBSTER2003):

> *We had a locum consultant that didn't know how the system worked and didn't coordinate things… it's just things seemed quite disorganized really. It seemed we had to do all the running around to get things going, and of course we were in a terrible state anyway.* (WEBSTER2003 [Webster et al., 2004], p. 20)

Parents and carers expressed their frustration at a lack of continuity and communication between services (BROWN2012, CARBONE2010, DYMOND2007, GREY2010, OSBORNE2008):

> *I find it very frustrating how social services, health and education… all work very much independently of one another.* (OSBORNE2008, p. 320)

> *They are very guarded in sharing information, and they're very reluctant to actually get around the same table.* (OSBORNE2008, p. 320)

The need for a more integrated process of assessment, treatment, management and support was a recurring theme (ALLARD2009, BROWN2012, DITTRICH2011, JONES2008C, MINNES2009, OSBORNE2008, REID2011):

> *Just one key worker who is responsible for liaison with all the other agencies. What can go wrong is when no one is responsible and referrals from agency to agency are not acted upon.* (ALLARD2009, p. 8)

> *I agree that the medical and educational assessment could be more coordinated to avoid repetition.* (REID2011, p. 28)

> *…a central place where you can be assessed and treated.* (MINNES2009, p. 253)

> *A support centre that offers support for parents during the week regarding health, social contact etc. Basically so services can pull together in one place so people don't have to go here, there and everywhere. It is very tiring.* (DITTRICH2011, p. 86)

The need for parents and carers to fight in order to access services was again raised, but with particular reference to transition (ALLARD2009):

> *My personal experience was that imminent judicial review (stopped at the 11th hour as a meeting was miraculously arranged!) was the only way to 'encourage' the people who should have planned my son's transition but consistently failed to do so?* (ALLARD2009, p. 8)

Information and support

Emotional support, empathy and respect

Parents and carers spoke about the unmet need for emotional support to help the child or young person adjust to their diagnosis (TOBIAS2009, WITTEMEYER2011):

> *To be in a position where he understands that he's autistic and that with autism there comes difficulties that he'd find magnified compared to other children… and then sort of learn how to manage them and to cope with them… and maybe use it to his advantage.* (WITTEMEYER2011, p. 30)

The unmet need for psychological support to help the child or young person to prepare for (MORRISON2009) and adjust to (CHELL2006) transitions was also discussed.

Involvement of, and support for, family and carers

Unmet need for post-diagnosis information for carers

Parents and carers highlighted the importance of being given information about autism post-diagnosis, including: what autism is (BERESFORD2012, CHELL2006, FLYNN2010, HACKETT2009, JONES2008C, MEIRSSCHAUT2010, MULLIGAN2010, PATTERSON2011, STIRLING1999); causes of autism (CASSIDY2008, FLYNN2010, JONES2008C); prognosis (BRAIDEN2010, MANSELL2004, MULLIGAN2010, OSBORNE2008); individualised information about the child or young person (BRAIDEN2010, JEGATHEESAN2010, WHITAKER2002); behaviour management strategies (JONES2008C, PICKERING2005, STIRLING1999); how they should tell their child or young person about the diagnosis (PICKERING2005); coping strategies for their own adjustment to the diagnosis (PICKERING2005); information about how to help siblings cope (FLYNN2010, JONES2008C, WITTEMEYER2011); and genetic advice about risk of recurrence and signs and symptoms (SELKIRK2009).

Parents and carers also expressed that post-diagnosis information should: be written to allow time to digest (BRAIDEN2010, CHELL2006, DITTRICH2011, KERRELL2001, MULLIGAN2010); include a care pathway, 'route map' or flowchart (CHELL2006, DITTRICH2011, MULLIGAN2010); be jargon-free or include a glossary (DITTRICH2011, HACKETT2009, MULLIGAN2010); and be consistent across different diagnosis settings (MULLIGAN2010).

Parents and carers wanted the following to be available promptly post-diagnosis: information about services available (BROWN2012, CARBONE2010, CHELL2006, DITTRICH2011, GLAZZARD2012, HACKETT2009, JEGATHEESAN2010, JONES2008C, KERRELL2001, MANSELL2004, MULLIGAN2010, OSBORNE2008, RENTY2006A, SANSOSTI2012, STIRLING1999, WADDINGTON2006, WEBSTER2003); initiation of a needs assessment and care plan (DITTRICH2011); and a named professional responsible for care coordination (CHELL2006).

Unmet need for post-diagnosis information for siblings

Siblings also wanted to know more about autism:

> *Lizzy: I'd just like to, to know how, to know more about Tyler, and the area around Tyler, and that sort of thing really.*
> *Interviewer: Do you mean autism?*
> *Lizzy: Yes. Autism, and handicapped people, I'd like to learn more about that.* (PETALAS2009, p. 390)

Unmet need for post-diagnosis support for families and carers

Parents and carers discussed the need for psychological support for themselves in the post-diagnosis period (BURROWS2010, HALL2010, MANSELL2004, PATTERSON2011, STIRLING1999):

> *…if they don't give us the services we need, they'll have not only the children on their books, they'll have parents and the whole family as well.* (BURROWS2010, p. 26)

They also discussed a desire to be put into contact with other parents and carers in the post-diagnosis period (GREY2010, HACKETT2009, STIRLING1999) or described an unmet need for parent support groups (BROWN2012, DITTRICH2011, DYMOND2007, OLIVIER2009, OSBORNE2008, STIRLING1999). They also wanted to be offered the opportunity for follow-up support (CASSIDY2008, DITTRICH2011, RENTY2006A, VALENTINE2010, WHITAKER2002):

> *The paediatrician who conducted the disclosure interview assured us that we were ever allowed to take contact with her to ask questions…. During the disclosure interview we were flooded with information. Because the disclosure of a diagnosis brings about a lot of emotions, we did not remember all that was said. Furthermore, a lot of questions arise a few days after the disclosure interview. Therefore, it is so important that you can call someone to answer those questions.* (RENTY2006A, p. 377)

Unmet need for post-diagnosis support for siblings

Siblings expressed an unmet need for psychological support for themselves (DITTRICH2011, PETALAS2009):

> *I have a sister with autism and most people that we have had contact with are happy to talk to her but nobody wants to hear how I feel. People make effort to include my sister, but often forget about me.* (DITTRICH2011, p. 65)

An unmet need for sibling/family support groups was also described by families and carers (BURROWS2010, DITTRICH2011, DYMOND2007, STARR2001):

> *I would like help and support for my daughter as she is left out as my son is a 24hrs and is not kind to her. She is really withdrawn and has no friends or just won't bring them home because of his behaviour. So siblings need to have a group thing and clubs*

> *and activities so they feel special too as I have no help and I am a single parent.* (DITTRICH2011, p. 87)

Positive family, carer and sibling experiences of post-diagnosis information and support
Families and carers described positive experiences of an information and resources kit (containing booklets, toys and communication aids) in that it provided greater understanding of autism and could be shared with other family members to help them too:

> *It gave us structure to work to. It was very well laid out and clear. Knowing now that N doesn't learn the same way (as other children). It also gave you lots of ideas.* (MCCONKEY2011, p. 325)

Parent workshops or parent training interventions were also discussed as a positive source of post-diagnosis information and support (BERESFORD2012, FLYNN2010), and some carers (MIDENCE1999) and siblings (PETALAS2009) talked about having access to 'someone to talk to' as being a comfort:

> *People need to talk about it but on their own terms, when they decide to do it without being pushed, but given the opportunity to do so.* (MIDENCE1999, p. 281)

Positive carer and sibling experiences of support groups
Families and carers discussed positive experiences of joining a support group (HUTTON2005, WHITAKER2002), including the opportunity to create supportive relationships (ALTIERE2009, BURROWS2010, DITTRICH2011, PHELPS2009, REID2011, RYAN2009, WEIDLE2006) and share experiences and advice (CULLEN2002A, HALL2010, JONES2008C, LIN2008, NASUNO2003):

> *The thing we have found most helpful has been our support group, who not only support us through the hard times but provide all the information and help you could get.* (REID2011, p. 14)

Siblings also described positive experiences with support groups and valued the opportunity to share their experiences with other siblings (MOYSON2011, PETALAS2009).

Negative carer experiences of post-diagnosis information and support

Parents and carers expressed frustration that inadequate information in the post-diagnosis period resulted in unacceptable delays in accessing intervention (ALTIERE2009, BRAIDEN2010, MCCABE2008A, SANSOSTI2012):

> *When he was first diagnosed as 'autistic', we were totally at a loss. We didn't know what to do or where to go… so we wasted a long period of time.* (MCCABE2008A, p. 42)

They spoke of surprise and disappointment at the lack of post-diagnosis support (CULLEN2002A, DITTRICH2011, GLAZZARD2012, OSBORNE2008):

> *I thought a diagnosis would mean we'd get support, but we didn't. It was just a label but nothing changed.* (DITTRICH2011, p. 104)

> *It got so bad that the autistic society stepped in and said, you know, this family is just going to fall to pieces, someone's going to get seriously hurt.* (OSBORNE2008, p. 316)

Negative carer experiences of support groups

Experiences of support groups were not universally positive; some parents and carers did not want to share problems (LUONG2009), others felt that differing abilities of the children and young people meant that they were unhelpful (KUHANECK2010) DITTRICH2011, OSBORNE2008), while others were concerned that they could be discouraging (JONES2008C):

> *You hear people complain about things you really wish your child could be doing.* (KUHANECK2010, p. 345)

> *They can very easily become a series of moans about how bad life is… and can therefore be a very discouraging experience – and best avoided if feeling fragile.* (JONES2008C, p. 36)

Unmet need for treatment/care information for carers

Parents and carers wanted more information from professionals about treatment options (CULLEN2002A, DITTRICH2011, DYMOND2007, HURLBUTT2011, JONES2008C, SANSOSTI2012):

> *Well this [touch therapy] is the only therapy that Helen has been offered. She is having no speech therapy, she is having nothing. You know people say go out and fight for the services, but what do you fight for because you don't know what you should be fighting for?* (CULLEN2002A [Cullen & Barlow, 2002b] p. 42)

Parents and carers also wanted information about available support from social care (DILLENBURGER2010, DITTRICH2011):

> *If we don't know the questions to ask, then we don't get any answers. Social services should be called secret services.* (DILLENBURGER2010, p. 18)

Moreover, they also emphasised their need for information about the educational provision available (JONES2008C, WADDINGTON2006, WHITAKER2002), age-appropriate information about treatment options and support (BURROWS2010, DITTRICH2011, JONES2008C), and individualised treatment/care information (DITTRICH2011, SPERRY1999):

> *…what I have not had is one person who has met and got to know my son and his particular needs so that they can help me to work out what the best strategies, education, counselling etc for him would be… I need help that is specific and relevant to my son.* (DITTRICH2011, p. 111)

Parents and carers also talked about wanting professional treatment recommendations provided by a strengths and difficulties assessment (LILLEY2011):

> *You know that it's a spectrum and every child has their strengths and their weaknesses. What I would have liked was for someone to come in after the diagnosis and say: 'Here are your daughter's strengths; here are your daughter's weaknesses; these are the kinds of services or treatments available; this is the way she might respond'. You don't know which way to go and you're just tossing it up in your head.* (LILLEY2011, p. 214)

Negative carer experiences of treatment/care information

Parents and carers spoke about their surprise (LILLEY2011, NISSENBAUM2002) and frustration (VALENTINE2010) at the lack of professional treatment recommendations and the strain that was associated with having to make these decisions themselves (LILLEY2011, SANSOSTI2012, VALENTINE2010):

> *We had a lot of people that we spoke with, and it was like 'you're the parents, you make a decision, it's okay', and we just wanted someone to tell us. Sometimes it's just easier to hear it. Because we had to make so many decisions that left didn't know what right was doing. (mother of 6-year-old boy with autism)* (VALENTINE2010, p. 954)

Some parents and carers said their decision to pursue an ABA programme for the child or young person had resulted in a withdrawal of support (TRUDGEON2007):

> *…so because we decided to go down that route, the help that we had originally had virtually stopped.* (TRUDGEON2007, p. 293)

Continuity of care and smooth transitions

Unmet need for information and support at key transitions

Carers wanted the following information and support to be available at key transitions: information about adult development and services, careers and further education (JONES2008C); planning for the transition from home intervention to mainstream school (TRUDGEON2007, WEBSTER2003), and through and between schools (BREWIN2008, STUART2006); an extended transition period that starts early (DITTRICH2011); regular review of the transition plan (DITTRICH2011); and planning for care after the death of the carer (BERESFORD2013, DILLENBURGER2010, HALL2010, WITTEMEYER2011):

> *…my biggest stressor is what's going to happen when I'm gone.* (HALL2010, p. 195)

Positive carer experiences of information and support at key transitions

Positive elements of transition planning (ALLARD2009, BEVANBROWN2010, CAMARENA2009, DANN2011, DITTRICH2011, STONER2005, TOBIAS2009) were described, including opportunities for the child or young person to have pre-visits and orientation sessions, training in daily living skills in advance of transition, access to a keyworker or mentor and psychological support during transitions.

Negative carer experiences of information and support at key transitions

Parents and carers described a lack of information available about transition:

> *…no one seems to really know what will happen post 18. It just appears there is a college route and then see what happens – no options are clearly explained – just the most popular one (local college). I would like better info at transition stating all possible options and how to access these.* (DITTRICH2011, p. 116)

Lack of support during the transition period (DITTRICH2011, GLAZZARD2012, HARE2004, JONES2008C) was also highlighted:

> *I feel that there are many services, help and support for children but that all seems to vanish post 16.* (DITTRICH2011, p. 116)

Parents and carers talked about how access to transition planning was particularly restricted for children and young people without coexisting learning disabilities (IQ>70) (ALLARD2009, DITTRICH2011).

They also expressed frustration at the lack of professional coordination for transition planning (DITTRICH2011) and described experiences of disagreements with professionals (including tribunal processes) that resulted in unacceptable delay and inadequate transition planning (DITTRICH2011, JINDALSNAPE2005, REID2011).

Assessment and referral in crisis

Involvement of, and support for, family and carers

Parents and carers felt that there was inadequate access to support when the child or young person was in crisis:

> *If you have a crisis that's it. If you have a crisis, you can phone up but you won't get the worker, so the poor receptionist, she's a receptionist she doesn't tell what to advise you to do. Their advice is usually 'contact social services if you're concerned.' They're about as much use as a chocolate teapot. They honestly do not understand autism at all. (parent of 16-18-year-old)* (NASUNPUBLISHED, p. 56)

> *It's still slightly bizarre or surreal in my own mind, because I rang this number, which I thought would be answered immediately, and I was told that I was in a queuing system, could I be patient and wait, while this adolescent was waving a knife in front of me.* (OSBORNE2008, p. 319)

Access to a 24-hour helpline would be welcomed by parents and carers as an effective source of support for periods of crisis (NASUNPUBLISHED).

CAMHS

Effective treatment delivered by trusted professionals

Parents and carers wanted CAMHS to offer a multidisciplinary service with professionals who are knowledgeable about the full autism spectrum (BROOKMANFRAZEE2012, NASUNPUBLISHED), provide individualised treatment and access to a mentoring system (NASUNPUBLISHED) and have more male members of staff (NASUNPUBLISHED).

They spoke about the struggles they had faced to get a referral to CAMHS, with many employing an advocate to represent them or resorting to a tribunal (NASUNPUBLISHED):

> *…CAMHS just didn't want to know when he was at his self-harming peak. My paediatrician didn't want to know. My husband had to threaten to go to the local papers. He took photographs and he sent them to the paediatrician and he said to her, 'If you don't refer him to CAMHS regarding the self harming and the fact he's attacking me, my wife and my two daughters, if you don't do it, then we will go the papers and show them what a shoddy health service we've got.' A week later they decided we could get a CAMHS appointment. (parent of 11-15-year-old)*
> (NASUNPUBLISHED, p. 22)

Many parents and carers were angry that the only way they seemed to be able to access CAMHS was in crisis, when earlier intervention might have been able to prevent such crises developing (DITTRICH2011):

> *The waiting lists are ridiculously long!! Why does a child/ family have to get to a crisis point before anything starts to move? My son's anxieties are getting worse for him and us – CAMHS will talk to me, but say talking is no good for Aspergers. What therapy is good for him? Why isn't he getting some help? Does he have to really hurt someone or himself before does something because that is WRONG!*
> (DITTRICH2011, p. 120)

Parents and carers expressed a desire for access to interventions with a more preventative approach (NASUNPUBLISHED):

> *By the time they develop mental health problems which they invariable do, nobody has actually done anything and then they just give you medication. Nobody is actually looking at ways to prevent mental health and to help families interact with their children in a better way to enable better communication, to enable the children to function better. So you, know, it seems that children are actually developing mental health problems because nobody is actually teaching families and the professionals*

don't seem to know what to do. (parent of 16-18-year-old) (NASUNPUBLISHED, p. 40)

Parents and carers talked about a lack of access to services including long waiting lists – one carer described being on a waiting list for 2 years for occupational therapy and another had been waiting for over a year for counselling (DITTRICH2011). Access to autism services was felt to be particularly restricted for children and young people with intellectual ability within the normal range (NASUNPUBLISHED). Parents and carers described how the lack of services left them feeling compelled to provide private therapeutic intervention (NASUNPUBLISHED):

We ended up finding an occupational therapist who focuses on management of stress and anxiety for autistic kids. Both of the boys have been using this programme with them. Basically, it's what we wanted from CAMHS, it's giving the boys strategies so they can cope. We pay for one privately and CAMHS now pays for the other one. (parent of two children under 10-years-old) (NASUNPUBLISHED, p. 49)

They also described experiences of receiving inaccurate reports from CAMHS, and many decided to privately fund psychologists to write statements in order to speed up the process:

*So they sit there and they say everything that you want to hear and then you get the report back from the meeting and it's as if you were in a different place. (parent of 11-18-year-old) (*NASUNPUBLISHED, p. 25)

Moreover, even after having gained access to CAMHS many parents and carers were told that there were no autism services:

Having got to CAMHS, it was like almost a building of mirrors in the sense you can get to the door thinking thank goodness, we've now got to the place where we're going to get help. Almost the first thing the psychiatrist did was to hold up their hands, 'I have to tell you before we start that we have no services in this health district for children on the autistic spectrum.' Something that you mentioned, they couldn't wait to get rid of you. I couldn't believe the speed at which they would say to me, 'Well, obviously I have explained to you what services we can offer here. You seem to be managing very well yourselves with the situation. You seem to recognise all the symptoms and H's obviously made progress because of the care you've put in place. So I think probably there's not much point in my maintaining his name on the list. Essentially, there's nothing in place to help. (parent of 11-15-year-old) (NASUNPUBLISHED, p. 22)

Parents and carers talked about how the child or young person did not feel understood by CAMHS staff:

Our kids know that they (CAMHS) don't understand them, so then they walk out and say, 'They don't get me, they don't understand me, they can't help.' They know full well they don't understand what their problems are or how to help them. It's not

> *like they want them to wave a magic wand or something, just to take it all away, they know they have to do work. They know that it's going to be hard, but they're very clever at picking up when people don't understand them. (parent of 11-15-year-old)* (NASUNPUBLISHED, p. 22)

Experiences of inadequate professional understanding leading to inappropriate treatment recommendations were described, such as 'talking' therapies with a stranger in Tier 1 with subsequent repercussions for how the child or young person felt about future referrals to CAMHS (NASUNPUBLISHED). The failure of CAMHS professionals to understand the importance of making autism-specific modifications to their communication with the service user was also raised by parents and carers:

> *The CAMHS lady spends more of the time talking to him but I always have to stay as a translator, because she hasn't learnt to reduce her language enough. He looks at her and once he even said, 'What are the hell are you saying?' He doesn't understand. He's got a severe language delay and disorder. (parent of a child under 10 years old)* (NASUNPUBLISHED, p. 24)

Parents and carers perceived speech and language therapists as understanding these needs:

> *His speech and language therapist when it was first offered to me, because he doesn't actually have a speech problem, I turned it down. It was quite a long time after actually, it was actually CAMHS who said to me and explained, you know, it wasn't anything to do with his actual speech, it was a communication thing. She was absolutely fantastic, every term going into school giving them fantastic programmes and she's just been the best. She just seems to really understand what he needs and what he needs for the future as well. The programmes for independence and that kind of thing, and she'll go in and make sure that they're done in school, because I could never get them to do anything before her. (parent of 11–15-year-old)* (NASUNPUBLISHED, p. 50)

In terms of specific treatment choices, parents and carers expressed frustration at a perceived preference for pharmacological interventions and a lack of time spent discussing other treatment options:

> *It's the quality of what they're doing that I've got a problem with. Every single time, the first strategy that they come up with is medication. Every single time, yes and that's really spending half a session explaining why we'd like them to come off it. So it's strategies instead of medication. (parent of child under 10 years old)* (NASUNPUBLISHED, p. 39)

Involvement of, and support for, family and carers

Carers would like CAMHS to offer the following (NASUNPUBLISHED): advice about behaviour management strategies; a non-judgemental, respectful, and collaborative approach of professionals towards the relationship with carers; a more efficient diagnosing, referral and statementing system, where parents would not

have to fund private therapeutic interventions or have to fight 'the system' in order to access services; information about services available; a drop-in centre within CAMHS as a helpful, and more informal, source of advice and support.

Parents and carers described negative relationships with CAMHS professionals, including feeling blamed for the child or young person's difficulties:

> *All that time, all the focus was on us as being these awful parents, which was a horrific experience. The point is she needed some really specific help at that point, you know? She wanted to die and all they could do was tell us that we were bad parents, which even if we were, even if we still are, that's not the issue at hand. The issue at hand is you've got a child here that isn't coping. What are you going to do about it? They had no way of helping her whatsoever. (parent of 11–15-year-old)* (NASUNPUBLISHED, p. 25)

The complex three-way relationship between service user, professional and parent/carer, was also discussed particularly in reference to parents feeling excluded from discussion about pharmacological treatment decisions:

> *…my daughter's psychiatrist asks her whether she wants to try a new tablet as opposed to me. It's one of the biggest problems we've had, because she's a complete control freak, again because of the anxiety. They keep giving her so much control. They keep putting her in charge of decisions that she just shouldn't be making. One thing I wanted to know was whether the fact that at the age of thirteen all children are allowed to make decisions about their care and whether that should be different for children with autism? (parent of 11–15-year-old)* (NASUNPUBLISHED, p. 40)

Conversely, parents and carers spoke positively about instances when they had been included in the therapeutic intervention. One parent attending occupational therapy acquired skills to help and support their child:

> *The occupational therapist was the best, she was fantastic, she was a specialist and told me how to adapt behaviour and so how to help him with his senses and to lower his anxiety as well. (parent of 11-15-year-old)* (NASUNPUBLISHED, p. 50)

Continuity of care and smooth transitions

Parents and carers described poor communication between CAMHS teams in different areas (DITTRICH2011) and a lack of communication and collaboration between CAMHS and educational services:

> *I must admit that our biggest problem has been the lack of communication between education and mental health. I used to work for school health, so I know that education don't listen to health, but if you have your diagnosis via, say, CAMHS or Family Guidance and stuff, education don't listen. They don't take on board the diagnosis. I mean when W was diagnosed the first thing I did was going and see his headmaster, and say he's been diagnosed with Asperger's. 'Oh yes, who told you that*

then?' 'Well the psychologist. And he replied 'What do you want us to do about it? (parent of 11-15-year-old) (NASUNPUBLISHED, p. 60)

Parents and carers describing community mental health services in the US highlighted problems with high staff turnover, particularly for individuals with autism who find adapting to change difficult:

> *The other difficulty with going with County Mental Health is their turnover…. That was really hard. Especially [if] there was one there that was really good… we had one that was like three months and then another one…. And I'm like, you know, this is really too hard for him… so that was the hardest part.* (BROOKMANFRAZEE2012, p. 540)

Transition (CAMHS to AMHS)

Continuity of care and smooth transitions

Parents and carers talked about their unmet need for a transition team and a plan to be in place in order to support the child or young person, particularly given that change may be especially challenging for individuals with autism (DYMOND2007, NASUNPUBLISHED). They discussed the importance of continuity of support between CAMHS and AMHS for the wellbeing of the child or young person:

> *Now she [daughter] consults an excellent child psychiatrist. Next month she will be 18 years old, thus she has to find a new psychiatrist. That won't be easy for her. Continuity of support is essential for L.'s wellbeing.* (RENTY2006A, p. 379)

There were experiences of how inadequate planning had led to an interruption in mental health support (with gaps of 3 and 9 months) and coincided with the stressful period of leaving school (BERESFORD2013).

Community services

Clear, comprehensible information and support for self-care

Parents and carers expressed a need for improved access to activities, clubs and social contact groups in their local area for the child or young person (BERESFORD2013, DITTRICH2011, DYMOND2007, SPANN2003), and felt that improved access to leisure activities should extend to children and young people with intellectual ability within the normal range (DITTRICH2011). They were also concerned that the lack of available community services would have a serious impact on their child's wellbeing, particularly after they had left school or college:

> *I mean I've got visions of him being on the dole… can't get an apprenticeship, can't get a job because he's got special needs and people are going to take able bodied first. He's going to be on, on the dole for years on, years and years and years, fed up, upset, his self-esteem will go through the floor again, and I won't be able to get him out of his bedroom and motivate him, even to take me shopping.* (BERESFORD2013, p. 163)

Involvement of, and support for, family and carers

Parents and carers also expressed an unmet need for support from community agencies to help them cope and prevent 'burnout' (HAY2005, JEGATHEESAN2010). Support through community cultural centres was also seen as a potential means of addressing cultural barriers to accessing support (JEGATHEESAN2010).

Therapeutic intervention

Effective treatment delivered by trusted professionals

Unmet need for interventions aimed at social skills

Parents and carers expressed an unmet need for interventions aimed at social skills for the child or young person (BERESFORD2007, BROWN2012, BUNDY2009, CHELL2006, DITTRICH2011, DYMOND2007, STARR2001, WHITTINGHAM2006, WITTEMEYER2011), and suggested that a mentoring system might facilitate access to social groups (DITTRICH2011, OSBORNE2008). Moreover, a greater need for support not just with teaching social skills, but also with generalising skills learnt to a natural context, was expressed:

> *…what I found was… what he learnt in theory… the role plays and what-have-you in the group… he came home and we discussed it and yes he knew exactly how he should perform outside in the big bad world but he still can't manage to do it. He can do it in a controlled environment as such, and he can do it if he thinks he's doing role play but I'm still finding that he has an awful lot of difficulty transposing that into the real world as such, you know.* (ROSE2009, p. 138)

Some parents and carers suggested that delivering social skills training in schools may address generalisation problems (BREWIN2008, DITTRICH2011, FISH2006, SPANN2003, SPERRY1999, WHITAKER2007), and some who had experienced peer tutoring or training in school described positive experiences (SPANN2003, WADDINGTON2006).

A desire for a less formal approach to social skills training was expressed:

> *…a social outlet in that they can get together and do things, you know like youth club type approach… where they can meet without being taught… and make friendships among themselves.* (ROSE2009, p. 138)

The need for long-term follow-up was also raised:

> *We, the parents, are very supportive of this new scheme to improve social skills and would be very keen for the group to be ongoing.* (ROSE2009, p. 135)

Unmet need for interventions aimed at communication

Parents and carers talked about the desire for improved access to communication interventions (DITTRICH2011, DYMOND2007, OLIVIER2009, SERPENTINE2011, WEBSTER2003) and an unmet need for speech and language therapy was discussed (DITTRICH2011, DYMOND2007, CASSIDY2008, JINDALSNAPE2005, MANSELL2004, STARR2001, STUART2006). They also wanted parent training about autism-specific modifications they could make to their communication (BURROWS2010).

Unmet need for interventions aimed at behaviour that challenges

Parents and carers expressed a desire for improved access to interventions aimed at behaviour that challenges (CASSIDY2008, WEBSTER2003, WITTEMEYER2011), including parent training in behaviour management (BUNDY2009, BURROWS2010, GLAZZARD2012, OLIVIER2009). In terms of preferred approaches to managing behaviour that challenges, they talked about the importance of anticipating and preventing behaviour that challenges rather than dealing with children and young people in a punitive manner (HURLBUTT2011, WHITTINGHAM2006):

> *You have to look at other reasons for why they do things.* (WHITTINGHAM2006, p. 372)

> *…if you ignore, you're not going to find that out.* (WHITTINGHAM2006, p. 372)

Unmet need for interventions aimed at daily living skills

Parents and carers described an unmet need for interventions aimed at teaching daily living skills, and expressed a desire for the child or young person to be equipped with the skills to become as independent as possible (BERESFORD2007, BERESFORD2013, BUNDY2009, DITTRICH2011, OLIVIER2009, SPANN2003, STARR2001, TOBIAS2009, WITTEMEYER2011). They felt that daily living skills were inadequately supported at school (FISH2006, HURLBUTT2011, SPANN2003) and some expressed a desire for improved access to occupational therapy (CASSIDY2008, DYMOND2007).

Unmet need for parent training on ways to approach the child or young person's sexuality

Parents and carers wanted to talk to the child or young person about sexuality and safety but did not feel like they had the skills to do so:

> *I want my daughter to learn to respect her body and teach partners to respect her. She needs to learn how to not be taken advantage of in relationships.* (NICHOLS2010, p. 79)

Unmet need for interventions aimed at vocational skills

Employment opportunities for the child or young person was described as a priority for many parents and carers (DITTRICH2011, WITTEMEYER2011) and an unmet need for vocational skills training was expressed (ALLARD2009, BERESFORD2013,

DITTRICH2011, DYMOND2007, SPANN2003, WITTEMEYER2011). A need for ongoing support to maintain a job was also emphasised (BERESFORD2013, DITTRICH2011):

> *My son is struggling to get employment. He has experienced discrimination and a complete lack of help by the job centre plus to the point of obstruction – they criticise but don't offer positive solutions. A key priority would be a mentoring and training service to help find employment and help cope with challenges once in employment.* (DITTRICH2011, p. 156)

Unmet need for interventions aimed at coexisting conditions

Parents in a parent training programme often placed as great, if not greater, an emphasis on interventions aimed at coexisting features as they did on interventions targeting the core features (WHITAKER2002).

Unmet need for interventions aimed at sleep problems

Parents whose child experienced sleep problems expressed a desire for an intervention targeting these problems (BERESFORD2007).

Unmet need for interventions aimed at motor problems

Parents and carers found dealing with motor difficulties a cause of stress (BUNDY2009).

Unmet need for interventions aimed at sensory sensitivities

Parents and carers described an unmet need for sensory integration therapy (DYMOND2007).

Unmet need for music therapy

Parents and carers expressed a desire for improved access to music therapy (DYMOND2007, SERPENTINE2011):

> *We would also like to take him to music therapy, because he really likes music, it calms him, but I don't know if that is offered around here.* (SERPENTINE2011, p. 226)

Experience of interventions for children and young people with autism

Parents and carers were positive about the opportunities to meet other children and young people with autism that group-based interventions social skills offered (CARTER2004, ROSE2009):

> *…when he came here he made friends, which was great and I thought it was fantastic that these children were all alike and understood each other and weren't looking at each other as if they were stupid or different or from a different planet and they all got on so well and to me that was the biggest strength of the group.* (ROSE2009, p. 137)

Parents and carers also described a music therapy group and the opportunities it provided for interaction between children:

> *…the first class they were all doing their own thing and then they all sort of got used to each other and interacted.* (ALLGOOD2005, p. 96)

A computer workshop intervention was also described as a valuable opportunity to meet other children and young people with autism with a shared interest (WRIGHT2011).

Parents and carers also described positive experiences of interventions developing the self-confidence of the child or young person. For instance, they felt that attending a support group had given the child or young person a stronger identity as an individual with autism (WEIDLE2006), and taking part in a computer workshop built self-esteem:

> *[One parent summarised the feelings of her child as] I'm good at this, and this is cool that I am good at something! Wahoo! I am finally good at something! Am I like the coolest guy in the whole world?* (WRIGHT2011, p. 142)

The accessibility of interventions was also discussed, with some parents and carers describing positive experiences of music therapy, which was accessible to a heterogeneous group of children and young people with autism:

> *That's really true because (my son's) disability is a lot more severe than (the others) but it was always a level playing field-just participate as much as you can participate. That was kind of nice.* (ALLGOOD2005, p. 96)

Parents and carers spoke about how opportunities need to be provided for children and young people to participate in activities in which they have a special interest (BREWIN2008), and how taking these interests (for example, a computer workshop) as a starting point for selecting the activity had left them feeling that they had really done something beneficial for their child (WRIGHT2011):

> *It was the first time I took him to something for him, that really turned out to be for him. Instead of me doing some checklist in my mom head – he's got to try basketball,… social skills class, art class.* (WRIGHT2011, p. 141)

The need for the intervention to be individualised to the needs of the child or young person was discussed (DYMOND2007, CULLEN2002A) and negative experiences associated with non-individualised therapeutic interventions were discussed:

> *The treatment was too rigid, too much like training a dog and the child rebelled. It caused temper tantrums. (mother of a 4-year-old boy with autism who had used ABA for 2 months).* (GREEN2007, p. 98)

Conversely, family-centred (BERESFORD2012) or individualised (MACKINTOSH2012) approaches were described positively:

> *…it [the initial assessment] felt personal to the family, not just something from a book.* (BERESFORD2012, p. 180)

Parents and carers also emphasised the importance of the professional understanding autism (AUERT2012, BROWN2012, WHITTINGHAM2006) and the individual needs of the child or young person in order to make appropriate treatment recommendations; for instance, strategies that involve touch may be inappropriate because of sensory sensitivities (WHITTINGHAM2006).

Involvement of, and support for, family and carers

Mixed experiences of high-intensity interventions (such as EIBI and ABA) were described. Some parents and carers felt that EIBI allowed them more free time for other activities (GRINDLE2009, WEBSTER2003):

> *There are times when [the child] is in his lessons and I can go to the gym! So there is the element that I get more free time.* (GRINDLE2009, p. 46)

While others reported that their social life had suffered as a result of time devoted to an EIBI programme, and they felt stressed (DILLENBURGER2004, GRANGER2012, MACKINTOSH2012, TRUDGEON2007, WEBSTER2003, WOODGATE2008):

> *We have no life, we only have a program [referring to the ABA program]!* (WOODGATE2008, p. 1078)

Some reported that time spent on the intervention left less time for siblings or spouses (DILLENBURGER2004, GLAZZARD2012, GRANGER2012, GRINDLE2009, TRUDGEON2007), while others believed that family relationships had been strengthened through involvement in high-intensity programmes (GRINDLE2009, TRUDGEON2007, WILLIAMS2003).

There were also mixed views about interventions being delivered in the home environment. The constant presence of therapists in the home was a problem (GRINDLE2009, TRUDGEON2007, WEBSTER2003):

> *Your home is never your own as there are always people trooping through it and in the most intimate way in that they come into the bedrooms.* (GRINDLE2009, p. 47)

However, the home setting also allowed for greater family involvement, with parents and carers describing benefits to siblings in terms of being able to understand more about autism (DILLENBURGER2004, GRINDLE2009, SMYTH2010, STONER2005, WILLIAMS2003). They also described the opportunity to pick up on behaviour management strategies from therapists (DILLENBURGER2004,

GRINDLE2009, STONER2005, TRUDGEON2007, WEBSTER2003) and get advice about sleep problems (WEBSTER2003).

Parents and carers expressed a strong need to be involved in interventions for the child or young person and for professionals to listen to them (BURROWS2010, DYMOND2007, SPERRY1999). They also wanted to be provided with information and research literature about the treatment rationale, involved in decision-making and taught how to deliver the intervention at home (AUERT2012). However, this was often not their experience and parents and carers reported feeling excluded from interventions (AUERT2012, CULLEN2002A, JEGATHEESAN2010, SHYU2010, WOODGATE2008):

> *Maybe my husband would not like me using this word, but really the total brutality of how parents are treated. You are really made to feel like an outsider in your child's life.* (WOODGATE2008, p. 1079)

Conversely, inclusion in interventions gave parents and carers a sense of empowerment (AUERT2012, BERESFORD2012, DILLENBURGER2004), a feeling that they were recognised as experts about the child or young person (BERESFORD2012) and an opportunity to spend time with their child (CULLEN2002A, DONALDSON2011). They reported that being involved in interventions (ABA, EIBI or parent training) had equipped them with behaviour management strategies (BERESFORD2012, DONALDSON2011, GRINDLE2009, NASUNO2003, WHITTINGHAM2009):

> *One of the other things was the, making you look at your own behaviour. The things you do that you don't realise you're doing… You, you understand more about why they do what they do, so you're inclined to take a step back before you react to it.* (BERESFORD2012, p. 162)

Parents and carers also felt that inclusion had given them a greater understanding of the child or young person and more effective ways of teaching or interacting with them (ALLGOOD2005, BERESFORD2012, DILLENBURGER2004, GRANGER2012, PATTERSON2011, WHITAKER2002):

> *I have a tendency to do something a couple of times and if (my son) doesn't come around then I try something else I can do. Where if I just give him a chance to keep going at it, which is what his therapists do all of the time, he'll probably get it.* (ALLGOOD2005, p. 97-98)

Parents and carers also described support that they had received for themselves through their involvement in interventions for their child, from both therapists (GRINDLE2009, TRUDGEON2007, WHITAKER2002) and other parents (ALLGOOD2005, BERESFORD2012, GRANGER2012, GRINDLE2009, MCCABE2008A, NICHOLS2010, PATTERSON2011, WHITAKER2002, WHITTINGHAM2009):

> *The so-called professionals, they might know, they might have read the textbook, but they don't understand. They don't understand the situation… until you've been in that situation, you don't know. But to have people around who does know and does understand, that makes a [difference].* (BERESFORD2012, p. 64)

However, the need for longer-term rather than opportunistic support was emphasised. For instance, those who had taken part in a parent training programme talked about the need for follow-up support from professionals (PATTERSON2011, WHITAKER2002) and the opportunity to reconnect with other carers in the group after group-based interventions had ended (BERESFORD2012):

> *You meet up with people and you, and you get to know them and they're sharing quite big things really, and then it just comes to a halt… you do wonder how they're getting on… so it might be good, you know, at some point, maybe just to have a, like a get together in a few months or six months or something.* (BERESFORD2012, p. 182)

However, some parents and carers described negative experiences associated with being included in interventions in terms of confusion between their role as intervention administrator and their role as a parent (GRANGER2012):

> *When you do 20 hr of intervention a week, you become an educator, and you're unsure about regaining your role as a parent.* (GRANGER2012, p. 73)

Some described a failure to take cultural differences and preferences into account. South Asian Muslim parents were frustrated at the play-based model of language intervention used with their child, expressing a preference for a more directive approach (JEGATHEESAN2010). They also disagreed with professionals when they were advised to speak only English at home with their child:

> *He has grandparents, and they cannot speak English. So how our child can communicate with his grandmother if he knows only English? What they (professionals) are asking is unreasonable. So it is best we don't tell them anything. They don't need to know what we speak at home because it's a headache for us to make them understand. They just don't. (Bangladeshi mother of 6 year old boy with autism)* (JEGATHEESAN2010 [Jegatheesan, 2011], p. 196)

Continuity of care and smooth transitions

Some parents and carers saw themselves as care coordinators facilitating communication between different professionals (GRANGER2012). Others described an unmet need for continuity between interventions delivered in and outside school (DITTRICH2011, WEBSTER2003, WHITTINGHAM2006). Where collaboration between home-based intervention administrators and school had been achieved, it was perceived to be beneficial (BERESFORD2012, WEBSTER2003, WHITAKER2002):

> *[South West Autism Programme Tutor] is a real bridge between home and nursery. For example, if we get X to understand a phrase we have been using at home, like 'tidy time', that gets introduced at nursery as well.* (WEBSTER2003, p. 41)

Primary care

Fast access to reliable health advice

Parents and carers described difficulties in accessing dental services and visiting the GP (BERESFORD2007, BEVANBROWN2010), including touch sensitivities and problems with new people, environments or situations (BEVANBROWN2010, STEIN2012). They suggested ways in which these difficulties could be addressed (BEVANBROWN2010), such as preparatory work including pre-visits, social stories, role playing, looking at photographs of the GP or dentist and arranging appointments to minimise waiting time. Carers who had experience of the latter talked about this as a very useful adaptation (DITTRICH2011).

Mixed experiences were described regarding relationships with professionals in primary care and how these affect access to these services. Some parents and carers described how lack of flexibility and unwillingness to make adaptations exacerbated the barriers to accessing dental services:

> *Dentistry was unwilling to give a general anaesthetic for routine check so service was unavailable and this persists to present day, even though it could be pain that is causing the behaviour.* (DITTRICH2011, p. 80)

While others had more positive experiences:

> *Our dentist always makes a little extra time to explain everything to our son. Also she always takes the time to answer his questions, which can be many and varied!* (DITTRICH2011, p. 122)

Effective treatment delivered by trusted professionals

Parents and carers described GPs and health visitors as lacking in knowledge about autism (CARBONE2010, DITTRICH2011, DYMOND2007, VALENTINE2010) and therefore became a source of referrals (CARBONE2010, VALENTINE2010) rather than treatment:

> *And to be perfectly frank with you, I don't go to the GP now and say anything except 'I want a referral to this sort of a specialist for this sort of a problem' because the GPs just know nothing about autism. It's frightening how little GPs know about autism. (mother of 8-year-old and 3-year-old boys with autism)* (VALENTINE2010, p. 955)

Parents and carers wanted GPs to be more knowledgeable about standardised screening tools and prescribing commonly used medications (CARBONE2010), seeing a role for specialist health visitors (CHELL2006) and GPs (OSBORNE2008) in treatment and support.

Involvement of, and support for, family and carers

Parents and carers reported a strong need to be recognised by their GPs as experts about their child:

> *Doctors need to recognize that parents do know something about their kids.* (CARBONE2010, p. 319)

Secondary care

Involvement in decisions and respect for preferences

Parents and carers suggested that an advocate to support children and young people with autism in engaging with professionals in secondary care would be beneficial (DITTRICH2011).

Attention to physical and environmental needs

Negative experiences associated with a lack of autism-specific adaptations to the hospital environment were described:

> *No awareness of social communication difficulties my son had in hospital. Poor preparation for treatments, poorly managed acute emergency follow up having to access a children's ENT service on an adult ward. Lots of painful treatments and heightened arousal and anxiety. No routine or preparation for change or explanations to my son in a clear and calm manner. No consent agreed by him before exposing him to painful stimuli. Left cannula in son's arm after surgery when they said they would remove it in the recovery department (my son has a needle phobia!) so he became angry and confused and walked out of the hospital not fully recovered. Very stressful for all concerned.* (DITTRICH2011, p. 121)

Continuity of care and smooth transitions

Parents and carers talked about gaps in care, and the lack of planning or preparation for transition from community paediatrics to AMHS (BERESFORD2013).

Social care

Clear, comprehensible information and support for self-care

Parents and carers talked about a lack of appropriate housing to enable the young person to live independently in the future:

> *I am very concerned about housing for my son when he reaches adulthood and hope that Hampshire will be making more supported living placements available in the future.* (DITTRICH2011, p. 152)

Attention to physical and environmental needs

Parents and carers spoke about unsuitable and unsafe day and short-term care environments after transfer from child to adult social care:

> *…she's still very much like a little, little girl, and there are men and women there up to the age of, in their seventies… and obviously she's very, very vulnerable, being around vulnerable males concerns me a little bit.* (BERESFORD2013, p. 124)

Involvement of, and support for, family and carers

Parents and carers spoke about poor response to their concerns and lack of support from social services:

> *Social Services never got back to me when I phoned due to my concerns for his safety due to his brother, although he had previously been identified as 'in need'.* (DITTRICH2011, p. 80)

Difficulty in getting a carer's assessments was also described (DITTRICH2011):

> *My family reached breaking point, but they [Children's Services] refused to assess the situation. Instead the only help I received was to be told that if I couldn't cope to call the police before I assaulted my son, and they would take him away.* (DITTRICH2011, p. 148)

Continuity of care and smooth transitions

Some parents and carers discussed positive experiences of social workers being involved in transition to adult services, which was successful because they made sure they were familiar with the needs of the family and the young person:

> *The children's team contacted the transition team on my son's 14th birthday. A transition team worker arranged a house visit immediately, to discuss possibilities for adult placements. An information pack on local facilities was left for us to consult. An adult learning disability social worker was chosen within two months, to match our son, and visited the house to agree the places chosen. The social worker spent the day on two boarding school annual reviews, between 14 and 18 (15+ and 16+), seeing our son alone for one hour each time, to get the feel [of him] and become familiar to him. He also drove down with us, to get to know us (95 miles). When our son was suddenly excluded from school at 17, the social worker visited our house, again spending time alone with him, and we rushed forward the plans for transition. Our son was relaxed, as he knew and trusted the guy. He transferred to a local horticultural training scheme within four months.* (ALLARD2009, p. 3)

However, others spoke about a lack of continuity in social services personnel and of a named contact during transition (BERESFORD2013, DITTRICH2011). Parents and carers described the loss of support from their key worker as 'quite extreme' particularly given that it coincided with the lack of a generic specialist within adult health care, and the perception that adult social services offered more reactive and passive support relative to the proactive support offered by children's services (BERESFORD2013).

Residential care: short breaks

Involvement of, and support for, family and carers

Parents and carers described an unmet need for respite services (BROWN2012, BURROWS2010, CASSIDY2008, DITTRICH2011, DYMOND2007, HALL2010, MEIRSSCHAUT2010, OSBORNE2008):

> *I'm absolutely desperate for respite care and I'm not receiving it.* (OSBORNE2008, p. 319)

Siblings also felt that their parents would benefit from respite services:

> *Someone could help my mum by taking my brother out so she can spend time with other people.* (DITTRICH2011, p. 65)

Parents and carers described the challenge of accessing respite services:

> *I had to fight to get respite when [child] was little, really fight.* **(**WITTEMEYER2011, p. 44)

Those who had received respite services said that they greatly reduced their stress (HUTTON2005, PHELPS2009):

> *Respite services have been a godsend in terms of our stress and coping.* (HUTTON2005, p. 186)

Siblings also described positive experiences of respite services; they were able to enjoy a day out with their parents, while the child with autism also had an opportunity to do something they enjoyed:

> *He had someone called Lana who took him out on days out which was fun for him, and gave us as a family some time to go to places that maybe he wouldn't like to go. Like just as a family, without him, so that he would go where he liked to go, and us where we liked to go. Like just daytrips.* (PETALAS2009, p. 392)

Residential care: long term

Effective treatment by trusted professionals

Parents and carers expressed mixed views about the impact of a group home on the child or young person with autism. Some said their child was happier living in a group home rather than the family home:

> *For me, it's very, very important that he's pleased, but still more important that he is taken care of properly, although seeing that he's pleased is almost as important. He's making more progress both in the group home and at school than he is at home.* (BENDERIX2007A, p. 636)

Others were dissatisfied, wanting more physical activities and an educational ethos (BENDERIX2007A). Parents and carers also discussed the importance of residential care staff understanding autism (DITTRICH2011).

Attention to physical and environmental needs

Parents and carers pointed out the importance of residential care taking into account the need for privacy and quiet space (DITTRICH2011).

Involvement of, and support for, family and carers

Parents and carers identified residential care as an unmet need (DYMOND2007). For those whose children were in a group home, a positive impact on reducing their own stress was described (BENDERIX2007A). Parents and carers were also positive about the contact they had with other parents through meetings organised by the group home (BENDERIX2007A).

Siblings talked about the potential benefits for them that their sibling being in a group home would bring, including the opportunity to enjoy activities undisturbed, not to worry about personal safety, to enjoy more time with parents; parents were seen as benefitting too (BENDERIX2007B).

Continuity of care and smooth transitions

Parents and carers spoke about concerns regarding the impact of inconsistency of group home staff on the child or young person:

> *I want to have complete control over what's being done, both during the day and at night. They may think I'm asking for too much, but it's my child and he's only 11 years old. There are too many people. I've asked for a schedule of who's working when, but I never get one. My son feels sad when we return there, and I don't feel good at all if he doesn't feel good. I don't feel confident about it anymore.* (BENDERIX2007A, p. 637)

Educational setting: mainstream

Emotional support, empathy and respect

Parents and carers described the child or young person as experiencing high levels of anxiety in school (KIDD2010, REID2011):

> *Our problem is that our son is too bright for special school and too stressed for mainstream school. Although he is bright he cannot cope with the stress of mainstream school and his teachers do not understand autism.* (REID2011, p. 7)

They described how this anxiety frequently culminated in a stress response at the end of the day as children managed to 'hold it together' at school but had a 'meltdown' when they got home (JONES2008C, KIDD2010):

> *…sometimes he'd come home from school and after he'd yelled and screamed and threw his bag and punched me he'd then go to bed and cry himself to sleep and sleep for 2 to 3 hours. And that often happened every day.* (KIDD2010, p. 264)

Effective treatment delivered by trusted professionals

Agreeing educational provision

Some parents and carers thought the process of agreeing an educational provision was bureaucratic (TISSOT2006):

> *The system seems to be a lumbering administrative sequence rather than a genuine attempt to meet the needs of the child.* (TISSOT2006 [Tissot, 2011], p. 8)

> *…to get an educational provision for any autistic child is a nightmare.* (TISSOT2006 [Tissot, 2011], p. 8)

Parents and carers also expressed frustration at the length of time it took to secure educational provision for the child or young person (TISSOT2006, WEBSTER2003):

> *The statementing process was tortuous and if I had to change anything about this early period it would be speeding this up…. We only got things to move along by phoning the LEA office every week from October to March.* (WEBSTER2003, p. 39)

Some described the struggle to agree upon acceptable educational provision (BROOKMANFRAZEE2012, DILLENBURGER2012, DITTRICH2011, TISSOT2006, WITTEMEYER2011):

> *Only parents with dogged determination and unlimited stamina will ever succeed for their children in the current system.* (TISSOT2006, p. 78)

They emphasised the importance of considering the needs of the child or young person when deciding on educational provision (DYMOND2007, FISH2006, WADDINGTON2006), and when this had happened they were positive about the experience:

> *Ours has been a positive experience. The local authority provided a support worker for the family. A local primary allowed us a trial place in a mainstream nursery as part of the assessment process. Nobody has ever made a 'guesstimate' of our daughter's potential they are only concerned with meeting her needs now and planning [for the future].* (TISSOT2006 [Tissot, 2011], p. 9)

Inclusion

Parents and carers felt that inclusion was positive in the opportunities it offered for the child or young person with autism to mix with typically-developing peers (DYMOND2007, GREY2010, TISSOT2006):

> *Ideally mainstream is the best because an autistic can emulate normal children.* (TISSOT2006 [Tissot, 2011], p. 9)

However, parents and carers felt that real inclusion often did not occur in mainstream schools (DYMOND2007, TISSOT2006):

> *The isolation of child and parent in mainstream school is awful.* (TISSOT2006 [Tissot, 2011], p. 9)

Parents and carers also thought inclusion was inadequately prepared for, with children finding the experience of going into mainstream classes very difficult (GREY2010, JINDALSNAPE2005).

Parents and carers explained that the child or young person often did not want the additional attention that support in school brings (DITTRICH2011) and described positive experiences of whole class teaching strategies that included lessons applicable to all students but particularly helpful for children with autism:

> *In my son's school they have values education which includes information about values such as being a friend, respect, resilience, and basic playing nicely guidelines. This has been great for him as everyone is leaning and the information he needs to understand – the social stuff. The teacher uses role play, comic strips in words or pictures and stories. We have discussed using learning stories as a class activity also.* (BEVANBROWN2010, p. 17)

Exclusion

Parents and carers expressed frustration that the child or young person was often excluded from school activities, such as trips:

> *Our son was excluded from his school trip (with all the subsequent effects of that exclusion on his school work). We were told that it was 'too much of a risk' to take [him] to the seaside, despite an offer of parental accompaniment on the trip.* (REID2011, p. 8)

They described how inadequate provision for their child meant they had to pick them up at lunchtime or be permanently 'on call' (DILLON2012, REID2011, STARR2012):

> *My family and I have been on tenterhooks since our son started primary school. At the ring of the phone I have become nervous, wondering whether I shall be asked to pick up my son. I am unable to plan anything as I am expected to be 'on call' all day.*

> *The phone rings, I am expected to drop everything and pick him up by 12 o'clock as there is NO provision for him… I have become reliant on medication to deal with my situation [and] am unable to work.* (REID2011, p. 8)

Individual education plans[14] and SEN statements

Parents and carers expressed a need for better individual education plans and for more regular review of them (STARR2001). They also noted that the quality of the individual education plan was dependent on the experience of the teacher:

> *I ended up at the end of year two with an eight or nine page tightly written dossier from teacher… Whereas for [my other child] I barely got two pages with twenty words.* (GREY2010, p. 115)

As with access to other supports, crisis often seemed to be the eligibility threshold for statementing:

> *I have been told that my son would not be granted a Statement as he is not severe enough. He has an IEP [individual education plan] but now nearing the end of reception year is already falling behind his peers. My understanding of the system is that we have to wait for him to fall a lot further behind before a statement would be considered. Unfortunately once he has slipped that far back he is unlikely to ever catch back up again. I fear he is just going to slip between the cracks.* (DITTRICH2011, p. 126)

Parents and carers discussed how individual education plan objectives, statements or intervention plans were often not implemented and described a lack of accountability (DITTRICH2011, DYMOND2007, FISH2006, KEENAN2010, PHELPS2009, REID2011):

> *It is in the paperwork and on the recording. It is written in the minutes, but it's just never done. It is a meeting they have to have, but really a lot of it is never really carried through.* (FISH2006, p. 62)

Lack of educational support

Parents and carers expressed a need for more academic support for the child or young person, including more teaching assistant time (BROWN2012, BUNDY2009, BURROWS2010, CAMARENA2009, CASSIDY2008, STARR2001, WITTEMEYER2011). Where academic accommodations were made they were regarded positively by parents and carers (BEVANBROWN2010, DITTRICH2011, JONES2008C, TOBIAS2009). However, they described how children with intellectual ability within the normal range were often not considered to be eligible for a SEN statement, which might mean that they were not able to access any academic support even though it was needed (DITTRICH2011, GLAZZARD2012, JONES2008C):

[14] Referred to as 'individualised education programs' in the USA.

> *Children with Aspergers syndrome are deemed as having 'mild autism', and because there is no specific learning need are classed as not needing a statement. This is a completely wrong attitude, most children with Aspergers syndrome have communication and socialising difficulties as well as sensory, mobility and coordination issues to name but a few. This means these children need specific support while learning and if this is not provided at the crucial stage in life, they are likely to fail and be a burden to the state in adulthood.* (DITTRICH2011, p. 126)

Individualised teaching

Parents and carers discussed the unmet need for teaching strategies to be individualised to the strengths and weaknesses of the child (BEVANBROWN2010, DITTRICH2011, JONES2008C, WITTEMEYER2011) and expressed dissatisfaction at the lack of individual and autism-specific modifications to teaching and academic supports (BREWIN2008, DILLON2012, KIDD2010, STARR2012):

> *…they refused or were unable to modify the curriculum to suit the needs of an autistic child, um they say on an ad hoc basis they have some success with it but they don't because the kids learn by rote, computer, most of them want to work on a computer and work has to be closed sort of questions, any concept of imaginative work is really difficult for them… so when you ask someone to modify it they simplify it, they don't modify it.* (KIDD2010, p. 263)

Conversely individualised treatment was described positively (BEVANBROWN2010, BREWIN2008, DILLON2012, SPANN2003, TOBIAS2009):

> *They allow Stephen to be Stephen, they don't try to slot him into with the other kids. … And, uh, there's certain things that, you know, you have to do differently. … And I think that in a way, it's a way of showing, the teachers of showing Stephen that they respect him as an individual. (parent of a 4-year-old boy with Asperger syndrome)* (BREWIN2008, p. 248)

Professional understanding of autism

Parents and carers emphasised the importance of teachers and teaching assistants having an understanding of autism (BERESFORD2013, BEVANBROWN2010, BREWIN2008, BROWN2012, BUNDY2009, BURROWS2010, DILLON2012, DITTRICH2011, DYMOND2007, GLAZZARD2012, GREY2010, HALL2010, JINDALSNAPE2005, JONES2008C, KEANE2012, MACKINTOSH2012, OSBORNE2008, PARSONS2009A, REID2011, RENTY2006A, SPANN2003, STARR2001, STARR2012, STONER2005, TIPPETT2004, WADDINGTON2006, WHITAKER2007, WHITTINGHAM2006). They spoke about how teachers failed to understand their child's uneven cognitive profile, and thus had unrealistic expectations in some areas:

> *Because he could do certain things in academics, they expected more out of him.* (KIDD2010, p. 263)

Inappropriate or inadequate behaviour management strategies were also described (DILLON2012, FISH2006, HUMPHREY2008A, KIDD2010, SPANN2003, STARR2012, WHITAKER2007):

> *Because he was having meltdowns all the time and because they weren't managing his environment or modifying the curriculum to suit his needs, they were still trying to get him to write with a pencil, still trying to get him to play football games, still trying to get him to accept relief teachers without prior warning. All the things that set them off they continued to do and they had a behaviour management plan and there were consequences for his bad behaviour but they were not willing to change and it was always like, we'll cure him of this by giving him a string of consequences or punishing him.* (KIDD2010, p. 265)

Attention to physical and environmental needs

Parents and carers found visual schedules in the educational environment particularly helpful for their children (BREWIN2008, STONER2005). They also talked about how the lack of lunch or break-time activities for the child at school was a cause of concern (BEVANBROWN2010, HAY2005):

> *Lunchtime is the worst, no friends and being teased, no activities. They just hide where they think it is safe, near the SEU [Special Education Unit].* (HAY2005, p. 147)

Parents and carers discussed unmet environmental needs including provision of a quiet room and more space in the classroom (BERESFORD2013, STARR2001, WEBSTER2003). However, where the following environmental modifications had been made parents and carers were positive: changes to room colour and smell (PARSONS2009A); changes to the type of paper provided (DILLON2012); creation of a quiet space in the classroom or school (BEVANBROWN2010, TOBIAS2009); and opportunity for regular breaks from the classroom (BEVANBROWN2010):

> *The dining room was painted yellow – he cannot deal with this colour due to his sensory sensitivities and he started to self harm – we discussed this and the dining room was repainted. He also had a problem with the smell of some plants they planted and started to self harm so again this was sorted out ASAP – because they understand him and they listen to me.* (PARSONS2009A, p. 48)

Parents and carers spoke about the differences between primary and secondary school and the problems that the child or young person had in adjusting to the noisy and busy secondary school environment and to the changing of rooms and teachers. Such negative experiences imply that support for environmental change might be an important aspect of transition planning (DILLON2012).

Involvement of, and support for, family and carers

Parents and carers spoke about their lack of understanding of the individual education plan statementing process or 'admission, review and dismissal' meetings

and how this made them feel distanced (FISH2006, KEENAN2010, LILLY2004, STONER2005). Some reported positive experiences of using external consultants for negotiating in individual education plan meetings (FISH2006, REID2011, STONER2005):

> *Yes, they were more respectful. I thought when my advocate was present.* (FISH2006, p. 61)

Parents and carers described feeling more generally excluded from the education of their child (FISH2006, GREY2010, KEENAN2010, LILLY2004, PHELPS2009, STARR2012, TIPPETT2004):

> *Our responsibility (to the school) as parents is to keep communication lines open and assist the school in educating our child appropriately. I have a right as a parent to have input and participate in (my daughter's) education, but my right is often violated. The school doesn't listen to me.* (LILLY2004, p. 37)

They expressed a wish to be treated as equal contributors to the child or young person's educational planning (DILLON2012, DITTRICH2011, REID2011), and spoke positively about experiences where they had been included and listened to (BEVANBROWN2010, RENTY2006A, SPANN2003, STARR2001, STARR2012, TOBIAS2009, WHITAKER2007):

> *I think the extensive personal experiences that we have with our child are very important. The teacher says that if we have a different opinion, we may always suggest alternatives for the benefit of our child's development. We act in close cooperation.* (RENTY2006A, p. 379–380)

Parents and carers spoke about the need for honest communication with the school, and highlighted this as important because of a lack of communication from their child about their school day (BUNDY2009, DANN2011, RENTY2006A, STONER2005, TIPPETT2004, WITTEMEYER2011) and because it built trust with the school (BEATSON2002, GREY2010, LILLY2004, STONER2005):

> *My major concern is communication between home and school. Pete won't tell me what is happening. I can only tell by his behaviour.* (TIPPETT2004, p. 15)

Lack of communication with the school was mentioned (GREY2010, HAY2005, JINDALSNAPE2005, SPANN2003, STONER2005, WHITAKER2007). Conversely, parents and carers discussed positive experiences of using a daily home-school diary (BEVANBROWN2010, STONER2005, RENTY2006A, WITTEMEYER2011):

> *We have daily contact with the teacher either by an exercise book or by our son's diary. I am very pleased with that. The teacher writes down how D. is doing and in which activities he participated. That's very important. If there are problems in school, the teacher writes how she has dealt with it.* (RENTY2006A, p. 379)

However, some felt that communication with the school was not always balanced; parents and carers described it as predominantly negative and perceived that the responsibility for solving the problem was placed on them (DILLON2012). More generally they talked about feeling blamed for the difficulties experienced by their child through interactions with educational staff:

> *They would intimidate me and act like I was doing something wrong. 'Are there any changes going on?' (individual education plan team members would ask). They would always try to make it like that there was something wrong with the home, and there really wasn't. They pointed fingers at me, and they asked 'did you do drugs when you were pregnant? Did you drink alcohol when you were pregnant? You and your husband?'* (FISH2006, p. 61)

Parents and carers reported finding the child or young person's school experience very stressful for them (KIDD2010), particularly when they felt they always needed to challenge the school in order to gain adequate services (CAMARENA2009, GREY2010, JONES2008C, REID2011, SANSOSTI2012, STARR2001, TISSOT2006).

Continuity of care and smooth transitions

Parents and carers spoke about problems for the child or young person caused by high turnover of educational staff:

> *Currently, the school has to deal with a large turnover of staff. It always takes a long time for our son before he becomes acquainted with these new people.* (RENTY2006A, p. 380)

They spoke positively about a carer-teacher record of the child's strengths and weaknesses, which was shared with the new teacher at the end of the year (STONER2005).

Parents and carers emphasised that direct skill development, preparation for transition (including preparing for the new social environment) and sharing information between old and new teachers were essential elements for easing the transition from primary to secondary school (KEANE2012).

Mixed views of the post-school transition planning process were described. Some parents and carers were positive about preparation for transition delivered by their child's school, including training in daily living skills to enable greater independence, arranging work experience placements and the opportunity for pre-visits to further education (BERESFORD2013). Where a key worker had coordinated transition, very positive experiences were described (BERESFORD2013). Parents and carers were also positive about opportunities to collaborate with the school in developing and reviewing transition plans (BERESFORD2013).

Conversely, others described inadequate transition planning for both leaving school (BERESFORD2013) and for the primary to secondary school transition

(DILLON2012). Parents and carers of young people leaving school expressed frustration at the lack of joined-up services and the need to find information for themselves through the internet or word-of-mouth rather than being provided with comprehensive information about post-school options:

> *I came away from [the meetings] worried to death what we're going to be doing with [the young person] later on. I never came away feeling confident, no.* (BERESFORD2013, p. 95)

Moreover, when formal support and transition planning were inadequate, parents and carers spoke about the additional strain that had been placed on them, and described feeling inadequately informed to fulfil this role themselves:

> *…absolutely stressed to the max, I was just crying all the time… it almost tipped me over the edge I think when I look back… and it was unnecessary.* (BERESFORD2013, p. 92)

The lack of transition support (from both primary to secondary school and secondary to further education) was emphasised for children and young people with autism who did not have a SEN statement (BERESFORD2013, DILLON2012):

> *…We were just left to fend for ourselves really. Unless there was things being done behind the scenes that I didn't know anything about… he was just the same as everybody else, he wasn't a child with special needs.* (BERESFORD2013, p. 97)

Even post-transition to further education, families and carers talked about a lack of adequate support, and attributed this to failures to implement transition plans and lack of professional understanding of autism:

> *…we've discussed all those sort of things that can be done, but when it comes to putting what we've discussed into practice it doesn't always happen the way it was discussed. So I think, to some extent, the impression I get is that they don't particularly understand Asperger's as well as I think they could do and should do.* (BERESFORD2013, p. 107)

Parents and carers also described negative experiences associated with the young person moving from further education into work or unemployment. Parents and carers of young people who were considered ineligible for adult social care support and were not in further education, talked about them having been 'lost to the system' as there was no support to help them find employment:

> *I think [son] needs more of a life than he is having at the moment and he's not got that opportunity cos there's nothing that's there that they can offer him.* (BERESFORD2013, p. 108)

Parents and carers also talked about how the strain of having the child or young person at home for long periods post-education resulted in them needing greater support in their caring role:

> *…it would be nice to, for me to have more support because… you're having to, people don't always understand what it's like to live with, with somebody like that, and it's always really on my shoulders to take him out and do different bits, but if I don't do it nobody will.* (BERESFORD2013, p. 109)

Educational setting: specialist

Effective treatment delivered by trusted professionals

Parents and carers discussed the need for greater availability of specialist playgroups and schools (CASSIDY2008), and particularly highlighted problems with accessing specialist provision for children and young people with autism without a coexisting learning disability:

> *…because he is at the able side of the spectrum, we won't be able to get him into a special school.* (WADDINGTON2006, p. 155)

Generally, parents and carers expressed satisfaction at the specialist educational provision for their child (JINDALSNAPE2005, REID2011) but highlighted the importance of regularly reviewing the educational provision to ensure that it continues to fit the developing needs of their child (JINDALSNAPE2005).

Some expressed a need for more regular review of the child or young person's individual education plan (PRUNTY2011), while others were satisfied with the schools' procedure for monitoring progress :

> *Very well monitored as far as I'm concerned.* (GREY2010, p. 115)

> *There's a formal psychological assessment done every year.* (GREY2010, p. 115)

Parents and carers emphasised the importance of teachers and teaching assistants having an understanding of autism, and were satisfied that specialist educational provision met this need (DITTRICH2011, GREY2010, JONES2008C, RENTY2006A, STUART2006):

> *The teacher has a lot of knowledge of ASD and that is very important. That is one of the advantages of attending a specialized school: they know what our son needs and have the know-how to respond to his needs.* (RENTY2006A, p. 380)

However, this positive experience was not universal with some parents and carers suggesting that lack of professional understanding and subsequent inappropriate treatment were not problems restricted to a mainstream education environment (DITTRICH2011, JONES2008C):

> *We had to fight to be allowed to escort our child into school so he could avoid the teenagers he was afraid of. This is a special school that should understand and proactively make suggestions. Even here teachers don't understand… Even when we communicate with teachers strategies that we pass on are forgotten... can't do PE- too chaotic/noisy etc- school agreed to Yoga- after 2 weeks back in PE! Chaos ensued, parents had to call repeatedly to ensure Yoga instead of PE.* (DITTRICH2011, p. 139)

Some parents and carers reported positive experiences of feeling involved in the education of their child (STUART2006), while others felt that their relationship with the school was not very good and would be improved by the school listening to and working with them (JONES2008C).

Siblings spoke positively about the specialist education their sister or brother was experiencing:

> *You know, I'm glad he can go to that special school for children like him. The teachers there know exactly how to treat him. (11-year-old brother of boy with autism)* (MOYSON2011, p. 49)

Families and carers expressed a desire for better facilities (KOYDEMIROZDEN2010) and a need for more academic support, including more individual and less group working (KOYDEMIROZDEN2010, STUART2006).

Involvement of, and support for, family and carers

Parents and carers expressed a desire to be more involved in the individual education plan process (PRUNTY2011) and some felt excluded from the child or young person's education (GREY2010, PRUNTY2011):

> *I also feel that parents should have a lot more input into their kids education and that if we have an objection…that should be taken on board.* (GREY2010, p. 120)

However, others were satisfied with their involvement and attributed this to the greater attention their child received in the smaller classes in specialist school:

> *In mainstream school there are 30 children, here only 7. The attention is different. You can't compare.* (WITTEMEYER2011, p. 43)

Parents and carers spoke about the need for regular meetings with the school (KOYDEMIROZDEN2010) and discussed positive experiences of having daily communication with staff (STUART2006). Parents and carers also expressed satisfaction with the school's methods for monitoring progress and the opportunities they had to discuss and be involved in the review (GREY2010, WITTEMEYER2011):

> *I feel like you can come here [special school] and talk and stay as long as you like.* (WITTEMEYER2011, p. 43)

However, some felt that communication with the school was not always honest or balanced, and sometimes 'rose tinted' (GREY2010, REID2011):

> *Now he is at special school they seem to cover up most things like poor behaviour and don't contact me like they did in mainstream, where they were in constant touch. I only find out he's done something months later and don't feel we are working together on any issues.* (REID2011, p. 19)

Parents and carers also spoke about involvement in the child or young person's education being restricted if they had been previously critical of the school:

> *The school closes ranks when you criticise and then stops communicating effectively.* (JONES2008C, p. 33)

Continuity of care and smooth transitions

Parents and carers discussed positive experiences of formal transition planning for moving from an ABA school to mainstream education (GREY2010):

> *Yes there is a written plan on how we can achieve that and it's a slow progression.* (GREY2010, p. 119)

Parents and carers described positive experiences of the school arranging for 'post-16' or 'options' evenings and 'taster days' in order to prepare the young person for post-secondary school transition (BERESFORD2013). Independent living skills training provided by special schools was also highlighted as a useful preparation for transition (BERESFORD2013).

Educational setting: home education

Effective treatment delivered by trusted professionals

Parents and carers discussed how stress and anxiety had motivated them to home educate and spoke of the beneficial effects of this decision on their child (KIDD2010, NASUNPUBLISHED):

> *…anxiety is less because he's at home… not being bullied… he's happier at home.* (KIDD2010, p. 265)

They spoke about how much easier it was to individualise the child's education at home, including the ability to schedule regular breaks and solitary time (KIDD2010).

Involvement of, and support for, family and carers

Parents and carers said that the responsibility for sourcing teaching resources placed an additional strain on them:

> *I have to do a lot of research on what will work with them ... that is time consuming.* (KIDD2010, p. 267)

Some also expressed a wish for educational support to help in home educating but had found it difficult or impossible to obtain (CASSIDY2008, KIDD2010, NASUNPUBLISHED, REID2011):

> *…looking at it from a teaching point of view. If you are a teacher in a school, at recess and at lunchtime you get together with the other teachers and can say, 'I'm having a problem here' or 'where could I find…?' So there is a huge amount of support in the school situation that you don't have as a homeschooler… I've needed it, it's not available. Um, I need it now. I keep ringing up and saying 'help me, help me!'* (KIDD2010, p. 268)

Parents and carers spoke about the sense of empowerment that home education had given them (KIDD2010):

> *I think it's more than what I thought. When people say 'Oh it must be so hard' I go 'No it's a piece of cake compared to the futile fights I was wasting my time on with school'. I've realised I've done a 360 degree and all that effort has been put into something so positive, I think it's more than I could ever have hoped for.* (KIDD2010, p. 269)

Other benefits of home education included closer family relationships (KIDD2010):

> *It's spending that time and I think just getting that closeness back with your child too ... Sometimes I felt that that was being lost a bit too.* (KIDD2010, p. 270)

However, funding home education was described as a burden (KIDD2010):

> *Huge, huge financial costs...* (KIDD2010, p. 269)

All points on the pathway

Effective treatment delivered by trusted professionals

Parents and carers talked about an unmet need for in-depth professional understanding of autism (CASSIDY2008, PHELPS2009). They spoke positively about services where they felt that their child or young person was treated as a 'person' and not as a 'problem' (DITTRICH2011).

Involvement of, and support for, family and carers

A desire to be treated with respect by professionals was expressed by parents and carers (DITTRICH2011, KEENAN2010), and negative experiences where they did not feel they had been respected were described (DILLENBURGER2010, DITTRICH2011, TISSOT2006):

> *Professionals talk to me as though I have no sense, very patronising.* (DILLENBURGER2010, p. 18)

They also described being treated like fussy or over-anxious parents by professionals (CHELL2006) or feeling blamed for the child or young person's difficulties:

> *The psychologist treated me like it was my fault. He said my child's behavior was because of his home environment.* (HUTTON2005)

It was also felt that cultural differences were not always respected by professionals:

> *[The system] walks all over poor, immigrant parents… who do not speak good English… I take their insults because I want to help my child… but reality is they are not helping us.* (JEGATHEESAN2010, p. 808)

Parents and carers expressed a desire for professionals to be more open-minded and take their opinions and preferences into account (CARBONE2010, OSBORNE2008):

> *…a much more open approach, and a much more honest approach.* (OSBORNE2008, p. 320)

4.2.8 Quantitative studies considered for service user experience

Two hundred and thirty two studies met the eligibility criteria for full text review. Ten of those studies met criteria and were included in the review. Four studies examined the experience of service users only (FALKMER2012 [Falkmer et al., 2012]; HUMPHREY2010A [Humphrey & Symes, 2010], PISULA2011 [Pisula & Lukowska, 2011], WEBB2004 [Webb et al., 2004]). Six studies examined the experience of both service users and carers (BERESFORD2013, CHEN2012 [Chen & Schwartz, 2012], DITTRICH2011, REID2011, WEIDLE2006, WITTEMEYER2011). All studies were published between 2001 and 2013, either online or in peer-reviewed journals.

The characteristics of the included primary quantitative studies for service user experience of care are summarised in Table 14 and the studies from which data was extracted categorised according to the key themes are summarised in the experience of care matrix in Table 15 and Table 16.

Table 14: Study information table for included quantitative studies of the experience of care of children and young people with autism

	Primary quantitative studies of the experience of care of children and young people with autism
Included studies	K = 10
Sample size	10-295 (mean: 56)
Autism population (Axis I/II disorders)	100% autism spectrum disorder (K=1) 100% Asperger's syndrome (K=2) 12% high functioning autism, 46% Asperger's syndrome, 32% autism and 15% autism spectrum disorder (K=1) 30% autism, 44% Asperger's syndrome, 7% high-functioning autism, 4% waiting for diagnosis and 15% other (K=1)

	Not reported (K=1)
Mean age (years)	7-25 (mean: 11.7)
Sex (percent female)	0-33 (mean: 15)
Focus of study	40% experience of education/school 20% experience of treatment/intervention (peer support/social skills group) 20% experience of bullying 10% experience of information and support 10% experience of transitions
Data collection method	40% survey 30% online survey 20% face-to-face questionnaire 10% postal survey
Setting	40% school 10% postal survey 10% community building 40% not reported
Country	50% UK 20% US 10% Sweden 10% Poland 10% Norway

4.2.9 Summary of themes from the quantitative analysis of service user experience

Information and support

Clear, comprehensible information and support for self-care

Lack of information

A survey based in Hampshire of children and young people with autism asked for their views on the availability of information for people with autism in the area (DITTRICH2011), specifically whether they agreed that there was adequate information available to them about services and support. More than 50% of the sample reported that they disagreed or strongly disagreed with this. In addition, more than 60% of the sample felt that they only received information related to autism if they asked for it, suggesting that it was not readily available.

Desired support

When asked to express what type of services they felt would be of use to them, young people with autism most commonly suggested services that could offer guidance about housing or general advice, both of which were rated as very useful by 50% of the sample (DITTRICH2011). Other services that were endorsed included venues that could act as a drop-in centre with an 'open-door' policy for people with autism and places that could provide information and advice about employment. In the same study, 37.5% of participants strongly endorsed the idea of having *one* location to which that they could go to get all the advice that they need. None of the people surveyed disagreed or strongly disagreed with this idea.

Table 15: Matrix of quantitative evidence for service user experience (part 1)

Dimensions of person-centred care	**Key points on a pathway of care**							
	Access	**Information and support**	**Assessment and referral in crisis**	**CAMHS**	**Transition (CAMHS to AMHS)**	**Community services (for example, leisure programmes)**	**Therapeutic intervention**	**Primary care**
Involvement in decisions and respect for preferences	-		-	-	-	-		-
Clear, comprehensible information and support for self-care	-	DITTRICH2011	-	-	-	-		-
Emotional support, empathy and respect	-		-	-	-	-		-
Fast access to reliable health advice	-		-	-	-	-		-
Effective treatment delivered by trusted professionals		DITTRICH2011	-	DITTRICH2011	-		DITTRICH2011 WEBB2004	DITTRICH2011
Attention to physical and environmental needs	-		-		-	-	DITTRICH2011	-
Involvement of, and support for, family and carers	-		-	-	-	-		-
Continuity of care and smooth transitions			-	-		-		-

Table 16: Matrix of quantitative evidence for service user experience (part 2)

Dimensions of person-centred care	**Key points on a pathway of care**							
	Secondary care	**Social care**	**Residential care: short breaks**	**Residential care: long term**	**Educational setting: mainstream**	**Educational setting: specialist**	**Educational setting: home education**	**Themes that apply to all points on the pathway**
Involvement in decisions and respect for preferences	-	-	-	-	-	-	-	-
Clear, comprehensible information and support for self-care	-	-	-	-	-	-	-	-
Emotional support, empathy and respect	-	-	-	-	HUMPHREY2010A FALKMER2012 PISULA2011	-	-	-
Fast access to reliable health advice	-	-	-	-	-	-	-	-
Effective treatment delivered by trusted professionals	DITTRICH2011	-	-	-	DITTRICH2011 REID2011 FALKMER2012 PISULA2011 CHEN2012	DITTRICH2011	-	-
Attention to physical and environmental needs	-	-	-	-	-	-	-	-
Involvement of, and support for, family and carers	-	-	-	-	-	-	-	-
Continuity of care and smooth transitions	-	-	-	-	DITTRICH2011	BERESFORD2013	-	-

Therapeutic intervention

Effective intervention delivered by trusted professionals

Satisfaction with interventions

Following an intervention investigating peer-support groups for young people with Asperger's syndrome, 21of the participants fed back about their experiences of the intervention (WEIDLE2006). The intervention was based on the TEACCH system (Schopler et al., 1995) and included the basic principles of understanding autism, understanding the child through the use of assessment, using clear instructions and expectations, and ensuring motivation by focusing on participants' special interests. Three quarters of the participants rated their satisfaction as high or very high, with only one feeling dissatisfied. While only 24% reported high motivation to continue at the start of the programme, by the end this figure had increased to 62%.

Another intervention, focusing on teaching social skills to ten 'high-functioning'[15] males, also received positive feedback (WEBB2004). The five skills taught ranged from giving compliments to others to exercising self-control. Just over half of the participants reported that they were very satisfied with what they had been taught. Similarly, 50% indicated that, following the intervention, they were very satisfied with their perceived ability to handle difficult situations and 60% felt very satisfied with their ability to get along better with others. Seventy percent of participants believed that others would benefit from completing the group.

In an evaluation of experiences of paid work, services users' were asked to identify what had contributed to this being more positive for them (DITTRICH2011); employers and colleagues understanding autism was valued by around 85% of the sample. Two-thirds also agreed that paid work was a better experience if things were explained to them in ways that they understood and 43% endorsed having a specific person to speak to when they were experiencing work-related problems.

When children and young people were asked their views on the types of support that would be useful to them, support groups specifically for people with autism were endorsed the most, with 65% of participants rating this as useful or very useful (DITTRICH2011). A large proportion (57%) also felt that social groups specifically for people with autism would be useful or very useful. Befriending services and social groups – not specifically for people with autism, but age appropriate – were rated as very or quite useful by 55% and 39% of young people with autism, respectively.

[15]Those with expressive and receptive language IQ scores of more than 70 and who were spending at least one lesson a day in mainstream education.

Primary care

Effective treatment delivered by trusted professionals

Satisfaction with services

Evidence of satisfaction with health services (specifically in Hampshire) was evident in one study (DITTRICH2011). The majority of feedback given by service users was positive, with the exception of experiences of health visitors. Of the six service users who had experiences of health visitors, none rated the experience as excellent, four rated it poor or very poor, and only one rated it as good. Dentists were rated most positively by services users, with 69% stating experiences were excellent or good. GPs were rated as excellent or good in 41% of the sample and as average in 41%.

Secondary care

Effective treatment delivered by trusted professionals

Satisfaction with services

Opinions about paediatricians, as reported by children and young people with autism, were mixed, and based on only a small number of encounters (DITTRICH2011). None rated their experience as excellent, just under half felt it was good and just over half described it as average. However, none rated their experience as poor or very poor.

Service users were also asked to rate their experience of general hospitals (DITTRICH2011). Fifteen provided feedback, with 7% describing general hospitals as excellent, 53% as good and 14% as either very poor or poor.

Educational setting: mainstream

Emotional support, empathy and respect

Experience at school

Children and young people with autism were asked to report on their experience of mainstream schools in a number of studies, with a particular focus on bullying and types of support they seek. Compared with children and young people with dyslexia and typically-developing controls, those with autism were likely to report more than twice as many incidents of bullying (HUMPHREY2010A). The same study found that when asked about the types of support they received (on a scale where 4 indicates high levels of support), the most commonly endorsed forms of social support were from teachers (3.23), parents (3.21) and friends (3.13). The least amount of support was received from classmates (2.66). In PISULA2011) social support from parents was most commonly endorsed, followed by teachers and peers.

A separate study asked children and young people with autism to rate their ability to communicate their needs in school (FALKMER2012). The results were mostly positive; the participants rated being able to talk to their teacher when they wanted

something an average of 4 out of 5, and being able to ask for help if they are hurt an average of 3.3 out of 4, where a higher score represents a more positive response.

Relationships at school

Children and young people with autism were also asked to express their views of their classmates in relation to inclusion and helping each other (FALKMER2012). Participants generally responded positively; where the high scores indicate a higher level of agreement, *helping* other classmates received an average score of 3.4 out of 5; *wanting* help from classmates received an average score of 3.5 out of 5 and actually *receiving* help from classmates had an average score of 3.2 out of 5. Students gave wanting to ask their classmates to join in with them a mean score of 3.5 out of 5, but actually asking to join in a slightly lower score of 3 out of 5. Similarly, students gave an average score of 3.4 out of 5 for wanting their classmates to ask them to join in, but the incidence of this happening was slightly lower (an average of 3 out of 5). During break times, wanting to spend time with classmates was rated as 4 out of 5. Actually being with classmates was rated lower at 3.8 out of 5.

Experience at school

Overall, feedback on experiences at school were mixed. In one survey of 22 students with autism, the responses were generally quite positive (FALKMER2012). For example, respondents were asked to rate their agreement with a statement saying that they spent as long as they wanted with their classmates. The average agreement score was 3.5 out of 5 (where 5 indicates strong agreement). Agreement with wanting to participate in physical education was 3.6 out of 5, and agreement with actually participating was slightly higher (4.5 out of 5). Similarly, the level of agreement for wanting to go on school outings was 3.9 out of 5, and agreement with actually going on school trips slightly higher (4.5 out of 5).

In a separate study, responses to school experiences were more negative (PISULA2011). Here, respondents rated their feelings of security at school (versus their feelings of threat) as 13.8 out of 40 (where 40 is very secure) and feeling appreciated by others at school at 14.44 out of 30 (where 30 is appreciated). The same students' tendency towards being socially isolated received a mean rating of 23.5 out of 45 (where 45 is very isolated).

In order to ascertain whether children and young people with autism were bullied or bullies within school, they were asked to provide feedback on their experiences (CHEN2012). In this sample of 33, 64% reported that they had participated in bullying others at school. The sample was then asked to rate whether they were a bully only (for example, had not been a victim of bullying themselves), a bully and a victim, or a victim only (for example, had not bullied others). Not one of the student participants stated that they were bullies only. More than a third of the sample reported being both bullies and victims of bullying and 28% reported that they were victims only. The rest of the sample reported no experiences of bullying.

Satisfaction with school

In Hampshire, 62.5% of children and young people with autism who had been in contact with the special educational needs coordinator (SENCO) in their school rated their experience as excellent or good (DITTRICH2011). However, for 25% their experience was very poor. Mainstream teachers received a more negative review, with none being rated as excellent, 27% as good and 40% as poor or very poor.

Professional awareness and understanding

One large-scale study found that just over half of the 239 service users surveyed reported that their teachers lacked understanding of autism (REID2011). The authors also noted that when students with autism were asked for examples of what they did not like about school, they often quoted teachers not understanding them, highlighting that this lack of understanding had a negative impact on their overall educational experience.

The Hampshire-based study further explored views on teacher understanding (DITTRICH2011). Children and young people with autism were asked to state whether they agreed that they were understood by their primary, secondary and further education teachers. The majority of responses about primary and secondary school teachers were that they were not understood in 52% and 47% of cases, respectively. Responses about further education teachers revealed that half of respondents felt they were not understood and half felt that they were.

Educational setting: specialist

Effective treatment delivered by trusted professionals

Satisfaction with school and professionals

Children and young people with autism provided positive feedback on their experiences of teachers in special schools; 37.5% rated their experience as excellent and 25% good, with no participants rating them poor or very poor (DITTRICH2011).

4.2.10 Quantitative studies considered for family and carer experience

Two hundred and thirty two studies met the eligibility criteria for full text review. Sixty of those studies met criteria and were included in the review. Six studies examined the experience of both service users and families/carers (BERESFORD2013, CHEN2012, DITTRICH2011, REID2011, WEIDLE2006, WITTEMEYER2011). The remaining 54 studies all focused on the experience of carers only (AHMEDANI2012 [Ahmedani & Hock, 2012], BIRKIN2008, BITTERMAN2008 [Bitterman et al., 2008], BRICKHOUSE2009 [Brickhouse et al., 2009], BROMLEY2004 [Bromley et al., 2004], BROWN2012 [Brown et al., 2012], CALLAHAN2008 [Callahan et al., 2008], CASSIDY2008 [Cassidy et al., 2008], DILLENBURGER2010, DILLENBURGER2012, DUNLAP1994 [Dunlap et al., 1994], FERRERI2011 [Ferreri & Bolt, 2011], FLYNN2010, GASPARDEALBA2011 [Gaspa de Alba & Bodfish, 2011], HANEY2012 [Haney, 2012], JONES2008C, KEANE2012, KEENAN2010, KOGAN2008 [Kogan et al., 2008], KOHLER1999 [Kohler, 1999],

KRAUSS2003 [Krauss et al., 2003], LAI2011 [Lai et al., 2011], LIPTAK2006 [Liptak et al., 2006], LITTLE2003 [Little, 2003], LUTHER2005 [Luther et al., 2005][16], MACKINTOSH2012, MANSELL2004, MILLER2012 [Miller et al., 2012], MOH2012 [Moh & Magiati, 2012], MONTES2009 [Montes et al., 2009], MORENO2008 [Moreno et al., 2008], NASUNPUBLISHED, NEWSOME2000 [Newsome, 2000], PERRY2010 [Perry & Condillac, 2010], PICKERING2005, RENTY2006A, ROWLEY2012 [Rowley et al., 2012], SANSOSTI2012, SIKLOS2006 [Siklos & Kerns, 2006], SIKLOS2007 [Siklos & Kerns, 2007], STARR2001, STARR2006 [Starr et al., 2006], STARR2012, STEIN2012, STIRLING1999, STUART2006, SWIEZY1996 [Swiezy & Summers, 1996], TISSOT2006 [one study reported across two papers: Tissot, 2011; Tissot & Evans, 2006], WHITAKER2002, WHITAKER2007, WHITE2010B [White et al., 2010], WHITTINGHAM2009, WILLIAMS2003, WONG2006 [Wong & Smith, 2006]). Apart from one unpublished study, which was provided by NAS, all studies were published between 2001 and 2013, either online or in peer-reviewed journals.

The characteristics of the included primary quantitative studies for family and carer experience of care have been summarised in Table 17 and the studies from which data were extracted categorised according to the key themes are summarised in the experience of care matrix in Table 18 and Table 19.

Table 17: Study information table for included primary quantitative studies of the experience of care of children and young people with autism

	Primary quantitative studies of the experience of care of family and carers of children and young people with autism
Included studies	K = 60
Sample size	7-2123 (mean: 248)
Mean age (years)	1-31 (mean: 9)
Sex (percent female)	9-30.4 (mean: 19)
Focus of study	23% experience of intervention 22% experience of education/school 12% experience of information/support 8% experience of healthcare services 7% experience of diagnosis 5% experience of transition 5% access to services/interventions 5% care (general) 3% access to healthcare 3% experience of bullying 3% psychological impact/coping 2% accessing information 2% after-school care
Data collection method	35% postal survey 30% survey 12% online survey 12% telephone 8% face-to-face interview

[16] Although Luther et al., 2005 met the criteria for inclusion in this review, there was no relevant data to extract and so it is not included in the summary of themes below.

	3% combination of methods
Setting	48% not reported 32% unknown (for example, postal or telephone) 15% home 1.6% academic 1.61% conference 1.6% multiple
Country	40% US 27% UK 13% Canada 4% Ireland 3% Australia 2% Belgium 2% Norway 2% New Zealand 2% Singapore 2% Spain 2% multiple

4.2.11 Summary of themes from the quantitative analysis of family and carer experience

Access

Effective treatment delivered by trusted professionals

Because of their complex needs, children and young people with autism need to utilise a wide range of services. Parents and carers reported that a large number of services outside of those that are offered through specialised education are often required, most commonly family physicians (94.9%), case managers or social workers (33.7%), respite providers (32.7%) and psychology teams (20.4%) (BROWN2012). Additional frequently-used services included paediatrics, audiology, psychiatry and speech and language therapy (BROWN2012).

Access to additional services was a major issue for parents and carers. In one study, 92% of responses to questions about access were negative (MACKINTOSH2012). In another, 14% of the 2,088 parents and carers reported that the child of young person had either experienced long delays in care or, worse, had missed out on required care altogether (KOGAN2008). The same study found that just under one third of parents and carers had experienced difficulty in obtaining referrals to required services. Elsewhere, in a sample of 152 parents and carers, 29% reported experiencing at least one problem with access (KRAUSS2003). In this survey, the most commonly reported problem was finding professionals who demonstrated the required skills and experience (18%), followed by actually obtaining an appointment (16%). Families also reported difficulties with the lack of collaboration and information sharing between the relevant agencies (16%). In addition, another study found that 69% of parents and carers felt the child or young person's needs had not been met by the services provided (MONTES2009).

Table 18: Matrix of quantitative evidence for family and carer experience (part 1)

Dimensions of person-centred care	Key points on a pathway of care							
	Access	**Information and support**	**Assessment and referral in crisis**	**CAMHS**	**Transition (CAMHS to AMHS)**	**Community services (for example, leisure programmes)**	**Therapeutic intervention**	**Primary care**
Involvement in decisions and respect for preferences	-	-	-	-	-	-	SWIEZY1996	-
Clear, comprehensible information and support for self-care	-	-	-	-	-	-	DITTRICH2011	-
Emotional support, empathy and respect	-	-	-	-	-	-	-	-
Fast access to reliable health advice	-	-	-	-	-	-	-	BROMLEY2004 LIPTAK2006
Effective treatment delivered by trusted professionals	REID2011 KOHLER1999 MONTES2009 BROWN2012 MACKINTOSH 2012	KEENAN2010 SWIEZY1996 LITTLE2003	-	DITTRICH2011 NASUNPUBLISHED REID2011	-	CASSIDY2008 LITTLE2003	BIRKIN2008 CASSIDY2008 DILLENBURGER2010 REID2011 WHITTINGHAM2009 WEIDLE2006 KOHLER1999 SIKLOS2006 WHITE2010B PERRY2010 SIKLOS2007 LITTLE2003 MILLER2012 BROWN2012 HANEY2012 MACKINTOSH2012 WONG2006	CASSIDY2008 DITTRICH2011 SIKLOS2006 KOGAN2008 LIPTAK2006 LITTLE2003 LAI2011 STEIN2012
Attention to physical and environmental needs	-	-	-	-	-	-	-	-

Involvement of, and support for, family and carers	DILLEN-BURGER2010 REID2011	DILLENBURGER2010 DITTRICH2011 FLYNN2010 JONES2008C KEENAN2010 MANSELL2004 PICKERING2005 STIRLING1999 KOHLER1999 SIKLOS2006 KOGAN2008 BROMLEY2004 MONTES2009 GASPARDEALBA2011 SIKLOS2007 BROWN2012 HANEY2012 MOH2012 LITTLE2003	-	NASUNPUBLISHED	-	-	DILLENBURGER2010 JONES2008C MANSELL2004 WHITAKER2002 WILLIAMS2003 BROMLEY2004	LIPTAK2006 BROMLEY2004
Continuity of care and smooth transitions	BROWN2012	DITTRICH2011	-	-	NASUNPUBLISHED BERESFORD2013	-	-	-

Table 19: Matrix of quantitative evidence for family and carer experience (part 2)

Dimensions of person-centred care	Key points on a pathway of care							
	Secondary care	**Social care**	**Residential care: short breaks**	**Residential care: long term**	**Educational setting: mainstream**	**Educational setting: specialist**	**Educational setting: home education**	**Themes that apply to all points on the pathway**
Involvement in decisions and respect for preferences	-	-	-	-	-	FERRERI2011 BROMLEY2004 MORENO2008 CALLAHAN2008	-	
Clear, comprehensible information and support for self-care	-	DITTRICH2011	-	-	-	-	-	
Emotional support, empathy and respect	-	-	-	-	STARR2012	-	-	SIKLOS2006 BROWN2012
Fast access to reliable health advice	-	-	-	-	-	-	-	
Effective treatment delivered by trusted professionals	CASSIDY2008 DITTRICH2011	CASSIDY2008 DITTRICH2011	LITTLE2003		CASSIDY2008 DITTRICH2011 KEENAN2010 REID2011 STARR2001 TISSOT2006 WHITAKER2007 WITTEMEYER2011 LITTLE2003 CHEN2012 KEANE2012 DILLENBURGER2012 STARR2012 BERESFORD2013	DILLENBURGER2010 DITTRICH2011 STUART2006 FERRERI2011 BITTERMAN2008 MORENO2008 STARR2006 LITTLE2003 CALLAHAN2008 ROWLEY2012 KEANE2012 BROWN2012 DILLENBURGER2012 HANEY2012	CASSIDY2008	SIKLOS2006 MONTES2009 LITTLE2003 BROWN2012 BERESFORD2013
Attention to physical and environmental needs	-	-	-	-	STARR2001 WHITAKER2007 KEANE2012	STARR2006 LITTLE2003	-	-
Involvement of, and support for, family and carers	BROMLEY2004	DITTRICH2011	DILLENBURGER2010 REID2011 SIKLOS2006 BROMLEY2004 BROWN2012 BERESFORD2013	-	DITTRICH2011 JONES2008C KEENAN2010 REID2011 STARR2001 TISSOT2006	JONES2008C BROMLEY2004 DUNLAP1994 CALLAHAN2008 DILLENBURGER2012	REID2011 STARR2006	SIKLOS2006 KOGAN2008 BROMLEY2004 MONTES2009 DUNLAP1994 BROWN2012
Continuity of care and smooth transitions	-	-	-	-	-	STARR2006 KEANE2012 5 BERESFORD2013	-	SIKLOS2006 KOGAN2008

Issues relating to long delays in accessing services were highlighted in several studies. Although figures varied, the number of parents reporting this problem ranged from 19% (AHMEDANI2012) to 55% (MONTES2009). The sample sizes on which these figures were based were 1,424 and 2,123, respectively. Most reported that these delays were caused by long waiting lists.

Families of children and young people with autism also reported problems with the limited number of services available in their local area, with 56.3% of participants experiencing a lack of availability of required services (MONTES2009). Families also communicated the challenges of trying to identify not just services, but also staff within services, that have the necessary knowledge and skills to successfully work with children and young people with autism (REID2011).

Continuity of care and smooth transitions

The evidence shows that once children and young people are receiving the relevant support, their parents and carers have concerns over the continuity of these services. Results from one survey found that a number of the needs that parents and carers felt were particularly important in relation to continuity were unmet in a large number (BROWN2012). In this study, 89.1% of families reported that receiving continuous services, rather than only during times of crisis, was important, yet this need was unmet in 74.4%. The same study, conducted in over 100 parents and carers, found that 73% felt it was important for therapies to continue throughout the summer and other school holidays. However, this need was unmet in 61%. Finally, 79% of those surveyed rated weekend and after-school activities as important for the child or young person, with 57% reporting that this need was unmet.

Information and support

Emotional support, empathy and respect

Access to information and support

In a survey of 101 parents and carers of children and young people with autism, 99% rated it an important need to have their questions about the child or young person answered honestly (BROWN2012). This was an unmet need for half of the sample.

Effective treatment delivered by trusted professionals

Access to information and support

In general, parents and carers expressed that there was not enough sharing of information about autism. This was particularly prevalent in a survey of 95 parents and carers, where all agreed that in order to better support children and young people with autism and their families, professionals working with them needed to share more information (KEENAN2010). In a separate study, families of children and young people with autism were asked about the information that was supplied to them by professionals regarding the medication that was prescribed to their child. This included what the medication was prescribed for and any potential side effects

(SWIEZY1996). The response from parents and carers was somewhat positive, with a mean score of 3.4 out of 5 (where 5 represents being given much information).

Desired support

In one study, parents and carers of children and young person with autism were asked to rate the types of support that would be useful to them. Nearly two thirds of the sample indicated that a daytime helpline facility would be either very useful (40%) or quite useful (20%); only 10% felt that it would not be useful. A slightly smaller number of participants felt that there was a need for a 24-hour helpline, with 30% rating it as potentially very useful and 25% as quite useful. Again, 10% felt that this would not be useful.

Involvement of, and support for, family and carers

Post-diagnosis information and support

The responses from parents and carers regarding post-diagnosis information and support to understand autism were somewhat mixed. In one study 37% reported that the help they received around the time of diagnosis was either 'very good', 'good' or 'quite good' compared with 49% who rated it as 'not very good', 'poor' or 'very poor' (STIRLING1999).

Parental and carer understanding of autism

Two studies found that, generally, parents and carers were positive about their knowledge of autism. In JONES2008C over 80% of the sample felt that they had either a great deal or quite a lot of knowledge about it. However, 62% would still have liked to have known more. In SIKLOS2006, the need to be educated about autism was rated as having been met 66% of the time.

A separate survey found that there are still a number of unmet needs for parents and carers when it comes to understanding the child or young person's condition (BROWN2012). Some felt it was important to receive advice and reassurance from others in order to support their child. For example, 63% of parents wanted to be told that they were making the right decisions and 48% wanted to have advice about how much to let their child do by themselves. These two important needs were rated as unmet 40% and 51% of the time, respectively. In addition, it was an important – yet often unmet – need for parents and carers to understand the way their child behaved (66% rating it as important, with 34% reporting an unmet need) and how to manage unusual behaviour or behaviour that challenges (71% rating it as important, with 48% reporting an unmet need).

Information about services and support available

The need for information about services, support and interventions to be available to families of children and young people with autism was considered important by two-thirds of parents (SIKLOS2006). However, the studies that asked parents and carers about their satisfaction with the information they had received around the time of diagnosis suggest that, generally, they were dissatisfied. They reported that

statutory providers failed to provide sufficient information in 77% of cases (KEENAN2010), particularly in relation to informing families about the multidisciplinary support available (DILLENBURGER2010). Participants also complained of a lack of information available within the local area (DITTRICH2011). Elsewhere 93% of families reported that it was important for them to have information about what services and/or interventions were available to them, yet 77% rated this as an unmet need (BROWN2012). In a separate sample of 55 participants, only 8% felt that the help they received at diagnosis was 'very good', compared with 17% who said it was 'very poor' (MANSELL2004). Parents also highlighted that it was a challenge to obtain help in identifying services once the diagnosis had been received (KOHLER1999). However, carers have been able to identify what information was useful at the time of diagnosis, including details of online resources and courses for parents to attend as well as information provided by the NAS (PICKERING2005).

Parents and carers were also able to identify what information would be useful to them in the future, including leaflets that provide a list of useful contacts within their local area, information regarding special education needs and details of parent support groups to enable them to have a support network around them (PICKERING2005). In a separate study, parents and carers expressed that they would like their GPs to have knowledge or information about alternative and complementary interventions that may be available (GASPARDEALBA2011).

Information about progress

Parents and carers of children and young people with autism reported a need for feedback on the child or young person's progress in both the educational and therapeutic setting. This was rated as important by 99% of the sample (BROWN2012), but just over half felt that this need was not being met by the service providers they were using. Elsewhere, 65% of a sample of 382 carers of children with autism reported satisfaction with the regularity of contact with the school and 57% satisfaction with the quality of communication with the school (WITTEMEYER2011).

Access to information and support

In addition to the frustrations that parents and carers reported regarding the information they received about services post-diagnosis, a number of studies highlighted that there were also difficulties in trying to access information and support in general. Just over two thirds of participants in one study 'disagreed strongly' or 'disagreed' with statements that implied it was easy to access the required information (DITTRICH2011). Less than 10% of the sample said that they 'strongly agreed' or 'agreed' with such statements. The same study asked parents and carers whether they were able to find someone who specialised in autism to support their family when needed. In this instance more than 70% of respondents disagreed compared with 14% who agreed. In a separate study, 59% of carers reported that they had not been able to access the information they required (MONTES2009) and 19% expressed that needs regarding family support services had not been met (KOGAN2008). Of the studies included, only one found that

parents were more positive about the level of information received, recording a mean score of 3.21 out of 5 (where 5 is very satisfied) (MOH2012).
Having access to information and resources about autism is of high importance to those supporting children and young people with the condition, with some rating this as the most useful source of help they had been offered (SIKLOS2007).
Information that parents and carers reported would be useful included books and websites providing more information about the diagnosis, the developmental trajectories that they can expect, and support groups (GASPARDEALBA2011).

Desired information and support

Parents (particularly mothers) and carers had a number of unmet needs in relation to the information and support that they had received. Advice around the future education of their child and the services that were available to the child were unmet in 83% and 79% respectively (BROMLEY2004). In addition, 65% of a sample of 101 parents and carers expressed that having a forum to discuss a child's disorder with other carers of children with autism was an important need. However it was reported as unmet in 45%.

Families of children and young people with autism identified a range of information and support that they would like to access. In general, there was agreement that more support should be available to families during the diagnostic process (KEENAN2010) as well as parent training and education in autism (DILLENBURGER2010). Similarly to service users with autism, carers endorsed the idea of having one place that provided all the information they needed, with 82% either strongly agreeing or agreeing with this statement (DITTRICH2011).

Professional awareness and understanding

The professionals whom parents and carers encountered had a lot of influence over the satisfaction they reported. When asked to rate which professionals provided useful information, carers rated speech therapists as most useful (17.2%), followed by school personnel (16.1%) and the multidisciplinary team (12.6%) (SIKLOS2007).
Several factors contributing to a positive relationship with professionals were reported by families, including being listened to by the professional and having their concerns taken seriously (MOH2012). Parents and carers also reported wanting to be included in decisions about the child's care and to be offered relevant information about their condition. A separate study also found that dissatisfaction with professionals and service providers came from a lack of communication with carers and a lack of collaboration among the various agencies involved in the child's care (KOHLER1999).

CAMHS

Effective treatment delivered by trusted professionals

Access to CAMHS

As with other points of the care pathway, access to CAMHS is a cause of frustration for those caring for children and young people with autism. NAS conducted an unpublished survey of 455 parents and carers of children and young people with autism, with a large focus on the experience of CAMHS. Nearly half of the sample reported having difficulty getting the initial referral to CAMHS (NASUNPUBLISHED). Once the referral had been made, 25% had to wait over 18 weeks for the initial appointment with 10% waiting between 13 and 18 weeks.

Satisfaction/dissatisfaction with CAMHS

NAS also found that 42% of parents and carers were dissatisfied with the service received from CAMHS, compared with 37% who were satisfied (NASUNPUBLISHED). In order to explore the experiences that may have led to families being dissatisfied, the responses of these families were compared with those who were satisfied. The vast majority (91%) of those who were dissatisfied reported that the planning for when their child turned 18 and moved to adult services was missing. Just over half of those who were satisfied with CAMHS reported this as a problem. In the dissatisfied group, 78% felt that at times of crises, local services had not been easily accessible, compared with just under one third of those who were satisfied. Other commonly reported problems reported by parents and carers who were dissatisfied included the belief that CAMHS and education services did not work together (75%) and the negative effect that the difficulty with accessing CAMHS had on the child's mental health (78%). The percentage of parents and carers in the satisfied group reporting those two concerns were 26% and 15%, respectively. The majority of the dissatisfied group, compared with the minority of the satisfied group, also felt that CAMHS had failed to provide support to the family when it was needed and disagreed with a statement that CAMHS understood autism as a condition.

In the Hampshire study, experiences of CAMHS were reported much more positively: 51% of 98 respondents who had had contact with CAMHS viewed their experiences as either good or excellent, compared with 21% who rated them as poor (DITTRICH2011).

Experience of CAMHS professionals

Parents and carers of children and young people with autism had mixed views on the professionals they encountered from CAMHS. Criticism of professionals came predominately in the form of their failure to work collaboratively with the school the child attended (NASUNPUBLISHED). Half of the parents in the NAS study felt that CAMHS and the school did not work well together, compared with 21% who felt that they had. However, half of the respondents in the same study were satisfied with the way CAMHS communicated with their child and felt that they showed a

good knowledge of autism. The most positive feedback came from those whose children had been supported by a member of the CAMHS team who specialised in autism; 42% endorsed statements suggesting the child's mental health was improved with the input of CAMHS. It was also this group who were more likely to say that they were satisfied with the service they received: 50% compared with 24% of those who did not have support from a professional that specialised in autism.

Transition (CAMHS to AMHS)

Continuity of care and smooth transitions

Satisfaction with transition support

One study focused on the views of parents and carers regarding support with transition from children's to adult services (BERESFORD2013). Although responses were somewhat mixed, generally carers were more dissatisfied with the support received than satisfied. For example, in terms of social care, 77% felt that their child's transition had been poorly managed, compared with 60% who felt the transition between mental health services was poorly managed. However, in the same sample, only 38% of parents reported that more help was needed in their child's transition from CAMHS to AMHS, compared with 27% who felt that they were receiving enough support in this area.

Therapeutic intervention

Effective intervention delivered by trusted professionals

Access to interventions

Parents and carers of children and young people with autism reported that they tended to base their decisions about interventions on information found in autism publications (86%), professionals within the field (85%) and information and recommendations reported by other parents (75%) (MILLER2012). There were a number of interventions that parents and carers thought were important for their child to access. The most frequently endorsed were regular behavioural and occupational therapy, which were highlighted as important by 73% of parents (SIKLOS2006); 71% of parents also felt that their child needed regular speech and language therapy. The same interventions were focused on in another survey, which also highlighted where there were unmet needs relating to this services (BROWN2012). First, 75% of carers felt that consistent behavioural therapy was important, with 62% reporting that this need was unmet. Occupational therapy and speech and language therapy were important to 63% and 51% respectively; however, these needs were reported as being unmet in 52% and 43% of people, respectively. Physical therapy was also considered important by 38% of the sample with 33% stating that their needs in this regard had not been met. In a separate study, interventions that carers felt were important for their child included training in social skills, family therapy and vocational training. In a relatively small sample (N = 25), 60% of parents reported that their child and family were not receiving the

services they required and 40% reported that they continued to need more from existing services (KOHLER1999).

Satisfaction with intervention

When parent and carers of children and young people with autism were reporting their important needs, one of the most commonly endorsed items related to being involved in their child's therapeutic care (endorsed by 99%) (BROWN2012). However, one-third of the 101 carers surveyed reported that this need had not been met.

Several studies evaluated the satisfaction of a specific group or intervention that had been written or run by the investigators. Support was found for a 'parent-training' intervention, with 86% of participants reporting that they found it very helpful (PERRY2010). One such study focused on a behavioural parent-training programme that encouraged 'positive parenting', such as using positive reinforcements and dealing with behaviour that challenges in a constructive rather than harmful way (WHITTINGHAM2009). The mean satisfaction score was 74 out of 91. The same families were also asked to provide feedback on the structure (a mix of group and individual work), which resulted in a mean score of 20 out of 25.

A further intervention where social skills were taught to young people with autism and an IQ higher than 70, received positive feedback (WHITE2010B). In general, parents and carers reported being satisfied with the programme, with particular emphasis on the content, the level of parental involvement and the fact that it gave participants the opportunity to socialise. Out of 16 parents and carers, 11 reported that they would recommend this programme to others, with only two stating that they would not. Participants went on to report that in order to improve the group, more communication between the group leaders and the parents, and the inclusion of more females, was necessary.

An early intervention programme run by a local education authority received mixed reviews from the 18 families that were involved (WHITAKER2002). As part of the programme, a 'support worker' provided ongoing home visits to deliver the NAS's EarlyBird Programme. The programme aims to support families to understand autism and show strategies to manage behaviour that challenges. Participants rated the majority of the components in the programme as either very useful or useful. However, the home visits in between sessions were reported by three families as not very useful. All but one participant reported using the approaches taught either a 'great deal' or 'quite often'.

The rest of the studies that focused on interventions did so more generally. Often respondents, the majority of whom were carers of children and young people with autism, were asked to provide feedback on the types of interventions they had encountered. When asked about which professionals had been helpful over the last 12 months, 84% of carers found the speech and language therapist helpful, compared with 5% who found them unhelpful (CASSIDY2008). Parents and carers were also

asked to rate their experience of autism-specific support, including special education facilities and home-based interventions (RENTY2006A). Of the 244 participants in this study, 59% received autism-focused support with their mean satisfaction reported as 4.12 out of 5 (5 being very satisfied).

The focus of one study was parent satisfaction of an ABA school, compared with schools where ABA is not as emphasised (DILLENBURGER2010). Just over two thirds of parents felt that the content of what was being taught in the ABA school setting was always appropriate to their child whereas just under one third felt that it was sometimes appropriate. None of the 95 parents in this sample reported being dissatisfied with their child's ABA-based education provision.

Dissatisfaction with interventions was not as frequently reported as satisfaction, with the majority of the dissatisfied comments being related to medication. In a small study with seven participants who were parents of children and young people with autism, the general consensus was that since starting their child on medication, they had observed their behaviours worsen in terms of both frequency and intensity (SWIEZY1996). The same group of parents rated their satisfaction with the changes in their child's behaviour since taking medication as 2.1 out of 5 (where 5 is very satisfied). A separate group of 64 parents expressed the view that giving 'drugs' to their child concerned them (MACKINTOSH2012). More than 70% of participants in this sample reported a negative relationship with service providers.

Other areas that caused carers to report being dissatisfied were when appointments and intervention sessions were either missed or shortened by services providers (reported by 28% participants), or when the intervention failed to meet the needs of the family involved (KOHLER1999).

Desired intervention and support

Throughout all the studies included in this section, parent and carers of children and young people with autism identified a wide range of interventions that they desired for their child. In a large study that included 295 service users and 739 carers, speech and language therapy was the intervention that participants felt was most needed, followed by befriending services and social skills training (REID2011).

The emphasis placed by parents and carers on the need for speech and language support was echoed in two other studies. In one sample of 56 participants, 20% felt that speech and language input was useful, along with behavioural interventions (20%) and family support (13%) (SIKLOS2007). Elsewhere 89% of participants surveyed expressed that a speech and language intervention was needed for their child, as well as sensory integration (82%) and support for motor skills (74%) (HANEY2012). Other areas where parents and carers felt that intervention was needed included diet (HANEY2012) and supporting healthy living (REID2011).

Complementary and alternative medicines

One study carried out in China investigated participants' experiences of a range of complementary and alternative interventions in children and young people with autism (WONG2006). Although the majority of included interventions had only been tried by a very small number of participants in the sample, there were several that were rated to have no perceived benefit; namely: aromatherapy (tried by N = 1); a caffeine-free diet (tried by N = 1); vitamin B supplements (tried by N = 1) and chiropractic therapies (tried by N = 4).

The most commonly tried interventions, which were also the ones that were considered to be the most beneficial, were: a casein-free diet (tried by N = 6; beneficial by N = 4); gluten-free diets (tried by N = 9; beneficial by N = 6); melatonin diets (tried by N = 4; beneficial by N = 4); nutritional supplements (tried by N = 4; beneficial by N = 4) and sensory integration (tried by N = 6; beneficial by N = 6). Other complementary and alternative interventions that were considered to have some perceived benefit included homeopathic remedies, massage therapy, therapeutic horse riding and music therapy.

Primary care

Much of the data around primary care has focused on dental care. However, it is not clear whether this is because this is an area where the need is greatest in children and young people with autism. It is also unclear from the data as to whether the concerns raised are only applicable to dental care, or whether these issues are applicable to other primary healthcare settings.

Fast access to reliable health advice

Access to services

A large-scale report found that almost one third of the 2,088 parents and carers surveyed reported unmet needs in relation to healthcare services (KOGAN2008). A much smaller study also found that 43% of mothers of children and young people with autism felt they had unmet needs in relation to emergency healthcare.

Access to specific primary care services was focused on in a report paying particular attention to dental care (LAI2011). A number of barriers to dental care were reported by the 568 participants included in the study. The most frequently reported were the child's anxiety in relation to dental treatment (34%) and their inability to cooperate in the surgery (30%). However, 19% reported difficulties in getting appointments for their child; 17% that no dentist was available; 14% that the time spent waiting in the surgery/office was too long for the child; and 10% that they were not told where to access dental treatment for their child.

BRICKHOUSE2009 also focused on access to dental treatment and found some mixed responses from families. Of their sample of 188 participants, 48% expressed that they found it either 'somewhat easy' or 'easy' to find a dentist for their child. However, 15% of the sample reported that it was either 'very difficult' or they had

not managed to find a dentist at all in the year preceding the study. The remaining 37% of participants found it 'somewhat difficult' to locate a dentist for their child. A quarter of the sample reported being refused dental treatment at some point.

Effective treatment delivered by trusted professionals

Satisfaction with service

Parents and carers' satisfaction with health services was prevalent in one Hampshire-based study (DITTRICH2011). Although the children and young people gave positive feedback, the responses from parents and carers were more varied, with 44% rating their experiences with health visitors as excellent or good and 37% as poor. When reporting on experience of dentists and GPs, participants rated them as good or excellent in 71% and 61% of cases, respectively. BROMLEY2004 looked at parents and carers' satisfaction with GPs and discovered that 43% of their sample found them sometimes helpful and 16% found them to be extremely helpful; however, 19% found GPs unhelpful and 21% described their GP as not available.

Professional awareness and understanding

The responses from parents and carers regarding the awareness and understanding of primary care professionals varied between studies and were linked to those in the access to, and satisfaction with, therapeutic interventions sections above. As is clear from the responses in both those sections, service users and carers feel that it is important for professionals to have an awareness and understanding of autism. In line with this, one report found that 36% of parents and carers feel that this is a met need in relation to doctors and dentists (SIKLOS2006). However, parents of children with autism were found to be more likely to disagree that doctors have the qualifications to manage their child's condition, compared with parents of children who have learning or physical disabilities (LIPTAK2006). This finding was in contrast to another study where carers were asked to rate how well educated they felt doctors and nurses were—the mean rating here was 6.11 out of 7 (with 7 being highly educated) (LITTLE2003). Compared with parents of children with physical or learning disabilities, parents of children with autism also awarded GPs lower ratings for their ability to answer questions about their child's condition and their knowledge of complementary and alternative interventions (LIPTAK2006).

In order to gain a deeper understanding into the reasons why parents and carers may be dissatisfied with primary care services (specifically dentists), 568 participants were asked to endorse items that were relevant to their experiences of dental surgeries (LAI2011). Responses identified that dentists and their staff were not able to handle the child or young person with autism appropriately in 9.6% of cases. It was also reported that some parents and carers had encountered dentists who did not treat children who had special needs (8.2%) or dental surgeries that were not special needs 'friendly' (7.5%). Some parents also reported a lack of respect towards them or their child as a reason for their dissatisfaction with dental services (4.2%). BRICKHOUSE2009 also found that 16% of their sample had experienced difficulty with finding dentists who treated patients with special needs.

There were also environmental factors that made dental appointments more challenging (STEIN2012). Parents and carers reported children having difficulties with instruments being put in their mouths in 69% of cases; loud noises in 53%; drilling in 50%; general sensory sensitivities in 47%; bright lights in 35%; and smells in 25%. In line with these difficulties, half of the same group of parents and carers also reported that there was an increase in uncooperative behaviours when their children were at the dental surgery.

Secondary care

Effective treatment delivered by trusted professionals

Satisfaction with service

When participants in Hampshire were asked to rate their experiences of paediatricians, 26% of parents and carers rated it as excellent, 45% good and 6% poor (DITTRICH2011). A second study also explored parents and carers' views on their experiences of paediatricians (CASSIDY2008), with 63% rating them as helpful and 11% not helpful.

Experiences of general hospitals were also rated by parents and carers (DITTRICH2011). Of 99 respondents to a question about general hospitals, 58% rated their experience as excellent or good compared with 17% who rated it as poor. Nine participants also rated their experiences of mental health hospitals, with 33% rating them as excellent or good and 54% as poor.

Involvement of, and support for, family and carers

Satisfaction with professionals

One study (BROMLEY2004) asked parents and carers of children and young people with autism to rate a range of secondary care professional services in terms of accessibility, appropriateness of support and sufficiency of support provided. The best ratings were given to clinical psychologists and speech therapists with scores of 75% and 91% respectively for accessibility, 100% and 91% respectively for appropriateness of support and 91% in both cases for sufficiency of support provided. Average scores were received by community learning disability nurses, alternative therapists, social workers and educational psychologists. The two professionals receiving the lowest scores for accessibility, appropriateness and sufficiency were psychiatrists with 54%, 62% and 6% respectively and support workers with 36%, 55% and 27% respectively.

Social care

Clear, comprehensible information and support for self-care

Access to support

In line with the majority of responses relating to access throughout this section, access to social care was generally seen negatively. The criteria that is used to determine the level of support children and young people with autism should receive – Eligibility Criteria for Specialist Services (Fair Access to Care) – was reported by parents and carers as reasonable and meeting the needs of the child in 16% of cases (DITTRICH2011). However, more than 50% either disagreed or strongly disagreed with the criteria being fair and meeting the child's needs. In addition, 70% of parents and carers disagreed or disagreed strongly with statements pertaining to the ease of receiving the assessment that determined whether the child or young person should have access to services. Only 15% agreed or agreed strongly with this statement.

Effective treatment delivered by trusted professionals

Satisfaction with services

Satisfaction with social services was generally low, although this was only examined in three studies. In the 12 months preceding CASSIDY2008, 38 parents and carers had been in contact with social workers and of those, 37% rated them as helpful. In the Hampshire-based study, parents were asked for their level of agreement with statements that social services have a good understanding of autism and the impact it has on their family; 18% agreed or strongly agreed whereas 50% either disagreed or strongly disagreed (DITTRICH2011). These parents and carers also rated social service transitions as poor in more than 50% of cases, compared with 17% who rated them as excellent or good. Of the parents participating in this survey, 64% reported that support from social services was only available when their family was in crisis.

NEWSOME2000 found somewhat mixed reviews for social workers. On a scale of 1 to 5 (where 5 indicated strong agreement), parents reported that: they had needed more contact with their social worker (3.4); they would seek services from a social worker again (2.75); their social worker had been an advocate for the child (2.43); their social worker had enhanced progress in their child (2.42); and their social worker appeared to have an interest in their child's condition (2.34). Social workers received low levels of agreement from parents for communication and whether this met their needs (1.85) and their use of approaches that were meaningful to the child (1.85).

Residential care: short breaks

Involvement of and support for family and carers

Unmet needs

A high proportion of parents and carers in one study (93%) felt that respite care was a future need for their family (DILLENBURGER2010), yet unmet needs relating to respite care were reported in four separate studies. In a sample of 739 parents and carers, an unreported majority expressed that short breaks were a form of support they did not receive, even though they wanted or needed them (REID2011). Elsewhere, 54% of carers felt that respite care was an important need that was unmet in 42% of cases (BROWN2012) and in another survey (BERESFORD2013) where 26 carers responded to questions about short breaks, 54% felt that more help was needed compared with 4% who felt that they were getting enough help; the remaining 42% felt that they did not need support through short breaks. Finally, in a sample of 68 mothers of children with autism, 55% reported unmet needs relating to respite care and 87% had unmet needs in relation to short breaks from caring for their child (BROMLEY2004). In line with those findings, respite care was only reported as a met need in 41% of a separate sample (SIKLOS2006).

In a sample where one third of parent and carers reported that their child had been in receipt of respite services (DILLENBURGER2010), 84% of these respondents expressed that this support only sometimes met the needs of the child or young person. Elsewhere families of children and young people with autism were asked to rate respite care services in terms of accessibility, appropriateness and sufficiency (BROMLEY2004). The 68 participants gave ratings of 46%, 85% and 62% respectively, which were average scores compared with those received by secondary care services.

Educational setting: mainstream

Emotional support, empathy and respect

Relationships at school

When a sample of 144 parents and carers of children and young people with autism were asked to reveal their experiences of relationships at school, many felt that either the staff within the school or other parents had shown prejudice, fear or resentment towards the parent of the child with autism, or the child themselves (STARR2012).

Experience at school

In order to examine experiences at school, parents and carers were asked to provide feedback about whether the child with autism had been identified as a bully or was bullied at school (CHEN2012). In this sample, 72% of parents expressed that the child had been a victim of bullying. To explore this further, parents and carers were asked to rate whether the child was a bully only (12%), a bully and a victim (24%), or a victim only (36%).

Effective treatment delivered by trusted professionals

Access to support

All of the responses in this section were from parents and carers of children and young people with autism and, in keeping with the pattern that has already emerged throughout this section, responses around access were generally negative. In one study (REID2011), in which the authors concluded that in order to get the support that parents and children needed, they had to 'fight every step of the way' (pg 7), 68% of parents reported it had not been easy to access support. Within this sample, participants said that they appealed an average of 3.5 times in order to get their child's education needs met. Nearly half of the 739 parents had to wait more than 1 year to access educational support, 27% more than 2 years and 15% more than 3 years. In addition, 47% parents reported that when concerns had been raised regarding their child's special education needs, they were not dealt with in a timely manner.
Parents went on to report that delays and a general lack of educational support had a negative impact on their child's educational progress (69%), social communication (75%) and mental health (60%). In a separate study (DITTRICH2011), 53% of parents disagreed or strongly disagreed that they had been offered support in obtaining a Statement of Educational Needs for their child.

Satisfaction with school

Satisfaction with education services was the focus of a number of studies with a range of elements being considered such as education content, teachers and SENCOs. The responses to these studies were mixed. Positive feedback relating to education provision and staff was given in a number of surveys. In a sample of 172 carers, satisfaction was reported by 61% (WHITAKER2007). A separate study found that 70% of a sample of 738 carers reported satisfaction with their child's education (TISSOT2006). In this sample, school staff were cited as the reason for feeling satisfied in 41% of cases. Similarly, another sample of 69 parents of children with autism reported that they were 'fairly satisfied' with the education that their child received (STARR2001). This was explored further and at least 70% of carers showed agreement with 17 of the 24 items rating education staff and 14 of the 19 items rating the classroom environment. In a separate study, 42% of parents who had been in contact with their child's educational psychologist in the year preceding the survey rated them as helpful, compared with 10% rating them as not helpful (CASSIDY2008). In the Hampshire study, 49% of carers rated their experience of SENCOs as good or excellent, compared with 31% who rated their experience as poor (DITTRICH2011). Mainstream teachers were rated as excellent or good in 27% of cases, compared with 41% that were rated as very poor. Parents were also asked to rate their child's school nurse: over half (58%) reported their experiences were excellent or very good; only 18% were very poor. In another study (JONES2008C), 81% of carers rated their relationships with school professionals as either good or very good.

In contrast with studies where carers reported satisfaction with educational services, REID2011 found that one third of parents were not satisfied with their child's education placement. More than half in this sample felt that it was important for their child to have access to autism-specific care in school (for example, an autism resource base). However, this need was only reported as met in 18% of cases. More mixed reviews came from a sample of 244 carers who were asked to rate satisfaction with mainstream nursery, primary and secondary schools (RENTY2006A). On a scale where '5' is excellent, the mean scores were 3.28, 3.12 and 3.43 respectively. Similarly, within the same study, parents were asked to rate their child's education provision in terms of the quality of support and education the child received. Out of a possible score of 10, the mean score received from the parents was 5.8.

Some parents and carers of children and young people with autism feel that the staff within mainstream schools do not have the necessary skills to manage their child. This was apparent in a sample of 69 carers, with 15% reporting that because of aggressive behaviour their child had been suspended from school at some point (STARR2012). However, all parents of these children also perceived that the suspension is a result of the staff within the school being unable to deal with the child's behaviour properly. Within this sample, one-third felt that their child was not making sufficient progress with their education. One-third also reported being called to collect their child from school when they were not ill (REID2011). Many (19%) parents reported that this had happened on multiple occasions.

Professional awareness and understanding

Based on the qualitative evidence included, it is clear that parents deemed it important for school staff to have an understanding of autism, yet this need was not always met. This particular issue was highlighted when 98% of a sample of parents felt it was an important need for their child's teacher to understand them (BROWN2012). However, two-thirds felt this need was unmet. It should be noted however, that this finding was not specific to special school teachers, but teachers in general. One large-scale study found that more than half of their sample of parents were dissatisfied with their child's teachers' understanding of autism (REID2011). Elsewhere, 42% of parents expressed that they felt teachers needed more education about autism (STARR2012) and that mainstream schools were not flexible enough to adapt to the needs of a child with autism (WHITAKER2007).

Educational setting: specialist

Involvement in decisions and respect for preferences

Satisfaction with school

Although feedback relating to carers' involvement in decisions and respect for their preferences was limited, it was touched on in several studies and the outcomes were generally positive. For instance, in a survey of 68 parents of children and young people with autism, nearly three-quarters reported that their child was attending their preferred school (BROMLEY2004). In another survey, parents gave a mean

score of 4.4 out of 6 (where 6 indicates high satisfaction) when rating whether their child's school took their opinions into consideration (MORENO2008).

Effective treatment delivered by trusted professionals

Access to services

A survey found that just over one-third of mothers reported that when trying to find a school for their child, their needs were unmet (BROMLEY2004). Yet when support was received from the school, 72% of parents reported that this was helpful. Within school, parents reported that the child or young person with autism needed and utilised a range of services, namely: part-time educational assistants (48%); full-time educational assistants (39%); occupational therapists (39%); speech and language therapists (34%); and physiotherapists (6%) (BROWN2012). Up to 88% of parents reported that their child received special services through educational facilities, as well as home-based services (SANSOSTI2012). However, in a separate survey, a quarter of parents reported that there were services that the school should be offering their child, which they were not currently receiving (BITTERMAN2008). The same sample of parents reported that in nearly 50% of cases there were further unmet needs, as children were receiving services that they needed, but not to an adequate level.

Satisfaction with school and professionals

Specialist education services received a range of positive feedback across a number of studies. In some, feedback was quite general and in others, it was focused on specific services. For example, one study surveyed carers of children and young people who had been part of a 'satellite class' primarily aiming to support students transitioning to mainstream education (KEANE2012). Elements of the class included gradually decreasing the amount of individual support students received, a high level of collaboration between staff of the satellite class and the future placement, and a focus on activities that required peer interaction. Of the parents surveyed, 67% reported that the class was excellent and 21% felt that it was very good, contrasting with 8% who rated the class as satisfactory or unsatisfactory. Finally, 67% rated the transition planning in the satellite class as excellent or very good, compared with 14% who rated it as satisfactory or unsatisfactory.

One study asked carers to rate how useful they found school professionals (LITTLE2003). The highest usefulness ratings went to classroom aides with 58% deeming them extremely helpful (compared with 4% not at all helpful), followed by education advocates (50% extremely helpful compared with 9% not at all helpful). These professionals were followed by special education teachers, tutors, occupational therapists, social skills trainers, sensory integration teachers and speech and language teachers and pragmatics trainers. Carers considered guidance counsellors the least helpful, with only 25% rating them as extremely helpful compared with 31% who rated them as not at all helpful.

When asked to rate their views on teachers in special schools, carers reported that their experiences were excellent or good in 82% of cases, compared with 5% who felt they were poor (DITTRICH2011).

In other studies, parents reported satisfaction with the way goals were set for students and their progress towards goals (FERRERI2011) and the use of visual schedules in educational settings (STUART2006). General satisfaction relating to schools was also reported in some studies, with one in particular finding that 96% of participating parents were very satisfied with services (BITTERMAN2008). In a separate study, half of participating parents reported satisfaction with their child's school, compared with 28% who were not satisfied (STARR2006).

A further study found that overall parent-reported satisfaction with schools was 4.6 out of 6 (where 6 was very satisfied) (MORENO2008). Elsewhere, in relation to educational content at an ABA-focused school, 45% of parents felt that the content was always appropriate for their child (DILLENBURGER2010). Finally, 244 carers were asked to rate how satisfied they were with the school meeting their child's needs (RENTY2006A). On a scale where 5 indicated 'very satisfied', secondary schools received an average score of 4, followed by special education nursery schools (average: 3.95) and primary schools (average: 3.75).

In contrast with the above, STARR2001 found that 36% of their sample felt that their child was not progressing as well as parents felt they should and 38% believed that the classroom environment within their child's school was not calm enough.

In the CALLAHAN2008 study, participants completed an extensive (99 item) survey, in which they were asked to give all items a rating of importance. The included items covered a wide range of education-related topics, such as: education content, classroom environment, teacher and other staff competencies, progress monitoring, resources, teaching aides and teaching methods. The combined responses of the 95 carers who completed the survey revealed that all but one item were considered at least quite important (with scores of 5.5 and above on a 7-point scale where 7 is extremely important). The one item that was scored lower than this was punishment and aversive stimuli, which was rated 3.6 out of 7. The highest scoring (6.90), and therefore the most important item, as rated by carers, pertained to the need for teachers and service providers to have the relevant knowledge and experience to be able to apply skills and interventions aimed at behaviour management, communication and social interaction, as well as academic and independent living skills. The second highest scoring item related to children having an individualised programme where the educational benefits were meaningful to that child (6.75).

Relationships at school

Parents of children and young people with autism were asked to rate how true it was that their child fought with or bullied other children. In a sample of 100 participants, 62% reported that this was not true, 24% felt it was somewhat true and 14% stated it was certainly true of their child (ROWLEY2012). Similarly, parents

were asked to rate whether it was true that their child was picked on or bullied by others. Here, 28% reported that this was not true, 39% felt it was somewhat true and 33% certainly true. Elsewhere (MORENO2008), carers gave positive feedback regarding teachers' attitudes towards carers (a rating of 5.17 out of 6 where 6 is highly satisfied) and their children (5.10 out of 6). Another survey asked parents to rate their relationship with staff in autism-specific schools (JONES2008C). The vast majority (96%) reported that it was either very good or good. Where the school was specialist, but not autism-specific, the same number of parents rated their relationship with the teacher as very good or good.

Inclusion

Feedback from parents about the inclusion of their children into mainstream education was somewhat mixed. One survey found that just over one-quarter felt that their child should be spending more time in school with typically-developing peers (BITTERMAN2008). However, in another survey 59% expressed that they were either satisfied or extremely satisfied with their child's level of involvement in mainstream education (FERRERI2011). In this study, parents were either extremely satisfied or satisfied with their child's opportunity to learn as a result of inclusion (61%) and the amount of time spent in mainstream settings (78%). However, parents' views were more varied in relation to satisfaction with peer relationships, with 44% reporting that they were extremely dissatisfied or dissatisfied compared with 41% who were extremely satisfied or satisfied.

Desired support

A survey carried out in Ireland with 95 carers of children and young people with autism who had attended an ABA-focused school, found that carers considered ABA training for teachers important (DILLENBURGER2012). In fact, 45% of the sample reported expecting teachers to be ABA trained in the future. In addition, a very high proportion of carers surveyed (99%) expressed that there should be increased opportunity for all families of children with autism to access ABA-focused education. Elsewhere, having a specialised individual education plan created by the school for children with autism was rated as an important need by 96% of parents (BROWN2012); however, this need was unmet in 40% of cases.

Continuity of care and smooth transitions

Satisfaction with transition support

One study in particular focused on the level of satisfaction parents felt with the support their child had received with transitions (BERESFORD2013). Responses from parents with children with 'high-functioning' autism and Asperger's syndrome were compared with those of children with a diagnosis of autism spectrum disorder, as well as responses from parents whose children were going through the transition at the time of the survey and those who had already been through the transition. Responses from parents whose children had a SEN statement were also compared with those who did not. In all groups, over 60% reported dissatisfaction with the level of support their child had received for transitions. The responses ranged from

60% dissatisfied (parents of children with 'high-functioning' autism and Asperger's syndrome who had completed their transition) to 80% dissatisfied (parents of children with autism spectrum disorder who had completed their transition).

Dissatisfaction with specific types of transitions was also explored, which yielded similar results to those above (BERESFORD2013). The most dissatisfaction related to transition from college to paid employment, with 100% of parents feeling that these were poorly managed. However, there was also dissatisfaction with transitions from school to day services (71%), to college (57%), to paid work (50%) and to voluntary work (50%) and from college to day services (50%).

Unmet needs

In line with the findings on dissatisfaction with support during transitions, the same study found that the 149 parents of children and young people with autism who returned the survey reported a range of unmet needs around transitions (BERESFORD2013). Most commonly, parents reported that having someone to support them with finding suitable future services for their child was an unmet need (two-thirds of parents endorsed this item), followed by having someone to talk to about their child's transition (endorsed by two-thirds of the sample). Additional unmet needs were having someone to coordinate their child's transition (66%) and provide support to the parents (54%). The service users in the same survey reported that their parents were the key people in supporting them with their transitions by discussing options and helping them to make decisions.

All points on the care pathway

In a number of surveys that have been included in this chapter, parents and carers of children and young people with autism provided more general feedback that was not specific to any one point on the care pathway.

Emotional support, empathy and respect

Professional awareness and understanding

Parents and carers reported some met needs relating to professional awareness and understanding across the care pathway (SIKLOS2006). For example, 64% felt that professionals had used terms that they understood when speaking to them. Also, 61% expressed that being shown respect by professionals was a met need. However, just under half felt that professionals had been discrete when talking about the child or young person with autism when they were in the room. This finding was similar to that of another study, where 70% of parents felt it was an important need for professionals to be discrete if the child or young person was in the room, with 36% reporting that this need was unmet (BROWN2012).

Effective treatment delivered by trusted professionals

Satisfaction with support

A survey of 149 parents asked respondents to rate their satisfaction in relation to support their child had received in a range of areas, including general skills and functioning, learning and achieving, promoting independence and coping with change (BERESFORD2013). Parents felt that their children needed more support in all areas, with the greatest need for help in the following areas: career opportunities (65%), preparing for change (64%), social life (63%), adult relationships and sex education (57%), and setting future goals (54%). The three areas where parents reported that their child received enough support were communication (44%), behaviour (38%) and transport and getting around (36%).

Involvement of, and support for, family and carers

Access to services and support

When parents and carers were rating the support they received from professionals in general, the responses were mixed. While 40% felt the professionals were generally extremely helpful and 28% sometimes helpful, 4% rated them as not at all helpful and 28% reported that professionals were not available (BROMLEY2004).
Parents reported that the services that they needed most were interventions that taught and developed skills for both them and their children (DUNLAP1994). Additionally, parents felt that general support for the family and support from professionals who are trained in managing behavioural problems were important.

Professional awareness and understanding

When parents of children and young people with autism were reporting their important needs, 94% endorsed professionals understanding the needs of their child. (BROWN2012). Yet, this need was in unmet for two-thirds of the sample. Being able to turn to professionals when help is needed was also important for 94% of carers, yet this was unmet for 61% of participants. Finally, 89% of carers deemed it important for professionals involved in their child's care to agree how the child should be helped, yet 47% reported that this need was unmet.

Elsewhere, 93% of mothers reported that support for their child during the school holidays was an unmet need (BROMLEY2004) and just under half of another sample of carers reported that family services were missing at least one element of family-based care (KOGAN2008).

Continuity of care and smooth transitions

Information and support at key transitions

The Hampshire-based study asked participants to rate professionals in general at any key transition point that their child went through between the ages of 14 and 18 (DITTRICH2011). This could include transitions between classes, progressing from school to college and moving from home to school. Here, more than half of

participants (55%) reported that professionals had a good understanding of autism, compared with 29% who did not agree. However, 55% felt that different professionals failed to work together during transition times, compared with 21% of participants who felt that they did. Additionally, 51% of participants reported that they did not feel that the impact that the transition would have on the child or young person was considered by professionals. Sixty-five percent of participants disagreed or disagreed strongly that they felt confident that the needs of the young person would be met during the transition into adulthood (and adult services).

5.1.1 Summary of evidence from the primary qualitative and quantitative review

Based on the review of the qualitative evidence for the experience of care of children and young people with autism and their carers and siblings, the GDG agreed initial recommendations based on the findings:

- All staff working with children and young people with autism should have an understanding of autism.
- In all settings, professionals should take into account the physical environment in which children and young people with autism are supported and cared for and make reasonable and appropriate adjustments. Where it is not possible to adjust or adapt the environment, processes should be adjusted to limit the negative impact of the environment.
- Children and young people with autism should have access to a keyworker approach in order to manage and coordinate treatment, care and support, including the management of transitions, for the child or young person with autism and their family and carers.
- Children and young people with autism should be offered evidence-based intervention aimed at preparation and coping strategies to facilitate access to community services, including the skills to access public transport, employment and leisure facilities.
- Children and young people with autism, and their family and carers, should have easy access to short breaks.
- Children and young people with autism, and their family and carers, should be provided with post-diagnosis information about services available and support, for example a family support worker.
- Treatment and care of children and young people with autism should involve shared decision making and a collaborative approach that takes into account service user preferences.
- All children and young people with autism should have access to healthcare and social care services, including mental health services, and access should not be restricted based on a child's intellectual ability, autism diagnosis, or any other eligibility criteria.

These initial recommendations were presented to the expert advisory group (see below) as part of a validation process and then feedback from this group was integrated with the initial findings in order to inform the final guideline recommendations.

5.2 EXPERT ADVISORY GROUP VALIDATION

5.2.1 Introduction

Individuals with direct experience of services – that is, experts by experience – are integral to provide a service user focus to the GDG and the guideline. The GDG included a sibling and two parents of children and young people with autism, who contributed as full GDG members to develop review questions, highlight sensitive issues and terminology associated with autism and to bring the experiences of carers and families to the attention of the GDG. Unfortunately, it was not possible to recruit a service user to the GDG, due in part to the time demands of the GDG member role and problems associated with the group-based environment and format of GDG meetings. However, it was considered crucial that the experiences of children and young people with autism were incorporated into the guideline. In order to achieve this, a consultation exercise with an expert advisory group of service users was commissioned from the NAS. The role of this expert advisory group or individual interviews with service users (as appropriate to the needs of the service users) was to consult on the recommendations for improving access to and experience of care that had been developed on the basis of the qualitative literature review in order to validate findings where appropriate and to allow feedback on areas where service users felt that the qualitative literature was either not representative of their views or where evidence was missing.

Material from these focus groups or individual interviews was used to supplement the literature review of service user and carer experience of care and organisation and delivery of care. This enabled a triangulation of the service user and carer experience findings – that is, it was possible to compensate for possible weaknesses in one data collection or analysis method by using additional methods, in this case, material from a systematic qualitative literature review was combined with that from focus groups and individual sessions conducted by the NAS.

5.2.2 Method

One consultation group (with nine participants) and 13 individual interviews were convened by the NAS and members of the GDG. Children and young people with autism were recruited by the NAS for the consultation group if they had had contact with services and were interested in taking part.

Potential participants who were initially contacted for recruitment to the expert advisory group included children and young people who had been members of the NAS Young Campaigners Group or who had been involved in other research by the NAS. The NAS also conducted individual interviews with children from one mainstream secondary school (five participants) and one autism-specific maintained

special school (seven participants) that were recommended by members of the GDG. Children and young people expressing an interest were given further information describing the purpose and methods of the consultation exercise and the role of participants and were required to complete a consent form. The consultation group and individual interviews were held in October 2012, facilitated by the NAS (Tom Madders and Shane Samarasinghe) and observed by members of the GDG (Barbara Parker and Alison Stewart). Eight females and 13 males, aged between 11 and 19 years, took part. Consultation took the form of individual and group work, with discussions centred on the issues that gave rise to each initial finding from the review of the qualitative literature (see Section 5.1.1). To ensure meaningful participation of those from across the autism spectrum, a variety of different consultative approaches were used. Thus, while it was possible to explicitly ask young people in the consultation group whether they agreed or disagreed with each initial finding, the NAS interviewers (assisted by the GDG member observers) had to infer the extent of agreement in most responses given by the children who were individually interviewed and this was not always possible. For all young people with higher levels of support (those who were individually interviewed), questions were presented in a structured format with a range of possible options to choose from. Where possible, the discussions were opened up to apply the issues in a broader context including what young people in general might want and how the principles might apply in hypothetical situations. Discussions were audio-taped, transcribed for analysis, and findings were written into a report by the NAS (see Appendix 18).

5.2.3 Summary of findings from the expert advisory group

Initial finding

All staff working with children and young people with autism should have an understanding of autism.

Views and feedback

The young people were very supportive of the suggested finding. They felt that all staff should have effective basic training but it was important that professionals understand that '*when you've met one person with autism, you've met one person with autism*', and their autism was not their defining characteristic:

> *My Teaching Assistant doesn't change things with me because I have Aspergers; she changes things with me because she understands me and what I find difficult, which is what's helpful. She got to know me.*

Commenting on another professional a young person trusted, they remarked:

> *He talks to me in a normal way and reads my body language and uses his own words to ask me if he is right. He doesn't presume he knows.*

One young person said that:

> *...knowledge [of autism] is ideal but may also hinder because they apply the same ideas to everyone.*

It was therefore important to learn by experience rather than follow what it says in a textbook, as that would be the same as '*learning to swim from a book*'. In this way, professionals were able to understand an individual child's triggers:

> *...she [my teacher] helps me calm down when other kids misbehave.*

The NAS asked service users to tell them about a professional with whom they liked working. They responded with the reasons why they liked those professionals, for instance '*listening to me*, *using a calm voice* or *giving me a break*'. From this, the NAS and GDG facilitators were able to infer some of the characteristics that young people with autism seek in professionals. However, it was difficult to infer from this line of questioning that the professionals they liked best necessarily had a good understanding of autism as opposed to simply a person-centred approach.

The young people's frustration with professionals stemmed from feeling that they were '*talked down to*', when they wanted to be '*treated like a teenager and not like a three year old*'. They also wanted professionals who were '*open to difference*' and respected them as individuals because '*my life is just as valid*'. They wanted professionals who were able to make adaptations based on the individual:

> *Some people may need to be spoken to differently; they need to approach them differently, but that's for some people.*

Initial finding

In all settings, professionals should take into account the physical environment in which children and young people with autism are supported and cared for and make reasonable and appropriate adjustments. Where it is not possible to adjust or adapt the environment, processes should be adjusted to limit the negative impact of the environment.

Views and feedback

The young people were very supportive of the suggested finding. They felt professionals did not always give due consideration to the impact the physical environment has on a young person's ability to cope during their appointments. The young people felt that the failure to simply be asked '*is there some stuff [within the physical environment] that you seriously object to?*' was demonstrative of this.
They commented that while '*it's not possible for them [professionals] to redecorate their room every time a new person comes in*', simple steps could be taken. For example, '*if you don't like fluorescent lights, it's not hard for them to turn them off*':

Every time I went to CAMHS there were just baby toys everywhere and I just felt like such a child ... . they could put them [toys] in the cupboard.

One young person said that people should be asked what adjustments they would like in the same way healthcare staff commonly ask about dietary requirements.

To ensure environments are safe, comfortable and welcoming, the young people wanted them to be clean, clear, spacious and tidy. They wanted the appointment buildings to be located where they might ordinarily go, rather than being out of the way, for example, '*in industrial estates or near busy roads*'. The young people expressed a desire to have more say on where their appointments should take place, particularly when adaptations could not be made or were in unfriendly settings.

The NAS asked the children in the individual interviews to tell them about a building or place they particularly liked and why they liked it. They were able to identify physical characteristics that they liked it (for instance, that it was '*bright*' or '*quiet*') and disliked (such as '*busy*' or '*smelly*'). From this, the NAS and GDG facilitators were able to infer that the physical and sensory characteristics of rooms and buildings are important to these groups, and that the young people consulted would support a recommendation to make physical adaptations to the sensory environment.

Initial finding

Children and young people with autism should have access to a keyworker approach in order to manage and coordinate treatment, care and support, including the management of transitions, for the child or young person with autism and their family and carers.

Views and feedback

The young people were broadly in agreement with the suggested finding, although there was confusion regarding the role of a key worker. Some of the young people had professionals they called key workers who worked within their schools and were often the named individual with whom they would discuss their problems. Within this context the young people valued the relationship they could establish with one individual because:

...building a relationship is hard and it takes time, and when that relationship is good and solid you move on, which is weird and tricky.

One young person noted that:

...as I got to know the lady and started to trust her enough, she had to leave.

Initial finding

Children and young people with autism should be offered evidence-based intervention aimed at preparation and coping strategies to facilitate access to

community services, including the skills to access public transport, employment and leisure facilities.

Views and feedback

The young people were supportive of the suggested finding. All the young people enjoyed participating in a range of hobbies and activities and were conscious of the support they needed to be able to do these:

> *I like swimming, but I need someone I know nearby to help if something goes wrong. Also, travelling to where the event is happening is the main issue.*
> *I was really scared about getting the buses and my mum did the routes with me on the buses.*

Consequently, the young people remarked that more independent skills training, such as travel training, should be taught across all schools. They expressed concern that those in mainstream schools were more likely to miss out on this type of learning, as it was more readily available in special schools:

> *I was scared about everything, and I wrote a really, really long letter, all the reasons why I wouldn't go to the corner shop, which literally is about twenty doors down. She did the walk with me and we went through the whole list and managed to cross off practically everything. But she was able to do that because she used to come to our house and do our meetings. Or it got to the point where she'd book a room, so there was a meeting room about ten doors up that way and make me walk to the appointment on my own.*

The NAS asked the children in individual interviews to tell them about activities they liked and why. Children were able to identify how different activities helped them (for example, '*it [art] makes me feel calm and happy*'). In some instances, children also talked about why they were able to access a particular activity:

> *I like basketball because it is on my schedule and I know what to do.*

Children and young people discussed how not having the right support acts as a barrier to accessing services that other young people would enjoy:

> *...clubs I find tricky because I find the rules I look for in a club never really took on when I was at school. For example, there's lots of clubs and even if they were good, I tended to eventually stop going.*

Initial finding

Children and young people with autism, and their family and carers, should have easy access to short breaks.

Views and feedback

The young people were supportive of the suggested finding, although only some had direct experience of accessing short breaks. One young person who had had an extended stay with foster carers described how she had not enjoyed it at the time, but overall felt it had been helpful for her and her family. All young people were able to identify activities they liked and acknowledged the positive impact it had.

Initial finding

Children and young people with autism, and their family and carers, should be provided with post-diagnosis information about services available and support, for example a family support worker.

Views and feedback

The young people were very supportive of the suggested finding. They valued having a person, who was often a family member, to whom they could turn for support and to help them understand their autism:

> *If I have one of my freak out moments, 'Oh, my God! I can't believe I'm about to do this!' she [my mum] sort of gets you, like, calm and puts everything into perspective for me, which is what I need. Because everything just blows up in my head and it's this massive, massive ordeal, but really it's not. She sort of makes me see that.*

However, having someone outside the family who could support them would also be beneficial, particularly if sensitive issues arise.

It was one young person's perception that '*when I got my diagnosis I always felt that I got it for other people, so that other people knew how to help me*', but that ultimately, '*it doesn't change how you already are*'. Children and young people spoke strongly about autism not being something '*to be got rid of, [because] it's an integral part of who you are*'. Nevertheless, they broadly agreed that knowing more about how the condition might affect them would help alleviate some uncertainty:

> *I would like to have known how anxious I would be.*
>
> *It was bad being diagnosed so late, particularly as I saw the problems my sister experienced with her mental health. It was difficult to accept the diagnosis. I was scared. It would have been helpful if someone had explained that I wouldn't necessarily develop mental health problems… that it wouldn't all be bad.*

One young person commented that if they had to give advice to a newly diagnosed peer they would say:

> *…not to get like discouraged if they found it difficult to do things that other people may necessarily find easier to do, like get on public transport and things like that, going out in the middle of town and mingle.*

Initial finding

Treatment and care of children and young people with autism should involve shared decision making and a collaborative approach that takes into account service user preferences.

Views and feedback

The young people were broadly supportive of the suggested finding, although there were mixed views on how much involvement they wanted in decision making. Each young person was asked to plot their current involvement across a number of different topics, and how much they would actually want. Every young person consulted wanted more involvement than they currently had, but the amount of input they wanted differed depending on individual preference and the issue at stake (see Appendix 18 for diagrammatic representations). The area where young people felt that their actual involvement and ideal involvement were closest together was in the level of explanation professionals give about the treatments and care needed. The areas where there were bigger gaps between actual and ideal involvement were in choice of professional and where appointments take place.

Some young people wanted to be heavily involved compared with their parents and relevant professionals, while others wanted equal involvement and some preferred it if professionals and their families took control (see Appendix 18 for diagrammatic representations). The young people felt that they could and should be given more choice than they currently had and that '*sometimes professionals think that she's got autism, she's not going to understand what I'm saying to her*' and that professionals '*don't think we're capable of knowing what we want*'. However, some young people were equally wary of taking on all the responsibility:

> *I know when I went through CAMHs I thought I was perfectly capable of making my decisions and that I don't need my parents. But I know that if they weren't around to sort things out I'd probably still be in that situation.*

Other comments included:

> *I like my Mum to decide as it's hard....*
>
> *...sometimes it's easier when teachers tell me what I need.*

Another factor was experience:

> *I reckon the more experience you have of the different types of treatment and you've had time to decide what works best, then, I reckon you would become more independent in deciding what kind of treatment you had.*

Initial finding

All children and young people with autism should have access to healthcare and social care services, including mental health services, and access should not be

restricted based on a child's intellectual ability, autism diagnosis, or any other eligibility criteria.

Views and feedback

The young people were very supportive of the suggested finding. They strongly believed that '*you should get exactly what you need*' and one young person summed up the prevailing attitude when she commented that:

> *...if you're not well, they give you tablets to make you better, so why wouldn't you get help if you have some problems? If you find things hard, well, why wouldn't you get help with that?*

5.3 THE ORGANISATION OF SERVICES

The analysis of the experience of care in the preceding sections is used in this section to help provide a framework to inform the organisation and delivery of services so as to maximise the impact of all the recommendations in this guideline. The purpose of this section is to briefly describe the organisation of services from a policy context and recent legislation regarding services for people autism.

High quality care not only depends upon the provision of effective and safe treatments underpinned by a positive experience of care, but also depends upon care being easily accessible and efficiently delivered. For health and social care professionals to provide the right high quality care to each service user at the right time, and in the right place, requires services to be organised, coordinated and strategically planned. The strategic development, organisation and effective coordination of services for children, young people and adults with autism spectrum conditions in England and Wales has been noticeably lacking, with considerable geographical variation.

In 2009 the Welsh Assembly Government (Adult Task and Finish Group, 2009) and the English Government (through the Autism Act 2009 [HMSO, 2009]) outlined their requirements for local authorities and health communities to create a strategic plan to develop a national network of local teams covering all parts of both nations. While they explicitly set out to develop efficient systems of effective care to address the needs of children, young people and adults with autism, these national initiatives acknowledged the disparate services and often poorly coordinated treatment initiatives. To improve this situation, local health and social care communities were required to develop a local strategy for the integrated provision of treatment and care organised through the development of integrated local teams and care pathways. The legal framework has been complemented by a suite of NICE guidelines: one for the recognition, diagnosis, treatment and management of adults with autism (NICE, 2012a); another for the diagnosis and assessment of children and young people with autism (NICE, 2011a); and this guideline on the treatment and management of autism in children and young people. All three NICE guidelines

have, at their heart, a locally developed, multi-agency strategy group and a local autism team for each area. The strategy team and the local autism team are derived from the Welsh and English legal frameworks specifically to ensure the efficient delivery of effective services for children, young people and adults with autism.

The strategy group's role, laid out in existing NICE guidelines (NICE, 2011a, 2012a), is to: plan the development of local autism services; develop protocols for referral and transition to adult services; develop training for health and social care professionals and others to underpin early recognition; to be able to monitor services; and to enhance the ethos of multidisciplinary working across autism services (NCCWCH, 2011). The local autism teams were derived from a survey of five 'best practice' services, identified through national contacts with the GDG. The five 'best practice' services were identified in rural and urban settings, some community based, some hospital based, but all were multidisciplinary with the specific skills to recognise, diagnose and assess children and young people with autism, and to deliver the evidence-based treatments identified in this suite of guidelines. The local autism team has been characterised based upon the description of these five 'best practice' teams. The guideline on the diagnosis and assessment of autism in children and young people (NICE, 2011a) restricted the role of the local autism team to that of assessment and diagnosis. The GDG for this guideline has extended the skills and services to be provided by these local autism teams to include treatment and management of autism in children and young people, and the coordination and/or provision of treatment and care (consistent with the NICE guideline for the diagnosis and management of autism in adults, NICE, 2012a). The precise composition of the local autism team will depend upon the distribution of skills and resources throughout a local health and social care community, as determined by the local multi-agency strategy group.

5.4 FROM EVIDENCE TO RECOMMENDATIONS

A recurring theme in the qualitative literature review of both service user and carer experience of care was barriers to accessing health and social care services. In particular, both service users and carers felt that access to services was especially restricted for children and young people without a coexisting learning disability (IQ>70). Moreover, carers expressed their frustration that crisis often appeared to be the eligibility criteria for accessing services, whereas early support might have prevented problems from escalating. Carers also talked about the need to 'fight the system' in order to access interventions, services or support. In addition, the evidence from the consultation process validated this finding and supported the need for a recommendation aimed at improving access to health and social care services. The GDG judged that unrestricted access to health and social care services would enhance provision of effective and cost-effective interventions for all children and young people with autism. Thus, the GDG recommended that children and young people should not have access to health and social care services restricted by their intellectual ability or the presence or absence of any coexisting conditions.

Another recurring theme in the qualitative review of the experience of care was negative experiences associated with a lack of professional understanding of autism, including inappropriate treatment recommendations and the failure of professionals to appreciate the need to modify their communication for children and young people with autism. In addition to understanding autism, the consultation process by the NAS also highlighted the importance of professionals understanding the person and not just the disorder so that individual adaptations to treatment and care could be made appropriately. The GDG was concerned that children and young people with autism and their carers felt 'let down' by professionals' lack of knowledge of autism and therefore made a recommendation that all health and social care professionals working with children and young people with autism in all settings should receive training in autism awareness and basic skills in managing autism. The GDG took into account the training costs entailed but judged that such costs were justified by the expected increase in provision of effective interventions by trained staff and improvements in satisfaction with services and overall quality of life.

The qualitative literature review found that both service users and carers described positive experiences associated with adjustments to the physical or social environment or processes of care that healthcare professionals had made, for instance, arranging appointments at the beginning or end of the day to minimise the time the child or young person needed to spend in a waiting room. The children and young people consulted by the NAS corroborated this finding and service users felt that professionals did not always give due consideration to the impact the physical environment has on a child or young person's ability to cope during their appointments. The children and young people in the consultation process suggested that young people should be asked what adjustments they would like in the same way as it is common practice to find out about dietary requirements. Based on this evidence and the expert knowledge and judgement of the GDG, the GDG concluded that individual and reasonable adaptations to the environment should be made as appropriate, such as providing a sufficient amount of space, considering individual needs associated with lighting and colour, and the availability of visual supports that are meaningful to the child, to provide cues as to expected behaviours in certain environments; the GDG judged that the expected improvement in the quality of life of children and young people with autism was worth the costs of making these kinds of adaptations. The GDG also took the view that it would be beneficial for the processes of health and social care to be adjusted to meet the needs of the child or young person, for example, ensuring that appointments are scheduled either at the start of the day so that waiting times are minimal.

Children and young people with autism (through both the qualitative literature review and through NAS consultation) and carers expressed a need for information about the types of support available and that this was particularly important during periods of transition. Parents and carers also discussed problems with accessing carers' assessments and talked about a need for improved access to short breaks. Children and young people with autism and their carers also wanted to be involved in decisions about treatment and care, although children consulted by the NAS

differed in terms of the amount of control they desired relative to their parents and professionals. However, all children and young people consulted wanted the opportunity to exercise more choice. Based on this evidence, the GDG recommended that families, carers and service users should be given information about support available and their rights and entitlements, and should be offered a collaborative approach to treatment and care that takes their preferences into account.

In the qualitative literature review carers and service users talked about an unmet need for interventions aimed at daily living skills and children and young people consulted by the NAS enjoyed the leisure activities that they undertook, but were aware of the increased support they needed in order to participate in such activities. The young people felt that more independent skills training, such as travel training, should be taught. Drawing on their experience, the GDG was also aware that problems in accessing leisure and community activities could exacerbate the social isolation experienced by children and young people with autism. In the absence of evidence for specific interventions aimed at daily living skills, the GDG recommended that children and young people with autism should be offered support in developing coping strategies and accessing community services, including developing skills to access public transport, employment and leisure facilities. The GDG felt that the cost of providing such support was justified by the considerable improvement in the quality of life of children and young people with autism as well as their carers.

Children and young people with autism and carers described some positive experiences of transition that involved planning, early meetings between child and adult services and a central point of contact to coordinate treatment such as a case coordinator or keyworker. Based on this evidence and the expert opinion and judgement of the GDG, it is recommended that transition planning should include a comprehensive needs assessment and early collaboration and communication between CAMHS or paediatric services and adult services, and that every child or young person with autism should have a case coordinator or keyworker who should manage and coordinate treatment, care, support and transitions for children and young people with autism. Although the cost of implementing such a recommendation is likely to be substantial, the GDG judged that effective transition services and coordination of care and transitions of children and young people with autism by case coordinators or keyworkers was essential in order to ensure continuity of care and provision of effective and cost-effective services in adult life.

With regard to monitoring progress, no evidence was identified that allowed recommendations to be made about the organisation of services.

The GDG considered the legal framework and the recommendations for a local multi-agency strategy group and local autism team in the two existing NICE guidelines on autism. In line with both, and with a view to ensuring that localities would be able to provide a comprehensive service for children and young people with autism, the GDG agreed that there should be a local multi-agency strategy

group and a local autism team. The latter should be able to recognise, diagnose and assess children and young people with autism, and be able to either provide or to coordinate the provision of, the health and social care interventions outlined in this guideline. The GDG also agreed that the local autism team should have the skills to provide interventions or coordinate the delivery of effective care, and be able to refer to national services if such local skills were lacking. The GDG recognised that some children and young people with autism will have particular needs, including those who have coexisting conditions, are looked after by a local authority, from immigrant groups or with regression in skills. However, the emphasis is clearly on the local provision of comprehensive care for all children and young people with autism wherever this is possible.

For those young people (aged 16 or older) whose needs are complex or severe, the GDG saw the benefit of using the care programme approach (CPA; Department of Health, 2008) in England (or 'care and treatment plans' as they are known in Wales[17]) when the young person is transferring between services because it provides an appropriate framework within which this should take place.

Finally, the GDG recognised that autism is well characterised as a chronic disorder with lifelong disability in some individuals, yet the current health management structure is usually organised around single episodes of care. There is a significant body of international research into the management of chronic conditions such as diabetes and asthma, but nothing on autism. Key to commonly accepted strategies in chronic illness is the provision of a key worker. The theory and practice of management of chronic illness, as well as widely expressed service user opinion, indicate that a chronic care model, using a key worker approach, for the organisation of autism services could be appropriate and cost effective, but this needs formally evaluating with a RCT.

5.5 RECOMMENDATIONS

5.5.1 Clinical practice recommendations

Access to health and social care services

5.5.1.1 Ensure that all children and young people with autism have full access to health and social care services, including mental health services, regardless of their intellectual ability or any coexisting diagnosis.

[17]Mental Health (Wales) Measure 2010. See: http://www.assemblywales.org/bus-home/bus-legislation/bus-leg-measures/business-legislation-measures-mhs-2.htm

Organisation and delivery of services

5.5.1.2 The overall configuration and development of local services (including health, mental health, learning disability, education and social care services) for children and young people with autism, should be coordinated by a local autism multi-agency strategy group (for people with autism of all ages) in line with Autism in children and young people (covering identification and diagnosis) (NICE clinical guideline 128) and Autism in adults (NICE clinical guideline 142).

5.5.1.3 The assessment, management and coordination of care for children and young people with autism should be provided through local specialist community-based multidisciplinary teams ('local autism teams') which should include professionals from health, mental health, learning disability, education and social care services in line with Autism in children and young people (covering identification and diagnosis) (NICE clinical guideline 128) and Autism in adults (NICE clinical guideline 142).

5.5.1.4 Local autism teams should ensure that every child or young person diagnosed with autism has a case manager or key worker to manage and coordinate treatment, care, support and transition to adult care in line with Autism in children and young people (covering identification and diagnosis) (NICE clinical guideline 128).

5.5.1.5 Local autism teams should provide (or organise) the interventions and care recommended in this guideline for children and young people with autism who have particular needs, including:

- looked-after children and young people
- those from immigrant groups
- those with regression in skills
- those with coexisting conditions such as:
  - severe visual and hearing impairments
  - other medical problems including epilepsy or sleep and elimination problems
  - motor disorders including cerebral palsy
  - intellectual disability
  - severe communication impairment, including lack of spoken language, or complex language disorders
  - mental health problems.

5.5.1.6 Local autism teams should have a key role in the delivery and coordination of:

- specialist care and interventions for children and young people with autism, including those living in specialist residential accommodation
- advice, training and support for other health and social care professionals and staff (including in residential and community

settings) who may be involved in the care of children and young people with autism
- advice and interventions to promote functional adaptive skills including communication and daily living skills
- assessing and managing behaviour that challenges
- assessing and managing coexisting conditions
- reassessing needs throughout childhood and adolescence, taking particular account of transition to adult services
- supporting access to leisure and enjoyable activities
- supporting access to and maintaining contact with educational, housing and employment services
- providing support for families (including siblings) and carers, including offering short breaks and other respite care
- producing local protocols for:
  - information sharing, communication and collaborative working among healthcare, education and social care services, including arrangements for transition to adult services
  - shared care arrangements with primary care providers and ensuring that clear lines of communication between primary and secondary care are maintained.

5.5.1.7 Refer children and young people with autism to a regional or national autism service if there is a lack of:

- local skills and competencies needed to provide interventions and care for a child or young person with a complex coexisting condition, such as a severe sensory or motor impairment or mental health problem, **or**
- response to the therapeutic interventions provided by the local autism team.

Knowledge and competence of health and social care professionals

5.5.1.8 Health and social care professionals working with children and young people with autism in any setting should receive training in autism awareness and skills in managing autism, which should include:

- the nature and course of autism
- the nature and course of behaviour that challenges in children and young people with autism
- recognition of common coexisting conditions, including:
  - mental health problems such as anxiety and depression
  - physical health problems such as epilepsy
  - sleep problems
  - other neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD)
- the importance of key transition points, such as changing schools or health or social care services

- the child or young person's experience of autism and its impact on them
- the impact of autism on the family (including siblings) or carers
- the impact of the social and physical environment on the child or young person
- how to assess risk (including self-harm, harm to others, self-neglect, breakdown of family or residential support, exploitation or abuse by others) and develop a risk management plan
- the changing needs that arise with puberty (including the child or young person's understanding of intimate relationships and related problems that may occur, for example, misunderstanding the behaviour of others)
- how to provide individualised care and support and ensure a consistent approach is used across all settings
- skills for communicating with a child or young person with autism.

Making adjustments to the social and physical environment and processes of care

5.5.1.9 Take into account the physical environment in which children and young people with autism are supported and cared for. Minimise any negative impact by:

- providing visual supports, for example, words, pictures or symbols that are meaningful for the child or young person
- making reasonable adjustments or adaptations to the amount of person space given
- considering individual sensory sensitivities to lighting, noise levels and the colour of walls and furnishings.

5.5.1.10 Make adjustments or adaptations to the processes of health or social care, for example, arranging appointments at the beginning or end of the day to minimise waiting time, or providing single rooms for children and young people who may need a general anaesthetic in hospital (for example, for dental treatment).

Information and involvement in decision-making

5.5.1.11 Provide children and young people with autism, and their families and carers, with information about autism and its management and the support available on an ongoing basis, suitable for the child or young person's needs and developmental level. This may include:

- contact details for local and national organisations that can provide:
  - support and an opportunity to meet other people, including families or carers, with experience of autism
  - information on courses about autism
  - advice on welfare benefits, rights and entitlements

- information about educational and social support and leisure activities
- information about services and treatments available
- information to help prepare for the future, for example, transition to adult services.

5.5.1.12 Make arrangements to support children and young people with autism and their family and carers during times of increased need, including major life changes such as puberty, starting or changing schools, or the birth of a sibling.

5.5.1.13 Explore with children and young people with autism, and their families and carers, whether they want to be involved in shared decision-making and continue to explore these issues at regular intervals. If children and young people express interest, offer a collaborative approach to treatment and care that takes their preferences into account.

Families and carers

5.5.1.14 Offer all families (including siblings) and carers verbal and written information about their right to:

- short breaks and other respite care
- a formal carer's assessment of their own physical and mental health needs, and how to access these.

5.5.1.15 Offer families (including siblings) and carers an assessment of their own needs, including whether they have:

- personal, social and emotional support
- practical support in their caring role, including short breaks and emergency plans
- a plan for future care for the child or young person, including transition to adult services.

5.5.1.16 When the needs of families and carers have been identified, discuss help available locally and, taking into account their preferences, offer information, advice, training and support, especially if they:

- need help with the personal, social or emotional care of the child or young person, including age-related needs such as self-care, relationships or sexuality
- are involved in the delivery of an intervention for the child or young person in collaboration with health and social care professionals.

Interventions for life skills

5.5.1.17 Offer children and young people with autism support in developing coping strategies and accessing community services, including developing skills to access public transport, employment and leisure facilities.

Transition to adult services

5.5.1.18 Local autism teams should ensure that young people with autism who are receiving treatment and care from child and adolescent mental health services (CAMHS) or child health services are reassessed at around 14 years to establish the need for continuing treatment into adulthood.

5.5.1.19 If continuing treatment is necessary, make arrangements for a smooth transition to adult services and give information to the young person about the treatment and services they may need.

5.5.1.20 The timing of transition may vary locally and individually but should usually be completed by the time the young person is 18 years. Variations should be agreed by both child and adult services.

5.5.1.21 As part of the preparation for the transition to adult services, health and social care professionals should carry out a comprehensive assessment of the young person with autism.

5.5.1.22 The assessment should make best use of existing documentation about personal, educational, occupational, social and communication functioning, and should include assessment of any coexisting conditions, especially depression, anxiety, ADHD, obsessive-compulsive disorder (OCD) and global delay or intellectual disability in line with Autism in adults (NICE clinical guideline 142).

5.5.1.23 For young people aged 16 or older whose needs are complex or severe, use the care programme approach (CPA) in England, or care and treatment plans in Wales, as an aid to transfer between services.

5.5.1.24 Involve the young person in the planning and, where appropriate, their parents or carers.

5.5.1.25 Provide information about adult services to the young person, and their parents or carers, including their right to a social care assessment at age 18.

5.5.1.26 During transition to adult services, consider a formal meeting involving health and social care and other relevant professionals from child and adult services.

5.5.2 Research recommendations

5.5.2.1 What is the value of a key worker approach (defined by protocol and delivered in addition to usual care) for children and young people with autism in terms of parental satisfaction, functioning and stress and child psychopathology? (See Appendix 11 for further details.)

6 INTERVENTIONS AIMED AT THE CORE FEATURES OF AUTISM

6.1 INTRODUCTION

Autism is diagnosed on the basis of impairments in reciprocal social interaction and social communication, and restricted repetitive interests and behaviours. Social communication impairments include: abnormalities or delays in the use and understanding of spoken language; impairments in non-verbal social skills (using or understanding eye contact, gesture, body language, facial expression and so on); failure to respond to, initiate or enjoy social interactions with others, particularly with peers, and lack of imaginative and/or reciprocal social play. Rigid and repetitive behaviours include: stereotyped motor movements; repetitive play patterns; unusual interests; dislike of change or new situations; adherence to set routines; insistence on following one's own agenda, and over- or under-reaction to sensory stimuli, for example textures, sounds, smells or taste.

It is important to note that most children with autism do not show difficulties in *all* the areas listed above, and the manifestations and severity of symptoms vary in different situations and with age. However, for almost all individuals, the combination of social deficits and rigid behaviour patterns has a profound and pervasive impact on their lives and on those of their families. Indeed parents' ratings of their stress levels is highly correlated with the presence of restricted, repetitive and stereotyped behaviours in their child (Gabriels et al., 2005).

Some aspects of the core deficits are developmental in nature (meaning that they are characterised by delayed acquisition compared with typically-developing children (for example, the use of gestures to communicate); others are largely atypical in type or intensity (for example, literal understanding of language and unusual interests or preoccupations). Recognition of these different types of deficit has helped to inform approaches to psychosocial interventions.

Difficulties associated with the core deficits also have a major impact on individuals' long-term development, their opportunities for learning, inclusion in society, and ability to live independently as adults. Thus, it is important that children and their families should have access to early intervention wherever possible (NCCWCH, 2011). It is also essential to recognise the need for intervention strategies that focus not only on the core symptoms but that can also address a broad range of developmental outcomes, help to reduce coexisting difficulties, and improve adaptation and family life. Common associated behaviours and difficulties are covered in Chapter 8.

Current practice

Only a limited range of interventions that target the core features of autism are available in the UK, and existing programmes are very variable in their availability

and quality. Furthermore, the evidence-base for effectiveness, even for those interventions that are more widely available, is often poor (Charman, 2011). Broadly, available interventions for the core features of autism fall into two areas:
(a) psychosocial interventions with the child/young person or parents/carers that provide information about the core features of autism but focus mainly on improving social and communication skills (these interventions usually also provide some information on repetitive, stereotyped or rigid behaviours and advice on the management of behaviours that challenge); and (b) the use of pharmacological interventions to reduce aspects of rigid or repetitive behaviours that appear to be associated with mental health problems or, behaviours that challenge. There are no psychosocial interventions with the child/young person or parents/carers that focus specifically on the understanding and management of repetitive, stereotyped or rigid behaviours.

6.1.1 Clinical review protocol – interventions aimed at the core features of autism

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 20 (further information about the search strategy can be found in Appendix 7).

6.1.2 Outcomes – core autism features

A large number of outcome measures for core autism outcomes were reported, outcome measures for which data were extracted are listed in Table 21.

Table 20: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s)	**RQ 4.1**: For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for the core features of autism (overall autistic behaviours, impaired reciprocal social communication and interaction, and restricted interests and rigid and repetitive behaviours)* when compared with alternative management strategies? *Subgroup analyses will examine and compare treatment effects on core autism features when the interventions are specifically aimed at these features (direct outcomes) and when the primary target of the intervention was another outcome but effects on core autism features are examined (indirect outcomes).
Sub-question(s)	**RQ 4.1.1**: For children and young people with autism, and their families and carers, is the engagement with or effectiveness of interventions aimed at the core features of autism different for: • looked-after children • immigrant groups • children with regression in skills? **RQ 4.1.2**: For children and young people with autism is the effectiveness of interventions aimed at the core features of autism moderated by: • the nature and severity of the condition • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional problems and disorders) • age • gender • the presence of sensory differences • IQ • language level • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special educational needs)? **RQ 4.1.3**: For children and young people with autism is the effectiveness of interventions aimed at the core features of autism mediated by: • the intensity of the intervention • the duration of the intervention • the length of follow-up • programme components?
Objectives	To evaluate the clinical and cost effectiveness of interventions aimed at the core features of autism for children and young people with autism.

Criteria for considering studies for the review	
Population	Children and young people (from birth until their 19th birthday) with autism, (across the full range of intellectual ability) and their families and carers. If some, but not all, of a study's participants are eligible for our review, we will ask the study authors for disaggregated data. If it is not possible to obtain the appropriate disaggregated data, then the study will be included if the majority (at least 51%) of its participants are eligible for review. If it is not possible to determine the exact percent of a study's participants who are eligible, then the study will be included if its participants are eligible on average (for example, the mean participant age is less than 19 years). Consideration will be given to the particular management and support needs of: • looked-after children • immigrant groups • children with regression in skills. Excluded groups include: • adults (19 years and older).
Intervention	Psychosocial, biomedical or pharmacological interventions aimed at improving the core features of autism as a direct or indirect outcome.
Comparison	No treatment or treatment as usual (includes placebo and waitlist control up until receiving intervention), other active interventions.
Critical outcomes	• **Overall autistic behaviours** (as measured by total scores on autistic behaviour checklists or scales, including the Childhood Autism Rating Scale [CARS]) • **Impaired reciprocal social communication and interaction** (as measured by: diagnostic scales including the Autism Diagnostic Observation Schedule [ADOS]/ADOS-Generic [ADOS-G] Communication and Social Interaction domains; social skills scales including the Social Skills Rating System [SSRS]; joint attention and engagement as measured by behavioural observations) • **Restricted interests and rigid and repetitive behaviours** (as measured by: diagnostic scales including the ADOS/ADOS-G Repetitive Behavior domain; repetitive behaviour scales; compulsions as measured by the Children's Yale-Brown Obsessive Compulsive Scale [CYBOCS])
Time points	Some studies may measure outcomes at multiple time points. We will run the following analyses: • post-intervention (end of treatment) • longest follow-up
Study design	• RCTs • Systematic reviews Non-English language papers will be excluded, as will books, dissertation abstracts, trade magazines, policy and guidance, and non-empirical research.

Include unpublished data?	Yes, but only where: • the evidence was accompanied by a trial report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	No limit
Minimum sample size	• N ≥ 10 per arm (ITT) Exclude studies with >50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
Study setting	• Primary, secondary and tertiary health and social care. This guideline will also be relevant to other health and social care settings (including forensic services and youth justice settings) although they are not explicitly covered. • The guideline will also address interventions relevant to early years services and educational settings.
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, HTA, IBSS, MEDLINE, PreMEDLINE, PsycEXTRA, PsycINFO, Social Policy and Practice, Sociological Abstracts, SSA, SSCI
Date searched	Systematic reviews: 1995 up to January 2013. RCTs: inception of database up to January 2013
Searching other resources	Hand-reference searching and citation searches of included studies, hand-searching of the 'Research Autism' website, and searching the ISRCTN and ClinicalTrials.gov website using the term 'autism'.
The review strategy	• The initial aim is to conduct a meta-analysis evaluating the clinical effectiveness of the interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. Consider subgroup meta-analyses that takes into account the effectiveness of interventions as moderated by: • the nature and severity of the condition • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional problems and disorders) • age • gender • the presence of sensory differences • IQ • language level • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs).

Table 21: Outcome measures for core autism features extracted from studies of interventions aimed at the core features of autism

Sub-category of the core features of autism	Scale
Overall autistic behaviours	• Autism Behaviour Checklist (Krug et al., 1980, 1993) – total score, and Sensory, Social Relatedness, Body and Object Use, Language, and Socialization subscales • ADOS (Lord et al., 1999) – Severity, total score • Autism Treatment Evaluation Checklist (ATEC; Rimland & Edelson, 1999) – total score, and Speech/Language/Communication, Sociability, Sensory/Cognitive Awareness, and Health/Physical/ Behavior subscales • Behavioural observation: individual education plan goal attainment for targeted objectives (study-specific measure; Ruble et al., 2010) • Child Behavior Checklist (CBCL) for ages 1.5–5 years (Achenbach, 2002) – PDD • CARS (Schopler et al., 1988) • Children's Global Assessment Scale (CGAS; Shaffer et al., 1983) • Children's Social Behavior Questionnaire (CSBQ; Luteijn et al., 1998) • Clinical Global Impressions scale - Improvement (CGI-I; Guy, 1976) adapted to autism – total score and Response to Social Interaction, Social Initiation, Use of Speech, Repetitive Behaviour, Behaviour Problem, Activity Level, Sleep Problem and Digestive Problem subscales • CGI-Severity (CGI-S; Guy, 1976) – total score • Developmental Behaviour Checklist (DBC; Einfeld & Tonge, 2002) • Diagnose of Psykotisk Adfærd hos Børn (DIPAB; Diagnosis of Psychotic Behavior in Children [Haracopos & Kelstrup, 1975]) – total score • Gilliam Autism Rating Scale (GARS; Gilliam, 1995) – Autism Quotient • Global Autism Composite Improvement (CGI Adapted to Global Autism [CGI-AD] and CYBOCS [Goodman et al., 1989] Compulsions subscale change score) • Parent Global Impressions-Revised (PGI-R) scale (study-specific; Adams et al., 2011) – Overall Improvement and Average Improvement • Parent's Rating Questionnaire (study-specific [Chan et al., 2009]) – total score, and Language, Social Interaction, Stereotyped Behaviour and Motor Functioning subscales • Pervasive Development Disorder Behavior Inventory (PDDBI; Cohen & Sudhalter, 2005) – Autism Composite, and Sensory, Maladaptive Behaviour, and Social, Language and Communication Abilities subscales • Positive treatment response (much improvement or minimal improvement on CGI-I) • Positive treatment response (number of participants showing an improvement in ADOS diagnostic classification based on total score) • Positive treatment response (study-specific [Wong et al., 2010] parent-reported 'better than before') for: social relatedness (social response, social initiation, eye contact, share, curiosity, patience); non-verbal and verbal communication (expressive language, receptive language, pointing, imitation); stereotypy interest and behaviour (temper, compulsive behaviour, adaptation to change); cognition (memory,

	learning ability); motor abnormalities (motor skill, coordination, drooling); other parent-reported changes (appetite, attention span, sleeping pattern, 'crafty') • Positive treatment response (>20% improvement on CARS) • Positive treatment response (decrease of >4.07 points on CARS) • Positive treatment response (>20% improvement on CGAS) • Ritvo-Freeman Real Life Rating Scale (RF-RLRS; Freeman et al., 1986) – total score, and Motor, Social, Affective, Sensory and Language subscales • Secretin Outcome Survey-Modified (SOS-M; study-specific [Unis et al., 2002]) – total score and Social, Communication, Repetitive Behaviour, Digestive, Mood, Sensory, Hyperactivity, Lethargy and Sleep subscales • Severity of Autism Scale (Adams et al., 2009c) – total score • Social Communication Questionnaire (SCQ; Rutter et al., 2003) – total score • Turgay DSM-IV PDD Rating Scale (Turgay, 1993)
Impaired reciprocal social communication and interaction	• A Developmental Neuropsychological Assessment – Second Edition (NEPSY-II; Korkman et al., 2007a, 2007b) – Affect recognition subscale • Adapted Skillstreaming Checklist (ASC; study-specific [Lopata et al., 2010] adapted from Skillstreaming curriculum [Goldstein et al., 1997; McGinnis & Goldstein, 1997]) – total score • Assessment of Perception of Emotion from Facial Expression (Spence, 1995a) • Assessment of Perception of Emotion from Posture Cues (Spence, 1995b) • Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) – Reciprocal Social Interaction and Non-Verbal Communication subscales • ADOS (Lord et al., 1999)/ ADOS-G (Lord et al., 2000) – Communication and Social Interaction subscales • ADOS-Toddler module (ADOS-T) (Lord et al., 2012) – Social Affect domain • Bayley Scales of Infant Development, 3rd edition (Bayley, 2005) – Social-Emotional scale • Behavior Assessment System for Children, 2nd edition, Parent Rating Scales (BASC-2-PRS; Reynolds & Kamphaus, 2004) – Social Skills subscale • Behavioural observation: positive social interactions (Starting/Maintaining Social Interactions subscale and Social Intention Without Initiating Interaction [for instance, proximity] subscale); negative social interactions (unpleasant social behaviours that stop or decrease the likelihood of positive social interaction) (study-specific, Hopkins et al., 2011) • Behavioural observation: child communication acts (study-specific, Aldred et al., 2004); parent–child joint/shared attention (study-specific, Aldred et al., 2004; Kaale et al., 2012; Kasari et al., 2010 or coded using the Precursors of Joint Attention Measure [PJAM; Yoder & Symons, 2010] in Schertz et al., 2013); parent–child joint attention responses (study-specific, Kasari et al., 2010; or coded using PJAM in Schertz et al., 2013); parent–child joint engagement (study-specific, Kaale et al., 2012; Kasari et al., 2010); teacher–child joint/shared attention (study-specific, Kaale et al., 2012) • Behavioural observation: mother–child interaction (study-specific [Kasari et al., 2006]) – Coordinated Joint Attention Looks, Showing,

	Pointing, and Giving, and Duration of Joint Attention (seconds; Bakeman & Adamson, 1984) subscales • Behavioural observations: number of intervals of social interaction with unfamiliar typically-developing peer or number of child-initiated social interactions with familiar and with unfamiliar typically-developing peer (using study-specific adapted version [Roeyers, 1996] of coding system developed in Lord, 1984; Lord & Hopkins, 1986; Lord & Magill, 1989); percentage of time in joint engagement in playground (Playground Observation of Peer Engagement; Kasari et al., 2005, 2011) • Behavioural observation: frequency of child-initiated social interactions with typically-developing peers and duration of all social interactions with typically-developing peers (study-specific; Owens et al., 2008) • Behavioural observation: socially engaged imitation (study-specific coding scheme [Landa et al., 2011] of structured imitation task modified from Rogers et al., 2003) • Behavioural observation ('Toy Play' condition of the standard functional analysis, Iwata et al., 1994) – appropriate vocalisation • Behavioural observation (study-specific; Johnson et al., 2010) – frequency of positive vocalisations, and frequency of social initiations • Behavioural observation (coded using PJAM) – focusing on faces and turn-taking • Benton Facial Recognition Test (Benton, 1980) – short form and long form • Brigance Inventory of Early Development (Brigance, 2004) – Social Skills subscale • CARS – Social Communication (composite of five subscales: Imitation, Verbal Communication, Non-Verbal Communication, Consistency of Intellectual Responses, and General Impressions) • Children's Communication Checklist-2 (CCC-2; Bishop, 2003 [translated by Geurts, 2007]) – total score, and Social Relations, Interests, Inappropriate Initialisation, Stereotyped Conversation, Context Use, Non-Verbal Communication, and Pragmatics Subscales • CSBQ (Hartman et al., 2006) – total score • Communication and Symbolic Behavior Scales Developmental Profile (CSBS-DP; Wetherby & Prizant, 2002) – Initiating Joint Attention and Shared Positive Affect subscales and social composite raw scores • Diagnostic Analysis of Non-verbal Accuracy 2 (Nowicki, 1997) – Child Faces subscale • DIPAB – Communication and Interaction (K-scores), Resistance to Communication and Interaction (M-scores), and Social Interaction or Isolation (I-scores) • Dylan is Being Teased (Attwood, 2004a) • Early Social Communication Scales (ESCS; Seibert et al., 1982; Mundy et al., 2003) – Initiating Joint Attention, Responding to Joint Attention, Initiating Behavioural Requests, Coordinated Joint Attention Looks, Joint Attention and Shared Positive Affect, and Utterance, Showing, Pointing and Giving subscales • Ekman emotion recognition photographs (Ekman & Friesen, 1975; 1976) • Emotion recognition in drawings (study-specific; Hopkins et al., 2011) • Emotion recognition – composite score from Ekman emotion recognition photographs and study-specific emotion recognition in drawings (study-specific; Hopkins et al., 2011)

	• Emotion Regulation and Social Skills Questionnaire (study-specific [Beaumont & Sofronoff, 2008]) – total score • Emotional vocabulary (study-specific; Golan et al., 2010) • Faces Task (Baron-Cohen et al., 1997) • Friendship Qualities Scale (Bukowski et al., 1994) – total score • GARS – Social Interaction and Communication subscales • Imitation tasks (Rogers et al., 2003) – Imitative Sequences score • Index of Empathy for Children and Adolescents (Bryant, 1982) • James and the Maths Test (Attwood, 2004b) • Let's Face It! Skills Battery (Tanaka & Schultz, 2008) – Matching Identity Across Masked Features, Featural and Configural Face Dimensions, Matching Identity Across Expression, Parts/Whole Identity, and Immediate Memory For Faces subtests • Levels of Emotional Awareness Scale for Children (LEAS-C; Bajgar et al., 2005) – total score • Loneliness Scale (Asher et al., 1984) – total score • Parent-Child Free Play Procedure (study-specific, Carter et al., 2011) – frequency of intentional communication (weighted) • Parent Interview for Autism-Clinical Version (Stone et al., 2003) – Non-Verbal Communication subscale • PDDBI – Social Pragmatic and Social Approach subscales • PGI-R – Socialiability Improvement and Eye Contact Improvement • Piers-Harris Self-Concept Scale (Piers, 1984) – Popularity subscale • Positive treatment response ('much improved/very improved' on CGI-I) • Positive treatment response (number of participants showing improvement in ADOS diagnostic classification based on Communication or Socialisation domain) • Positive treatment response (much improvement or minimal improvement on CGI-I) • Quality of Play Questionnaire (QPQ; Frankel & Mintz, 2011) – Guest, Engage and Disengage subscales • Scales of Independent Behavior-Revised (SIB-R; Bruininks et al., 1996) – Social Interaction subscale • Situation-Facial Expression Matching – Distant Generalisation subscale (study-specific; Golan et al., 2010) • Skillstreaming Knowledge Assessment (study-specific [Lopata et al., 2010]) – total score • Social Behavior Rating Scale (Roeyers & Impens, 1993) • SCQ – Reciprocal Social Interaction, Communication, Social Peer Interest, Eye Contact, and Gaze Aversion subscales • Social Competence Inventory (Rydell et al., 1997): Pro-Social index and Social Initiation index • Social Dissatisfaction Questionnaire (Asher & Wheeler, 1985) – total score • Social engagement task (Dawson et al., 2004) – Mean Social Orient I and Mean Orient to Joint Attention • Social Network Survey (SNS; study-specific [Kasari et al., 2012]) – social network salience ratio, indegrees (number of received friendship nominations) and rejects (number of times child identified as someone other children do not like to 'hang out with') • Social Responsiveness Scale (SRS; Constantino, 2002; Constantino & Gruber, 2005) – total score and Social Awareness, Social Cognition, Social Communication, Social Motivation and Autistic Mannerisms

	subscales • Social Self-efficacy Scale (Ollendick & Schmidt, 1987) – total score • Social Skills Questionnaire (SSQ; Spence, 1995c) – total score • SSRS (Gresham & Elliott, 1990) – Standardised Social Skills score or total score and Assertion subscale • Teacher Perception of Social Skills (TPSS; study-specific [Kasari et al., 2012]) – total score • Test of Adolescent Social Skills Knowledge (Laugeson & Frankel, 2006) – total score • Theory of Mind test (ToM test; Muris et al., 1999) – total score
Restricted interests and rigid and repetitive behaviours	• ADOS/ADOS-G – Repetitive Behaviours domain • ADOS-T – Restricted, Repetitive Behaviours domain • Behavioural observation ('Toy Play' condition of the standard functional analysis, Iwata et al., 1994) – vocal stereotypy and physical stereotypy • CYBOCS -PDD Version (Scahill et al., 2006) – Compulsions subscale • DIPAB – unusual or bizarre behaviour (B-scores) • GARS – Stereotyped Behaviours subscale • PDDBI – Sensory/Perceptual Approach Behaviours, and Ritualisms/ Resistance to Change subscales • Positive treatment response ('much improved/very improved' on CGI-I; >25% improvement on CYBOCS-PDD and 'much improved/ very improved' on CGI-I) • Repetitive Behavior Scale (RBS; Bodfish et al., 1998) – total score • RBS-Revised (RBS-R; Bodfish et al., 1999) – Compulsive, Restrictive, Ritualistic, Sameness, Self-injurious, and Stereotyped subscales • SCQ – Stereotyped Behaviour subscale

6.2 PSYCHOSOCIAL INTERVENTIONS – CORE FEATURES OF AUTISM

6.2.1 Introduction

Psychosocial interventions to improve social and communication outcomes[18]

Many clinical teams now offer group and/or individualised parent training programmes for families, usually in the immediate post-diagnostic period. These are designed to increase parental knowledge and confidence and to improve their ability to manage their child's behaviour and successfully communicate and interact with their child. It is proposed that this early support will, in turn, result in improvements in the social communication development of the child. However, to date even the most widely accessed programmes have not been well evaluated (for example, the NAS EarlyBird/ EarlyBird Plus programmes[19] and the Hanen More than Words® programme). There are various other speech and language therapy interventions

[18] For interventions with a focus on specific speech and language problems see Chapter 8.
[19] http://www.autism.org.uk/our-services/residential-community-and-social-support/parent-and-family-training-and-support/early-intervention-training/earlybird.aspx

available, either on a group or individual basis, which aim to promote speech and language (see Chapter 8, Section 8.3.3).

Additional programmes or frameworks that aim to ameliorate some aspects of the core features of autism include the Treatment and Education of Autistic and Communication-Handicapped Children (TEACCH) programme (Mesibov et al., 2004) and the Social-Communication, Emotional Regulation, and Transactional Support approach (Prizant et al., 2006). These are often implemented in education settings and aim to provide a structure for everyday activities; particular emphasis is placed on the use of pictorial prompts and cues to help the child/ young person to move from one activity to another. Social-Communication, Emotional Regulation, and Transactional Support has a particular focus on helping adults to alter their interactive style towards the child and to make activities motivating and engaging. Some parents seek a programme of intensive and targeted education for their children that extends beyond the remit of most parent training interventions; these are often delivered in the home and sometimes in school settings. Such interventions are designed to teach new skills, to minimise the negative consequences of impairments and to assist in the generalisation of learning. These programmes are not routinely delivered within the NHS or social care services, and, when publicly funded, are usually supported from education budgets.

Some of these targeted interventions are known as ABA interventions, although strictly, ABA is an applied science rather than a single intervention approach for autism or any other condition. In practice, the extent to which educational interventions are described as 'ABA' depends on the style of record keeping used for teaching and measuring progress, the extent to which teaching strategies are formalised and structured, the terminology used to define these strategies (such as prompting and reinforcement) and the professional background of the person overseeing the intervention. In this sense, ABA was not addressed as a discrete intervention within this guideline because the emphasis was on outcomes rather than intervention type. However, it should be noted that several interventions described in the guideline incorporate behavioural principles

Early intensive behavioural interventions (EIBI) are reviewed in Howlin and colleagues (2009). Within the above programmes, specific systems to promote communication may be used. For example the Picture Exchange Communication System (PECS; Frost & Bondy, 1994) is an approach to teaching communication that is widely used in educational, clinic and home-based settings and is behaviourally-based and designed to develop spontaneous communication in preverbal children. PECS is not a specific intervention and its success depends entirely on the competency of those using it to facilitate the development of vocal verbal behaviour.

For school-age children and young people, some local services (both health and education) offer time-limited (typically around six to 12 sessions) group-based social skills training. These interventions aim to improve participants' ability to understand social situations, to communicate with others and to develop coping

strategies, such as the use of mental 'toolboxes' in difficult social situations. Another common approach is the use of behavioural principles such as rehearsal, aided by the use of narratives and picture books ('stories') to help children and young people with autism better understand social situations. The aim is to improve social interaction and self-regulation and to reduce anxiety, temper tantrums and outbursts. Social stories provide individual problem solving approaches to skill development and managing problematic behaviour (Sansosti, 2004).

Psychosocial interventions to ameliorate negative impacts of repetitive, stereotyped or rigid behaviours or sensory sensitivities

There are no parent training programmes, or other programmes or frameworks, currently delivered in education settings that focus specifically on helping parents and carers to understand and manage children and young people's repetitive stereotyped and rigid behaviours. Most of the intervention programmes described above will include some information about repetitive stereotyped and rigid behaviours typical of autism with the aim of minimising the maladaptive aspects of the behaviours and thus countering the developmental 'downstream' effects. For example, over-focus on a particular object or topic of interest may limit opportunities for incidental learning from listening, observation or participation in other activities. Similarly, rigidity of routines or sensory impairments may well reduce opportunities for engaging with a range of people, places and experiences. As with the social-communication problems, manifestations of repetitive, stereotyped and rigid behaviours will vary with age as well as with context. Thus, rather than aiming to eliminate such behaviours completely, the focus is usually on minimising the *impact* of the behaviour on individuals' lives. For example, the opportunity to indulge in stereotyped mannerisms, at least at certain limited times of the day (when they are not otherwise occupied and/or observed by other children) may be a crucial form of stress release for some young people with autism. As children get older and more aware, many learn to carry out some repetitive behaviours more discreetly (for example, carrying an unusual attachment object in their pockets rather than in their hands) to prevent drawing attention to themselves. Special interests can also be a great motivator and can be paired with less desirable activities or be given at the end of an activity as a reward. Some interests can be built upon and lead into potential employment or leisure pursuits.

Although the impact of rigid behaviours and insistence on routines and rituals can be effectively reduced by taking a 'problem solving' approach to intervention, as described above, it is important to recognise that a more individualised approach to understanding and devising strategies to target these behaviours may be helpful for parents, carers and the child or young person with autism. Further restricted, stereotyped and repetitive behaviours can also result in behaviours that challenge. Unexpected interruption of the child or young person's routines, or sudden restricted access to topics or objects of special interest, can give rise to irritability or aggression, resulting in risk to other people, self or the environment. In such instances, a thorough assessment of the possible causes of the behaviour and, if

necessary, the implementation of additional interventions are likely to be required (see Chapter 7).

6.2.2 Studies considered[20]

Ninety-seven papers from the search met the eligibility criteria for full-text retrieval. Of these, 39 RCTs provided relevant clinical evidence and were included in the review. Twenty-nine of these studies examined the efficacy of psychosocial interventions on core autism features as a direct outcome (target of intervention), and ten provided data on core autism features as an indirect outcome. All studies were published in peer-reviewed journals between 1996 and 2013. In addition, 58 studies were excluded from the analysis. The most common reasons for exclusion were that the study was a systematic review with no new useable data and any results from meta-analysis were not appropriate to extract, group allocation was non-randomised, the study was a non-systematic review, or the sample size was smaller than ten participants per arm. Summary tables of included studies can be found in the clinical evidence subsections below; further information about both included and excluded studies with direct outcomes aimed at core autism features can be found in Appendix 12b.

Psychosocial interventions – overall autistic behaviours

Data were extracted from seven studies for direct and indirect effects of psychosocial interventions on overall autistic behaviours (as defined by scores on autism behaviour rating scales).

One behavioural intervention study examined effects on overall autistic behaviours as an indirect outcome (DAWSON2010[21] [Dawson et al., 2010]).

Two educational intervention trials examined effects on overall autistic behaviours as a direct outcome (RUBLE2010 [Ruble et al., 2010]; STRAIN2011 [Strain & Bovey II, 2011]).

Of three parent training studies, one examined intervention effects on overall autistic behaviours as a direct outcome (JOCELYN1998 [Jocelyn et al., 1998]), and two examined effects on overall autistic behaviours as indirect outcomes (TONGE2006[22] [one trial reported across two papers: Tonge et al., 2006; Tonge et al., 2012] and PAJAREYA2011[23] [Pajareya & Nopmaneejumruslers, 2011]).

One social-communication intervention examined effects on overall autistic behaviours as an indirect outcome (ALDRED2001 [one trial reported across two papers: Aldred et al., 2001; Aldred et al., 2004]). The target (direct outcome) of the

[20] Here and elsewhere in the guideline, each study considered for review is referred to by a study ID in capital letters (primary author and date of study publication, except where a study is in press or only submitted for publication, then a date is not used).
[21] See Chapter 8, Section 8.2.3, for direct outcomes from DAWSON2010.
[22] See Chpater 8, Section 9.2.2, for direct outcomes from TONGE2006.
[23] See Chapter 7, Section 8.2.3, for direct outcomes from PAJAREYA2011.

social-communication intervention in ALDRED2001 was the core autism feature of impaired reciprocal social communication and interaction (see Section 6.2.5).

Psychosocial interventions – core autism feature of impaired reciprocal social communication and interaction

Data were extracted from 33 studies for direct and indirect effects of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction.

One alternative and augmentative communication (AAC) study examined effects on reciprocal social communication and interaction as an indirect outcome (HOWLIN2007[24] [one trial reported across two papers: Howlin et al., 2007; Gordon et al., 2011]).

One animal-based intervention examined effects on reciprocal social communication and interaction as a direct outcome (BASS2009 [Bass et al., 2009]).

One arts-based intervention study examined effects on reciprocal social communication and interaction as an indirect outcome (GATTINO2011[25] [Gattino et al., 2011]).

Of two behavioural intervention studies, one examined effects on reciprocal social communication and interaction as a direct outcome (INGERSOLL2012 [Ingersoll, 2012]), and one examined indirect effects on social communication and interaction (ROGERS2012 [Rogers et al., 2012]).

Seven cognitive intervention trials examined effects on reciprocal social communication and interaction as a direct outcome (BEAUMONT2008 [Beaumont & Sofronoff, 2008], BEGEER2011 [Begeer et al., 2011], GOLAN2010 [Golan et al., 2010], HOPKINS2011 [Hopkins et al., 2011], RYAN2010 [Ryan & Charragain, 2010], TANAKA2010 [Tanaka et al., 2010] and YOUNG2012 [Young & Posselt, 2012]).

Two educational intervention studies examined effects on reciprocal social communication and interaction as an indirect outcome (STRAIN2011[26] and WHALEN2010[27] [Whalen et al., 2010]).

Of three parent training studies, one examined intervention effects on reciprocal social communication and interaction as a direct outcome (DREW2002 [Drew et al., 2002]), and two examined effects on reciprocal social communication and interaction as indirect outcomes (SOFRONOFF2004[28] [Sofronoff et al., 2004] and WELTERLIN2012[29] [Welterlin et al., 2012]).

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[24] See Chapter 7, Section 8.3.3, for direct outcomes from HOWLIN2007.
[25] See Chapter 7, Section 8.3.3, for direct outcomes from GATTINO2011.
[26] See Section 6.2.3, for direct outcomes from STRAIN2011.
[27] See Chapter 7, Section 8.3.3 for direct outcomes from WHALEN2010.
[28] See Chapter 7, Section 7.2.2 for direct outcomes from SOFRONOFF2004.
[29] See Chapter 8, Section 8.3.3 for direct outcomes from WELTERLIN2012.

Sixteen social-communication intervention trials examined effects on reciprocal social communication and interaction as a direct outcome (ALDRED2001, CARTER2011 [Carter et al., 2011], DEROSIER2011 [DeRosier et al., 2011], FRANKEL2010 [Frankel et al., 2010], GREEN2010 [Green et al., 2010], KAALE2012 [Kaale et al., 2012], KASARI2006 [one trial reported across three papers: Kasari et al., 2006; Kasari et al., 2008; Lawton & Kasari, 2012], KASARI2010 [Kasari et al., 2010], KASARI2012 [Kasari et al., 2012], KOENIG2010 [Koenig et al., 2010], LANDA2011 [Landa et al., 2011], LAUGESON2009 [Laugeson et al., 2009], LOPATA2010 [Lopata et al., 2010], OWENS2008 [Owens et al., 2008], ROEYERS1996 [Roeyers, 1996], SCHERTZ2013 [Schertz et al., 2013]).

Psychosocial interventions – the core autism feature of restricted interests and rigid and repetitive behaviours

Data were extracted from five studies for indirect effects of psychosocial interventions on the core autism feature of restricted interests and rigid and repetitive behaviours.

Two behavioural intervention studies examined effects on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (DAWSON2010[30] and ROGERS2012[31]).

One cognitive intervention study examined effects on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (YOUNG2012[32]).

One study examined effects of parent training (as an adjunct to antipsychotics) on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (AMAN2009[33] [one trial reported across three papers: Aman et al., 2009; Arnold et al., 2012; Scahill et al., 2012]).

Finally, one social-communication intervention study examined effects on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (GREEN2010[34]).

[30] See Chapter 8, Section 8.2.3 for direct outcomes from DAWSON2010.
[31] See Chapter 8, Section 8.4.3 for direct outcomes from ROGERS2012.
[32] See Section 6.2.5 for direct outcomes from YOUNG2012.
[33] See Chapter 6, Section 7.2.2 for direct outcomes from AMAN2009.
[34] See Section 6.2.5 for direct outcomes from GREEN2010.

6.2.3 Clinical evidence – effect of psychosocial interventions on overall autistic behaviours

Behavioural interventions for overall autistic behaviours as an indirect outcome

The behavioural intervention trial (DAWSON2010) involved a comparison between the Early Start Denver Model (ESDM; Rogers & Dawson, 2009) and treatment as usual in preschool children with autism (see Table 22).

Evidence for the effectiveness of the one included behavioural intervention (ESDM) on overall autistic behaviours and the quality of evidence are presented in Table 23. The full GRADE evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 22: Study information table for included trials of behavioural interventions for overall autistic behaviours

	ESDM versus treatment as usual
No. trials (N)	1 (48)
Study IDs	DAWSON2010
Study design	RCT
% female	29
Mean age (years)	2.0
IQ	60.2 (assessed using the Mullen Scales of Early Learning [MSEL]: early-learning composite score; Mullen, 1995)
Dose/intensity (mg/hours)	1,581 with a trained therapist (20 hours/week). Parents reported spending 1,695 hours using ESDM strategies.
Setting	Academic research (university) and home
Length of treatment (weeks)	104
Continuation phase (length and inclusion criteria)	104

Table 23: Evidence summary table for effects of behavioural intervention on overall autistic behaviours as an indirect outcome

	ESDM versus treatment as usual	
Outcome	Overall autistic behaviours	Autism DSM-IV diagnosis
Outcome measure	ADOS: Severity	Number of participants who showed improvement in diagnosis from autistic disorder to PDD not otherwise specified (NOS)
Study ID	DAWSON2010	
Effect size (CI; p value)	SMD -0.16 (-0.75, 0.43; p = 0.60)	OR 0.12 (0.01, 1.07; p = 0.06)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	Low[2,3]
Number of studies/participants	K = 1; N = 45	K = 1; N = 39
Forest plot	1.1.1; Appendix 13	

Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators

and participants were non-blind, and risk of detection bias is unclear/unknown as blinding of outcome assessment is unclear.
[3]Downgraded for serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm.

The single included behavioural intervention trial examined indirect effects on overall autistic behaviours. The ESDM intervention was based on developmental and applied behavioural analytic principles and teaching strategies were consistent with the principles of ABA, such as the use of operant conditioning, shaping and chaining, and each child's plan was individualised. This study found no evidence of statistically significant effects for ESDM relative to treatment as usual as measured by the improvement in autism based on DSM-IV diagnosis or the ADOS.

Educational interventions for overall autistic behaviours as a direct outcome

One of the educational intervention studies (RUBLE2010) compared the Collaborative Model for Promoting Competence and Success (COMPASS) with treatment as usual for children with autism, their parents and teachers. The second study (STRAIN2011) compared direct training according to LEAP with a LEAP intervention manual-only control (see Table 24).

Evidence for the effectiveness of educational interventions on overall autistic behaviours and the quality of evidence are presented in Table 25. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 24: Study information table for included trials of educational interventions for overall autistic behaviours

	COMPASS versus treatment as usual	**LEAP training versus manual-only control**
No. trials (N)	1 (35)	1 (294)
Study IDs	RUBLE2010	STRAIN2011
Study design	RCT	RCT
% female	17	Not reported
Mean age (years)	6.1	4.2
IQ	46.8 (assessed using the Differential Ability Scales [DAS]; Elliott, 1990)	61 (assessed using the MSEL – early-learning composite score)
Dose/intensity (mg/hours)	9 (one initial 2.5-3 hour consultation and four 1.5-hour coaching sessions approximately 6 weeks apart)	23 full days of training
Setting	Educational	Educational
Length of treatment (weeks)	39 weeks (one school year)	104 weeks
Continuation phase (length and inclusion criteria)	39 weeks (one school year)	104 weeks

Table 25: Evidence summary table for effects of educational intervention on overall autistic behaviours as a direct outcome

	COMPASS versus treatment as usual	**LEAP training versus manual-only control**
Outcome	Individual education plan goal attainment for targeted objectives (social skills, communication, and independence)	Overall autistic behaviours
Outcome measure	Behavioural observation	CARS: total
Study ID	RUBLE2010	STRAIN2011
Effect size (CI; p value)	SMD 1.42 (0.63, 2.20; p = 0.0004)	SMD -0.42 (-0.66, -0.19; p = 0.0005)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1,3]	Low[2,3]
Number of studies/participants	K = 1; N = 32	K = 1; N = 294
Forest plot	1.1.2; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance bias as intervention administrators were non-blind. There was also a high risk of detection bias as the primary outcome assessor was the non-blind investigator with a blinded secondary outcome assessor only rating 20% of behavioural observations. In addition, because only 20% of observations were double-coded and a standardised observation measure was not used the reliability and validity of this outcome measure is unclear.
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors were not reported.
[3]Downgraded for serious imprecision (N <400).

RUBLE2010 examined direct effects of the COMPASS programme on overall autistic behaviours. The aims of COMPASS were to improve objectives of individual education plans for children with autism by promoting home-school collaboration and teacher training. The three targeted goal areas for children with autism were social skills, communication and independence. This study found evidence for a large and statistically significant effect of COMPASS relative to treatment as usual for individual education plan goal attainment for targeted objectives as measured by behavioural observation (see Table 25). However, the confidence in the effect estimate (GRADE) was low because of risk of bias (non-blind outcome assessment) and imprecision (small sample size).

STRAIN2011 examined effects of LEAP training relative to manual-only control on overall autistic behaviours as a direct outcome. Core components of the intervention included: social skills training for typically developing peers to facilitate the social and communicative competence of their class peers with autism; teacher training (in the LEAP programme, autism, classroom organisation and management, teaching strategies. teaching communication skills, providing positive behavioural guidance, monitoring progress and collecting data on individual education plan goals, and promoting social interactions with typically-developing peers); and family skills training of adult family members in behavioural teaching strategies. This study found evidence for a small and statistically significant effect of LEAP training on overall autistic behaviours as measured by CARS total score (see Table 25). However, this evidence is of low quality (GRADE) because of risk of bias (the identity and

blinding of outcome assessors were not reported) and imprecision (small sample size).

Parent training interventions for overall autistic behaviours as a direct or indirect outcome

Two of the parent training intervention trials (TONGE2006, PAJAREYA2011) compared parent training programmes with treatment as usual for children with autism. The third trial (JOCELYN1998) compared parent and day care staff training with standard day care for children with autism (see Table 26).

Table 26: Study information table for included trials of parent training interventions for overall autistic behaviours

	Parent training versus treatment as usual	**Parent and day care staff training versus standard day care**
No. trials (N)	2 (137)	1 (36)
Study IDs	(1) TONGE2006 (2) PAJAREYA2011	JOCELYN1998
Study design	(1)-(2) RCT	RCT
% female	(1) 16 (2) 13	3
Mean age (years)	(1) 3.9 (2) 4.5	3.6
IQ	(1) 59.2 (assessed using the Psychoeducational Profile-Revised [PEP-R] – developmental quotient; Schopler et al., 1990) (2) Not reported	Performance IQ (PIQ) 63.1 (assessed using the Leiter International Performance Scale [LIPS]; Leiter, 1948)
Dose/intensity (mg/hours)	(1) 25 (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions) (2) 197.6 (15.2 hours/week)	50 hours (3 hours/week of educational seminars for 5 weeks and 3 hours/week of on-site day care staff consultation for 10 weeks, and three parent-staff review meetings at day care centre [estimated at 3 hours] and 2 in-home visits [estimated at 2 hours]; equating to 4 hours/week)
Setting	(1) Not reported (2) Home	Outpatient, educational (day care centre) and home-based
Length of treatment (weeks)	(1) 20 (2) 13	12
Continuation phase (length and inclusion criteria)	(1) 46 (including 6-month post-intervention follow-up) (2) 13	12

Evidence for the effectiveness of the parent training interventions on overall autistic behaviours and the quality of evidence are presented in Table 27. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 27: Evidence summary table for effects of parent training interventions on overall autistic behaviours as a direct or indirect outcome

	Parent and day care staff training versus standard day care	**Parent training versus treatment as usual**	
Outcome	Overall autistic behaviours (direct outcome)	Overall autistic behaviours (indirect outcome)	
Outcome measure	Autism Behavior Checklist: total	DBC: Autism Screening Algorithm (ASA)	CARS: total
Study ID	JOCEYLN1998	TONGE2006	(1) TONGE2006 (2) PAJAREYA2011
Effect size (CI; p value)	SMD -0.40 (-1.08, 0.27; p = 0.24)	SMD -0.06 (-0.47, 0.34; p = 0.76)	SMD -0.42 (-0.81, -0.03; p = 0.04)
Heterogeneity (chi²; p value; I²)	Not applicable		Chi² = 0.02, df = 1 (p = 0.89); I^2 = 0%
Quality of the evidence (GRADE)	Low[1]	Low[2,3]	Low[2,4]
Number of studies/participants	K = 1; N = 35	K = 1; N = 103	K = 2; N = 102
Forest plot	1.1.3; Appendix 13		

Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as parent-rated and parents were non-blind and involved in the intervention.
[4]Downgraded for strongly suspected publication bias – risk of selective reporting bias in TONGE2006 as trial protocol is not registered on ClinicalTrials.gov or ISRCTN and there is a potential conflict of interest as the manuals used in this study have been published by Jessica Kingsley Publishers, and the authors receive royalties (5%) from sales.

JOCELYN1998 examined direct effects of parent and day care staff training (over and above standard day care) on overall autistic behaviours. The intervention was delivered through: hospital-based educational seminars (covering an introduction to autism, behaviour analysis techniques, interventions aimed at communication, techniques to improve social interaction and engage the child in play, and problem solving); on-site consultations to day care centres (conducted in parallel with seminars to facilitate practical application of techniques); and psychoeducational and supportive work with the family (including review meetings at the day care centre with the parents, and home visits to parents where written information about autism was provided, parents were given the opportunity to discuss concerns and questions, expectations and goals for the child were discussed, and videotapes of the child at day care were reviewed to share intervention strategies and techniques). This study found no evidence for a statistically significant effect of parent and day care staff training relative to standard day care for overall autistic behaviours, as measured by the Autism Behaviour Checklist total score (see Table 27).

TONGE2006 examined effects of the Preschoolers with Autism (Brereton & Tonge, 2005) programme relative to treatment as usual on overall autistic behaviours as an indirect outcome. This study included two active intervention arms, the parent education and behaviour management (PEBM) training intervention as the

experimental intervention and the parent education and counselling (PEC) intervention as an attention-placebo condition to control for non-specific effects of the intervention. The intervention consisted of small group parent training sessions and individual family sessions. Group sessions (for both PEBM and PEC) included: education about autism; features of communication, social, play, and behavioural impairments; principles of managing behaviour and change; teaching new skills; improving social interaction and communication; services available; managing parental stress, grief and mental health problems; and sibling, family and community responses to autism. The key 'active' ingredient that was different in the PEBM and PEC intervention arms was that the parents were provided with workbooks, modelling, videos, rehearsal (with child when present), homework tasks and feedback in the PEBM individual family sessions, while for the PEC intervention although the educational material in the manual was the same, no skills training or homework tasks were set for the individual sessions and the emphasis was on non-directive interactive discussion and counselling. Initially the two active intervention arms were compared and there was no statistically significant difference between them for overall autistic behaviours as measured by the DBC-ASA score (SMD = -0.36 [-0.84, 0.12]; test for overall effect: Z = 1.46, p = 0.14). As a result, the two active intervention arms were combined and compared with the treatment as usual control group. This study found no evidence for a statistically significant effect of the Preschoolers with Autism programme (PEBM and PEC combined) on overall autistic behaviours as measured by the DBC-ASA score (see Table 27).

Both TONGE2006 and PAJAREYA2011 examined effects of parent training relative to treatment as usual on overall autistic behaviours (as measured by the CARS) as an indirect outcome. Further information on the Preschoolers with Autism programme in TONGE2006 is outlined above. PAJAREYA2011 examined effects of the Developmental Individual-difference, Relationship-based/Floortime™ intervention (Greenspan & Lewis, 2005) relative to treatment as usual. This programme involved parent training (with no contact with the child) and parents received didactic instruction about the principles of the intervention and psychoeducation about autism and one-on-one interactive home visits. During the home visits parents were trained to observe their child's cues and follow the child's lead and were taught to implement the Floortime techniques appropriate to their child's current level of functional development. As above, because of the two active intervention arms (PEBM and PEC) in TONGE2006, these two conditions were compared first and a statistically significant difference was found favouring the PEBM condition (the experimental arm over and above the attention-placebo, PEC, arm) for overall autistic behaviours as measured by the CARS score (SMD = -0.71 [-1.21, -0.22]; test for overall effect: Z = 2.85, p = 0.004). As a result the PEBM data were entered into the meta-analysis. The meta-analysis with data from two studies found evidence for a small and statistically significant effect of parent training on overall autistic behaviours as measured by the CARS total score (see Table 27). However, this evidence is of low quality (GRADE) due to imprecision (small sample size) and concerns regarding publication bias (trial protocol not registered and potential conflict of interest).

Social-communication intervention for overall autistic behaviours as an indirect outcome

The social-communication intervention trial (ALDRED2001) compared a caregiver-mediated social-communication intervention, Child's Talk (Aldred et al., 2001), with treatment as usual in young children with autism (see Table 28).

Table 28: Study information table for included trial of social-communication intervention for overall autistic behaviours

	Caregiver-mediated social-communication intervention (Child's Talk) versus treatment as usual
No. trials (N)	1 (28)
Study IDs	ALDRED2001
Study design	RCT
% female	11
Mean age (years)	Mean not reported (median ages: 4 years for the experimental group and 4.3 years for the control group).
IQ	Not reported
Dose/intensity (mg/hours)	Number of hours of intervention not reported (parents and children attended monthly intervention sessions for 6 months, followed by a further 6 months of less frequent maintenance sessions).
Setting	Not reported
Length of treatment (weeks)	52
Continuation phase (length and inclusion criteria)	52

Evidence for the effectiveness of the social-communication intervention (Child's Talk) on overall autistic behaviours and the quality of evidence are presented in Table 29. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 29: Evidence summary table for effects of social-communication intervention on overall autistic behaviours as an indirect outcome

	Caregiver-mediated social-communication intervention (Child's Talk) versus treatment as usual
Outcome	Overall autistic behaviours
Outcome measure	ADOS: total score
Study ID	ALDRED2001
Effect size (CI; p value)	SMD -0.76 (-1.53, 0.01; p = 0.05)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 28
Forest plot	1.1.4; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

The single included social-communication intervention trial examined indirect effects on overall autistic behaviours. The Child's Talk intervention (Aldred et al., 2001) aimed to increase the quality of parental adaptation and communication with

their autistic children. Techniques included initial psychoeducation (teaching parents about the developmental stages of early social communication) followed by parent–child sessions in which parents were encouraged to establish shared attention between themselves and their child, decrease intrusive demands they made on their child, model language output based on the child's capabilities and consolidate and expand their child's social communication by establishing predictable routines and repetition in rehearsed interactive play and adding variations and expansions to the child's play and language, for instance, leaving openings for the child to fill with a social and verbal response. This study found no evidence for a statistically significant effect of the Child's Talk intervention relative to treatment as usual for overall autistic behaviours as measured by the ADOS (see Table 29).

6.2.4 Clinical evidence summary – effect of psychosocial interventions on overall autistic behaviours

There was low quality evidence of an effect in favour of the educational interventions (ESDM, COMPASS and LEAP) when compared with treatment as usual or manual-only control. Low to very low quality evidence for the behavioural intervention (ESDM), parent training and a social-communication intervention (Child's Talk) was inconclusive.

6.2.5 Clinical evidence – effect of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction

AAC intervention for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

The AAC intervention trial (HOWLIN2007) was a three-armed trial comparing Picture Exchange Communication System (PECS) training (Frost & Bondy, 2002) for teachers (immediate or delayed treatment) with treatment as usual in children with autism (see Table 30).

Evidence for the effectiveness of PECS training for teachers on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence, are presented in Table 31. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

The single included AAC intervention trial examined indirect effects on impaired reciprocal social communication and interaction. PECS teacher training began with a 2-day workshop (13 hours of training) that four to six staff (mean: five) and zero to seven parents (mean: three) per class attended. Training followed the PECS manual (Frost & Bondy, 2002). PECS is an augmentative communication system where children are taught to exchange a picture card for something they like and want. The workshop was followed 1 week later by an active training period involving six half-day consultation visits over 5 months to each class. These visits were intended to

encourage teachers to facilitate children's use of PECS in various sessions during the school day and PECS consultants recommended and demonstrated strategies to teachers, monitored teachers' progress and provided feedback including written summaries, agreed action points and future goals. It was not possible to analyse the data from this study using conventional pair-wise methodology as the data came from three groups (immediate treatment group [ITG], delayed treatment group [DTG] and no treatment) across three time points (Time 1, which was baseline; Time 2, which was post-intervention for the ITG and waitlist for the DTG; and Time 3, which was follow-up for ITG and post-intervention for DTG), and there were statistically significant baseline differences between groups (DTG children had a significantly higher ADOS language impairment score [mean = 3.4] than those in the ITG [2.7] and no treatment group [2.5] and children in the ITG had a significantly higher non-verbal developmental quotient [25.9] than children in the DTG [22.7]). As the authors reported the OR results from a multilevel ordinal regression model that corrected for baseline differences by taking into account within-child and within-class correlations, these values were extracted and entered into the data analysis using the generic inverse variance method. This study found no evidence for a statistically significant effect of PECS training for teachers relative to treatment as usual for communication as measured by the ADOS-G post-intervention (see Table 31) and no OR was reported for follow-up time point. There was also no evidence for a statistically significant treatment effect on social interaction (as measured by the ADOS-G) at post-intervention (see Table 31). However, at 10-month follow-up there was evidence for a large and statistically significant treatment effect on social interaction (see Table 31), with the authors reporting that participants who received PECS training were over three and a half times more likely to be in a lower ordinal category on the ADOS-G Social Interaction subscale than participants who had received treatment as usual. However, the evidence quality was low to very low (downgraded because of non-blind outcome assessment and sample size in the case of the former, and additionally for imprecision in the case of the latter).

Table 30: Study information table for included trial of AAC intervention for the core autism feature of impaired reciprocal social communication and interaction

	PECS training for teachers versus treatment as usual
No. trials (N)	1 (88)
Study IDs	HOWLIN2007
Study design	RCT
% female	13
Mean age (years)	6.8
IQ	Not reported (100% learning disabilities [LD])
Dose/intensity (mg/hours)	Planned intensity was approximately calculated at 32.5 hours with an initial 2-day workshop (13 hours) followed by six half-day consultations over 5 months
Setting	School (specialist education)
Length of treatment (weeks)	24
Continuation phase	Mean interval between Time 1 (baseline) and Time 3 (follow-

(length and inclusion criteria)	up for ITG and post-treatment for DTG) of: 78 weeks (for ITG); 63 weeks (for DTG); 65 weeks (for no treatment control)

Table 31: Evidence summary table for effects of AAC intervention on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	PECS training for teachers versus treatment as usual	
Outcome	Communication	Social interaction
Outcome measure	Odds of being in a higher severity category on ADOS-G	
Study ID	HOWLIN2007	
Effect size (CI; p value)	*Post-intervention* OR 0.52 (0.24, 1.12; p = 0.10)	(1) *Post-intervention* OR 0.55 (0.25, 1.20; p = 0.13) (2) *10-month follow-up* OR 0.28 (0.09, 0.88; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	(1) Very low[1,2] (2) Low[1,3]
Number of studies/participants	K = 1; N = 84	(1) K = 1; N = 84 (2) K = 1; N = 53
Forest plot	1.2.1; Appendix 13	

Note. [1]Downgraded for risk of bias – high risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind.
[2]Downgraded for very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm.
[3]Downgraded for serious imprecision as number of events <300..

Animal-based intervention for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

The animal-based intervention trial (BASS2009) compared a horseback riding intervention with waitlist control in children with autism (see Table 32).

Table 32: Study information table for included trial of animal-based intervention for the core autism feature of impaired reciprocal social communication and interaction

	Horseback riding versus waitlist control
No. trials (N)	1 (34)
Study IDs	BASS2009
Study design	RCT
% female	15
Mean age (years)	7.3
IQ	Not reported
Dose/intensity (mg/hours)	12 hours (1 hour/week)
Setting	Equestrian training centre
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of horseback riding on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 33. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

The single included animal-based intervention trial examined effects of horseback riding on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome. Participants were trained in: mounting and dismounting (aimed at stimulating verbal communication, proprioception and vestibular processing); warm-up exercises; riding skills (aimed at stimulating sensory seeking, balance and coordination, and fine and gross motor skills); individualised and group games while on the horse, such as 'Simon says' and catch and throw (aimed at developing social and communication skills); and grooming activities. Throughout the intervention participants were verbally and physically reinforced (for instance, with high-fives and hugs). This study found evidence for a moderate and statistically significant effect of the horseback riding intervention relative to waitlist control for social impairment as measured by the total score on the SRS (see Table 33). The effects on the individual subscales that were reported were non-significant (see Table 33). The evidence quality for the total score and subscale outcome measures was downgraded to very low (based on non-blind parent-rated outcome measures, small sample size and selective reporting as data were not reported for all SRS subscales).

Table 33: Evidence summary table for effects of animal-based intervention on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Horseback riding versus waitlist control
Outcome	Social impairment
Outcome measure	(1) SRS: total (2) SRS: Social Cognition (3) SRS: Social Awareness (4) SRS: Social Motivation
Study ID	BASS2009
Effect size (CI; p value)	(1) SMD -0.73 (-1.43, -0.03; p = 0.04) (2) SMD -0.44 (-1.13, 0.24; p = 0.21) (3) SMD -0.40 (-1.08, 0.28; p = 0.25) (4) SMD -0.58 (-1.27, 0.12; p = 0.10)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2)-(4) Very low[1,3,4]
Number of studies/participants	K = 1; N = 34
Forest plot	1.2.2; Appendix 13

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents were non-blind.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as data not reported for selected subscales (the Social Communication and Autistic Mannerisms subscales of the SRS).
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Arts-based intervention for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

The arts-based intervention trial (GATTINO2011) compared relational music therapy (RMT; Gallardo, 2004) with waitlist control in children with autism (see Table 34).

Evidence for the effectiveness of RMT on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence, is presented in Table 35. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

The single included arts-based intervention trial examined indirect effects of RMT on the core autism feature of impaired reciprocal social communication and interaction. This intervention was based on psychodynamic principles (free association, unconscious conflicts, drive component, transference and counter-transference) and aimed to help participants through interactions with the music therapist based around music, for instance, singing, composing, improvising and playing musical games. The music therapist began each session by providing various instruments on the floor or table and allowed the participant to select one or several instruments and the focus was on the actions of the participant, with the music therapist taking a non-directive role and prioritising participant initiatives and behavioural observation. The intervention also involved a parent component with parents being encouraged to attend some sessions so that the therapist could observe how the child interacts with his/her family through musical activities. This study found no evidence for a statistically significant treatment effect on social communication as measured by a composite score based on five subscales of the CARS (see Table 35).

Table 34: Study information table for included trial of arts-based intervention for the core autism feature of impaired reciprocal social communication and interaction

	RMT versus waitlist control
No. trials (N)	1 (24)
Study IDs	GATTINO2011
Study design	RCT
% female	0
Mean age (years)	9.8
IQ	Not reported (based on N = 22, 27% LD as assessed using the Raven's Coloured Progressive Matrices for Children [Pasquali et al., 2002])
Dose/intensity (mg/hours)	Planned intensity was 8 hours (16 weekly sessions; 0.5 hours/week)
Setting	Outpatient
Length of treatment (weeks)	30 (because of school activities and vacations, the 16 sessions were completed over 7 months)
Continuation phase (length and inclusion criteria)	30

Table 35: Evidence summary table for effects of arts-based intervention on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	RMT versus waitlist control
Outcome	Social communication
Outcome measure	CARS: Social Communication
Study ID	GATTINO2011
Effect size (CI; p value)	SMD 0.23 (-0.58, 1.03; p = 0.58)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 24
Forest plot	1.2.3; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

Behavioural intervention for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

One behavioural intervention trial (INGERSOLL2012) compared reciprocal imitation training (RIT; Ingersoll, 2008) with treatment as usual in preschool children with autism, and the other (ROGERS2012) compared a parent-mediated and brief version of the Early Start Denver Model (P-ESDM) with treatment as usual in preschoolers with autism (see Table 36).

Table 36: Study information table for included trial of behavioural intervention for the core autism feature of impaired reciprocal social communication and interaction

	RIT versus treatment as usual	**P-ESDM versus treatment as usual**
No. trials (N)	1 (29)	1 (98)
Study IDs	INGERSOLL2012	ROGERS2012
Study design	RCT	RCT
% female	11	31
Mean age (years)	3.2	1.7
IQ	Not reported	Not reported (inclusion criteria developmental quotient >35 as measured by MSEL)
Dose/intensity (mg/hours)	30 (3 hours/week)	Planned intensity of 12 hours (1 hour/ week) and weekly mean intensity of all the intervention was 1.48 hours
Setting	Not reported	Three university clinics
Length of treatment (weeks)	10	12
Continuation phase (length and inclusion criteria)	23 (including 2-3 month follow-up)	12

Evidence for the effectiveness of behavioural interventions on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence, is presented in Table 37 and Table 38. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 37: Evidence summary table for effects of behavioural intervention (RIT) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	RIT versus treatment as usual	
Outcome	Examiner–child joint attention	Social and emotional development
Outcome measure	ESCS: Initiating Joint Attention	Bayley Scales of Infant Development: Social-Emotional
Study ID	INGERSOLL2012	
Effect size (CI; p value)	(1) *Post-intervention* SMD 0.89 (0.09, 1.68; p = 0.03) (2) *2- to 3-month follow-up* SMD 0.86 (0.06, 1.65; p = 0.03)	*2- to 3-month follow-up* SMD 0.41 (-0.36, 1.17; p = 0.30)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1,2]	Very low[3,4]
Number of studies/participants	K = 1; N = 27	
Forest plot	1.2.4; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and the risk of detection bias is also high as outcome assessors were not blinded.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and the risk of detection bias is also high as parent-report measure and parents were non-blind.
[4]Downgraded for very serious risk of imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 38: Evidence summary table for effects of behavioural intervention (P-ESDM) on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	P-ESDM versus treatment as usual			
Outcome	Social affect	Imitation	Orienting to social stimuli	Orienting to joint attention
Outcome measure	ADOS-T: Social Affect	Twelve imitation tasks (Rogers et al., 2003): Imitative Sequences	Social engagement task (Dawson et al., 2004): Mean Social Orient I	Social engagement task (Dawson et al., 2004): Mean Orient to Joint Attention
Study ID	ROGERS2012			
Effect size (CI; p value)	SMD -0.07 (-0.46, 0.33; p = 0.73)	SMD 0.24 (-0.16, 0.63; p = 0.24)	SMD 0.13 (-0.27, 0.52; p = 0.54)	SMD 0.00 (-0.40, 0.40; p = 1.00)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Low[1,2]	Very low[3,4]		Low[2,3]
Number of studies/participants	K = 1; N = 98			
Forest plot	1.2.4; Appendix 13			

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as outcome assessor reported only as 'laboratory personnel' with no information about blinding.
[2]Downgraded for serious imprecision as N <400.

[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as the identity and blinding of outcome assessors not reported and reliability and validity of outcome measure unclear.
[4]Downgraded for very serious risk of imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

One of the included behavioural intervention trials (INGERSOLL2012) examined effects of RIT on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome. RIT uses naturalistic techniques to teach imitation during social interaction. Techniques included contingent imitation, description of the child's actions using simplified language, expanding the child's utterances, modelling, verbal markers to describe actions, and physical prompting. This study found no evidence for a statistically significant treatment effect on social and emotional development as measured by the Bayley Social-Emotional subscale. Evidence for large, statistically significant and enduring (significant at post-intervention and 2- to 3-month follow-up) treatment effects were observed on proximal measures of impaired social communication and interaction, namely child-initiated joint attention during examiner–child interaction as measured by the ESCS (see Table 37). However, this evidence was downgraded to low quality because of non-blind outcome assessment and small sample size.

The other included behavioural intervention trial (ROGERS2012) examined indirect effects of P-ESDM on the core autism feature of impaired reciprocal social communication and interaction. The P-ESDM intervention used the same curriculum, procedures and manual as in Vismara and colleagues (2009). P-ESDM was a briefer, less intensive, parent-mediated version of the ESDM intervention examined in DAWSON2010. P-ESDM was delivered to parents via highly-structured sessions. Each session began with a 5-minute 'warm-up' where parents and children engaged in a play-based activity. The topic for the session was then explained to the parents (with written materials offered to support learning) and the required skill was demonstrated with the child. Parents then applied the skill themselves, with feedback and support from the therapist, before the skill was applied to a range of other activities. Parents were given written materials to take home to support the application of the new skill. The intervention focused on a range of skills including: joint attention routines; developing non-verbal skills; encouraging speech; and conducting functional assessments of behaviour. There was no evidence for statistically significant treatment effects of P-ESDM on social communication or interaction as an indirect outcome, as measured by the ADOS-T social affect domain, structured imitation tasks or social engagement tasks (see Table 38).

Cognitive interventions for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Three of the cognitive intervention trials (BEAUMONT2008, GOLAN2010, RYAN2010) compared emotion recognition training (ERT) with treatment as usual for children with autism. One of the cognitive intervention studies compared face recognition training (FRT) with waitlist control (TANAKA2010) and another compared theory of mind (ToM) training with waitlist control (BEGEER2011) for

children with autism. Finally, two of the cognitive intervention trials used an attention-placebo comparator with one trial comparing computer-based ERT with computer software training (HOPKINS2011) and another compared enhanced DVD-based ERT with standard DVD-based ERT (YOUNG2012) (see Table 39).

Evidence for the effectiveness of ERT, FRT and ToM training on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence, is presented in Table 40, Table 41, Table 42, Table 43 and Table 44. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 39: Study information table for included trials of cognitive interventions for the core autism feature of impaired reciprocal social communication and interaction

	ERT versus treatment as usual	FRT versus waitlist	ToM versus waitlist	Computer-based ERT versus software training	Enhanced ERT versus standard ERT
No. trials (N)	3 (121)	1 (117)	1 (40)	1 (51)	1 (25)
Study IDs	(1) BEAUMONT2008 (2) GOLAN2010 (3) RYAN2010	TANAKA2010	BEGEER2011	HOPKINS2011	YOUNG2012
Study design	(1)-(3) RCT	RCT	RCT	RCT	RCT
% female	(1) 10 (2) 26 (3) 9	22	8	10	Not reported
Mean age (years)	(1) 9.7 (2) 5.9 (3) 9.5	10.9	10.3	10.2	Not reported
IQ	(1) 107.3 (assessed using the Wechsler Intelligence Scale for Children [WISC-III; Wechsler, 1991]) (2) Verbal IQ 98.8 (British Picture Vocabulary Scale [BPVS, 2nd edition; Dunn et al., 1997a) (3) For N = 25 (group allocation not reported) mean VIQ 85.6-90.2 (Peabody Picture Vocabulary Test-Revised [PPVT:R; Dunn & Dunn, 1981a]), mean PIQ 98.6-104.6 (Raven	94.7 (assessed using the Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999], the WISC-III, the Wechsler Adult Intelligence Scale, 3rd edition [Wechsler, 1997], or the DAS)	101.6 (assessed using WISC-III Short-form)	75.71 (assessed using the Kaufman Brief Intelligence Test – 2nd edition [KBIT-2; Kaufman & Kaufman, 1990])	Not reported

	Standard Progressive Matrices; Raven et al., 1977)				
Dose/ intensity (mg/hours)	(1) 15 (2 hours/week for 7 weeks followed by 1 hour in the final week) (2) Planned intensity of ≥7 hours (1.75 hours/ week) (3) Planned intensity of 4 hours (1 hour/week)	20.2 (1.06 hours/week)	24 (1.5 hours/week)	Planned intensity was 2-5 hours (0.3-0.8 hour/week)	Planned intensity of >5.25 hours (1.75 hours/week)
Setting	(1) Academic (2) Home (3) Not reported	Home	Not reported	Educational (school or after school club)	Home
Length of treatment (weeks)	(1) 7 (2)-(3) 4	Mean 19.1 weeks	16	6	3
Continuation phase (length and inclusion criteria)	(1) 22 weeks (including 6-week and 5-month follow-ups but control data only available for post-intervention, because following this the control group began the intervention) (2) 4 (3) 18 (including 3-month follow-up but no control group data for follow-up)	Mean 19.1 weeks	16	8 (post-intervention measures were collected within 2 weeks of the final intervention session)	3

Table 40: Evidence summary table for effects of cognitive interventions (ERT) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	ERT versus treatment as usual				
Outcome	Emotion recognition	Recognising emotion from posture	Emotion understanding	Emotion regulation	Social skills
Outcome measure	(1) Assessment of Perception of Emotion from Facial Expression (2) Situation-Facial Expression Matching: Distant generalisation (3) Ekman emotion recognition photographs	Assessment of Perception of Emotion from Posture Cues	Emotional vocabulary	(1) Emotion Regulation and Social Skills Questionnaire: total (2) James and the Maths Test (3) Dylan is Being Teased	SSQ: total
Study ID	(1) BEAUMONT2008 (2) GOLAN2010 (3) RYAN2010	BEAUMONT2008	GOLAN2010	BEAUMONT2008	
Effect size (CI; p value)	SMD 0.65 (0.27, 1.03; p = 0.0008)	SMD 0.17 (-0.40, 0.73; p = 0.56)	SMD 1.02 (0.34, 1.70; p = 0.003)	(1) SMD 1.39 (0.76, 2.02; p <0.0001) (2) SMD 1.23 (0.62, 1.85; p <0.0001) (3) SMD 1.29 (0.67, 1.91; p <0.0001)	SMD 1.42 (0.79, 2.05; p <0.0001)
Heterogeneity (chi²; p value; I²)	Chi² = 8.79, df = 2; p = 0.01); *I²* = 77%	Not applicable			

Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,4]	Low[3,5]	Low[3,6]	Low[3,7]
Number of studies/ participants	K = 3; N = 119	K = 1; N = 49	K = 1; N = 38	K = 1; N = 49	K = 1; N = 49
Forest plot	1.2.5; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and risk of detection bias is unclear/unknown as identity and blinding of outcome assessors are unclear.
[2]Downgraded for very serious inconsistency because of substantial to considerable heterogeneity.
[3]Downgraded for serious imprecision as N <400.
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and high risk of detection bias as outcome assessor was a non-blind investigator and there was a study-specific outcome measure with no independent measures of reliability or validity data.
[6]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and there was a high risk of detection bias as outcome assessors were non-blind
[7]Downgraded for serious risk of bias – high risk of performance, response and detection bias. The questionnaire was parent-rated and parents were not blind and participated in the intervention.

Three studies (BEAUMONT2008, GOLAN2010, RYAN2010) examined effects of ERT relative to treatment as usual on emotion recognition as a direct outcome, a proximal measure of the core autism feature of impaired reciprocal social communication and interaction. The formats of these cognitive interventions were variable but the content and target of interventions were comparable. In BEAUMONT2008 a combined computer game (the Junior Detective Training Program), social skills group and parent training approach was used to train emotion recognition and social skills. GOLAN2010 used an animated DVD (The Transporters) featuring vehicle characters with real human faces designed to enhance the understanding and recognition of emotions. In RYAN2010 children were taught emotion recognition skills within a more didactic format incorporating role play, face-emotion matching and homework assignments. The meta-analysis with data from all three studies found evidence for a moderate and statistically significant effect of ERT on this proximal indicator of reciprocal social communication and interaction as measured by the Assessment of Perception of Emotion from Facial Expression, a study-specific measure of situation-facial expression matching and the Ekman emotion recognition photographs (see Table 40). However, this evidence is of very low quality (GRADE) because of unclear blinding of outcome assessors, small sample size and substantial to considerable heterogeneity (I^2 = 77%). The individual studies also report additional measures of emotion recognition. BEAUMONT2008 found no evidence for a statistically significant effect of ERT on recognising emotion from posture (see Table 40). There were, however, statistically significant treatment effects from individual studies on: emotion understanding measured by a study-specific emotional vocabulary test; emotion regulation measured by the Emotion Regulation and Social Skills Questionnaire, James and the Maths Test and Dylan is Being Teased test; and social skills measured by the SSQ (see Table 40). However, the confidence in all effect estimates is low because of sample size and risk of bias concerns.

TANAKA2010 examined direct effects of the Let's Face It! computer program on face recognition, a proximal measure of the core autism feature of impaired reciprocal social communication and interaction. The program was made up of seven games that teach skills necessary for processing faces, specifically targeting areas of difficulty in children with autism including inattention to the eye area, impaired recognition of identity, and failure to perceive faces holistically. The program aimed to develop skills in attending to faces generally, recognising identity and expression in faces and interpreting cues in faces. This study found no evidence for statistically significant effects of FRT on this proximal measure of reciprocal social communication and interaction as measured by multiple subscales from the Let's Face It! Skills battery (see Table 41).

Table 41: Evidence summary table for effects of cognitive interventions (FRT) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	FRT versus waitlist control
Outcome	Face recognition
Outcome measure	The Let's Face It! Skills Battery subtests: (1) Matching identity across masked features (percent correct) (2) Featural and configural face dimensions (percent correct) (3) Matching identity across expression (percent correct) (4) Parts/whole identity (percent correct) (5) Immediate memory for faces (percent correct)
Study ID	TANAKA2010
Effect size (CI; p value)	(1) SMD -0.07 (-0.52, 0.37; p = 0.75) (2) SMD -0.02 (-0.47, 0.42; p = 0.91) (3) SMD -0.43 (-0.88, 0.02; p = 0.06) (4) SMD 0.06 (-0.39, 0.51; p = 0.78) (5) SMD -0.26 (-0.71, 0.19; p = 0.25)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2) Very low[1,3,4] (3)-(5) Very low[1,2,3]
Number of studies/participants	(1)-(2) K = 1; N = 78 (3) K = 1; N = 79 (4)-(5) K = 1; N = 77
Forest plot	1.2.5; Appendix 13

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrator and participants non-blind, and risk of detection bias unclear/unknown as identity and blinding of outcome assessors were not reported and there was no independent reliability or validity data for outcome measure.
[2] Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for strongly suspected publication bias as the paper states that other experimental measures were taken that were not reported.
[4]Downgraded for serious imprecision as N <400.

BEGEER2011 examined direct effects of ToM training (Gevers et al., 2006; Steerneman et al., 1996) on theory of mind understanding, emotional awareness and empathy, proximal measures of the core autism feature of impaired reciprocal social communication and interaction. The intervention used a didactic approach and children were taught in matched age groups (age difference <3 years) about theory of mind and social skills such as listening to others, making friends, perception and imitation, fantasy-reality difference, assessing social situations, emotion recognition, first- and second-order mental state reasoning, deception, imagination and humour. The intervention also included a parent training component where parents were given suggestions on how to facilitate social cognition at home to promote generalisation. This study found no evidence for statistically significant effects of ToM training on proximal measures of reciprocal social communication and interaction, including: theory of mind understanding as measured by total score on the ToM test; self-reported empathy as measured by the Index of Empathy for Children and Adolescents; emotional awareness as measured by the LEAS-C; or maladaptive social behaviour as measured by the CSBQ (see Table 42).

Table 42: Evidence summary table for effects of cognitive interventions (ToM) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	ToM versus waitlist			
Outcome	Theory of Mind	Empathy	Emotional awareness	Maladaptive social behaviour
Outcome measure	ToM test: total	Index of Empathy for Children and Adolescents	LEAS-C: total	CSBQ: total
Study ID	BEGEER2011			
Effect size (CI; p value)	SMD 0.04 (-0.61, 0.70; p = 0.90)	SMD -0.17 (-0.82, 0.49; p = 0.62)	SMD 0.46 (-0.20, 1.13; p = 0.17)	SMD -0.31 (-0.97, 0.35; p = 0.35)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Very low[1,2]	Very low[2,3]	Very low[1,2]	Very low[2,4]
Number of studies/ participants	K = 1; N = 36			
Forest plot	1.2.5; Appendix 13			

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as identity and blinding of outcome assessor were not reported.
[2] Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as self-completed.
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as parent-completed and parents non-blind.

Two of the cognitive intervention studies (HOPKINS2011, YOUNG2012) adopted an attention-placebo comparator rather than a treatment as usual or a waitlist control group. HOPKINS2011 compared use of the FaceSay computer software program (Symbionica, LLC, San Jose, California) with a drawing software program (Tux Paint) and examined direct effects on emotion and face recognition, which are proximal measures of the core autism feature of impaired reciprocal social communication and interaction. This study also examined effects on a more direct measure of social interaction (assessed through behavioural observation). FaceSay used interactive avatars (animated photographs of real people) to teach children social skills, including joint attention, holistic facial processing and face recognition and emotion recognition. Program activities included eye gaze following, matching and manipulating facial expressions and completing face puzzles. This study also reported subgroup analyses by IQ (<70 and >70). These subgroups were initially entered into the data analysis and the test for subgroup differences was examined. Where there were significant differences between the two IQ groups the subgroups were maintained, and where this difference was non-significant subgroups were combined. HOPKINS2011 found evidence for large and statistically significant effects of FaceSay on emotion recognition for the IQ <70 and >70 subgroups combined (no significant subgroup difference) as measured by the Ekman face

recognition photographs, a study-specific emotion recognition in drawings test and the composite score based on these two measures (see Table 43). There was also evidence for large and statistically significant effects of FaceSay on face recognition for the IQ <70 and >70 subgroups combined (no significant subgroup difference) as measured by both the short form and long form versions of the Benton Facial Recognition Test (see Table 43). However, the quality of the evidence for both these outcomes was low due to risk of bias concerns with unclear blinding of outcome assessors and imprecision limitations (small sample size). For social skills (as measured by the SSRS) there was a significant difference between the IQ <70 and >70 subgroups (test for subgroup differences: $Chi^2 = 4.11$, df = 1, p = 0.04) and only the IQ <70 subgroup showed a statistically significant effect of FaceSay on social skills (see Table 43). The quality of this evidence was moderate (downgraded for sample size only). Finally, statistically significant treatment effects were also observed on the more direct observational measures of social interaction with a moderate effect of FaceSay on initiating/maintaining social interactions and a moderate effect on negative social interaction (see Table 43) for the IQ <70 and >70 subgroups combined (no significant subgroup difference), and the quality of this evidence was moderate (downgraded for sample size only). The only statistically non-significant effect was on social intention without initiating interaction (see Table 43).

Table 43: Evidence summary table for effects of cognitive interventions (computer-based ERT with attention-placebo comparator) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Computer-based ERT versus software training				
Outcome	Emotion recognition	Face recognition	Social skills	Positive social interaction	Negative social interaction
Outcome measure	(1) Ekman emotion recognition photographs (2) Emotion recognition in drawings (3) Composite emotion recognition (photographs and drawings) score	Benton Facial Recognition Test: (1) Short form (2) Long form	SSRS: Social skills (standardised score)	Behavioural observation: (1) Initiating/ maintaining social interactions (2) Social intention without initiating interaction (for example, proximity)	Behavioural observation
Study ID	HOPKINS2011				
Effect size (CI; p value)	(1) SMD 0.96 (0.37, 1.56; p = 0.001) (2) SMD 1.10 (0.50, 1.70; p = 0.0004) (3) SMD 1.09 (0.48, 1.69; p = 0.0004)	(1) SMD 0.88 (0.29, 1.47; p = 0.003) (2) SMD 1.13 (0.53, 1.74; p = 0.0003)	(1) *IQ<70* SMD 0.92 (0.08, 1.75; p = 0.03) (2) *IQ>70* SMD -0.29 (-1.09, 0.52; p = 0.49) (1)+(2) SMD 0.29 (-0.29, 0.88; p = 0.32)	(1) SMD 0.60 (0.02, 1.17; p = 0.04) (2) SMD -0.12 (-0.68, 0.45; p = 0.69)	SMD -0.88 (-1.47, -0.29; p = 0.003)
Heterogeneity (chi²; p value; I²)	Not applicable[1]		Test for subgroup differences: Chi² = 4.11, df = 1; p = 0.04; I^2 = 75.7%	Not applicable[1]	
Quality of the evidence (GRADE)	(1) Low[2,3] (2)-(3) Low[3,4]	Low[3,5]	(1) Moderate[3] (2) Low[6]		Moderate[3]

Number of studies/ participants	K = 1; N = 49	(1) K = 1; N = 25 (2) K = 1; N = 24	K = 1; N = 49
Forest plot	1.2.5; Appendix 13		

Note. [1]Where the test for subgroup differences was not statistically significant the IQ<70 and IQ>70 subgroups were combined.
[2]Downgraded for serious risk of bias – high risk of performance bias as intervention administrator non-blind and risk of detection bias is unclear/unknown as identity of outcome assessor was not reported.
[3]Downgraded for serious imprecision as N <400.
[4]Downgraded for serious risk of bias – high risk of performance bias as intervention administrator was non-blind and risk of detection bias is unclear/unknown as identity of outcome assessor was not reported and there was no independent reliability or validity data for this outcome measure.
[5]Downgraded for serious risk of bias – high risk of performance bias as intervention administrator was non-blind and risk of detection bias is unclear/unknown as identity of outcome assessor was not reported and there is only reliability or validity data for the short form of this outcome measure.
[6]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

YOUNG2012 examined direct effects of ERT on emotion recognition, a proximal measure of the core autism feature of impaired reciprocal social communication and interaction. This study examined treatment effects of 'The Transporters' DVD which was also examined in GOLAN2010 (see above), however, in YOUNG2012 the comparator was a standard ERT DVD (a 'Thomas the Tank Engine' DVD created for the 'Thomas Discovers Emotions' study) rather than treatment as usual. The main difference between the active and control conditions was the greater emphasis placed on emotions in 'The Transporters' DVD, for instance, through the use of real human faces and a less distracting background to encourage focus on character faces. Thus, the comparison in this study was between enhanced and standard ERT. Evidence was found for a large and statistically significant effect of 'The Transporters' DVD on emotion recognition as measured by the Faces Task and the Affect Recognition subscale of the NEPSY-II (see Table 44). However, evidence quality is low because of concerns regarding risk of bias (unclear blinding of outcome assessor) and imprecision (small sample size). The study also examined effects of enhanced ERT on more direct measures of the core autism feature of impaired reciprocal social communication and interaction as assessed by the SCQ. However, no statistically significant effects were found for social peer interest, eye contact or gaze aversion (see Table 44).

Table 44: Evidence summary table for effects of cognitive interventions (enhanced ERT with attention-placebo comparator) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Enhanced ERT versus standard ERT		
Outcome	Emotion recognition	Positive social behaviours	Gaze aversion
Outcome measure	(1) Faces Task (2) NEPSY-II: Affect Recognition	(1) SCQ: social peer interest (2) SCQ: eye contact	SCQ: gaze aversion
Study ID	YOUNG2012		
Effect size (CI; p value)	(1) SMD 1.20 (0.34, 2.07; p = 0.006) (2) SMD 1.55 (0.63, 2.46; p = 0.0009)	(1) SMD 0.33 (-0.46, 1.12; p = 0.41) (2) SMD 0.04 (-0.74, 0.83; p = 0.92)	SMD -0.14 (-0.93, 0.64; p = 0.72)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1,2]	Very low[3,4]	
Number of studies/participants	K = 1; N = 25		
Forest plot	1.2.5; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance bias as intervention administered by non-blind parents and risk of detection bias is unclear/unknown as identity (beyond stating 'researcher') and blinding of outcome assessor unclear and the reliability and validity of this outcome measure is unclear.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and detection bias as parents were non-blind and were intervention administrators and outcome assessors.
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Educational interventions for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

One of the educational intervention trials (STRAIN2011) compared direct training of the LEAP approach with a LEAP intervention manual-only control for young children with autism. The second (WHALEN2010) compared combined computer-assisted educational intervention (TeachTown: Basics) and intensive behavioural intervention (IBI) day class programmes (Intensive Comprehensive Autism Programs) with IBI day class programmes only for young children with autism (see Table 45).

Table 45: Study information table for included trials of educational interventions for the core autism feature of impaired reciprocal social communication and interaction

	LEAP training versus manual-only control	**Combined TeachTown and IBI versus IBI-only**
No. trials (N)	1 (294)	1 (47; 8 classrooms)
Study IDs	STRAIN2011	WHALEN2010
Study design	RCT	RCT
% female	Not reported	Not reported
Mean age (years)	4.2	Not reported
IQ	61 (assessed using the MSEL – early-learning composite score)	Not reported
Dose/intensity (mg/hours)	23 full days of training	351 (preschool)/390 (kindergarten and first grade) hours for IBI (of which 43.33 hours for computer-assisted intervention)
Setting	Educational	Educational (Intensive Comprehensive Autism Programs)
Length of treatment (weeks)	104	13
Continuation phase (length and inclusion criteria)	104	13

Evidence for the effectiveness of LEAP training or combined TeachTown and IBI on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 46. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

STRAIN2011 examined effects of LEAP training relative to manual-only control on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome. This intervention targeted overall autistic behaviours (see Section 6.2.3 for core components of the LEAP intervention). Evidence was found for a moderate and statistically significant effect of LEAP training relative to manual-only control on social skills as measured by the SSRS (see Table 46). However, evidence quality is low because of concerns regarding risk of bias (unclear blinding of outcome assessor) and imprecision (small sample size).

WHALEN2010 examined effects of TeachTown and IBI relative to IBI-only control on the core autism feature of impaired reciprocal social communication and

interaction as an indirect outcome. All participants in this study attended Intensive Comprehensive Autism Programs for 27 to 30 hours per week where children were taught in classes of no more than eight pupils, with an adult to child ratio of 1:2 using an ABA approach (typically discrete trials) to target language/ communication, sensory issues, and behaviour within a classroom organised according to TEACCH principles. In addition to this IBI intervention, participants in the experimental group also received computer-assisted instruction (using the TeachTown: Basics program). This computer-assisted instruction intervention included computer lessons and off-computer natural environment activities to target additional skills and encourage generalisation. The computer lessons incorporated the basic principles of ABA with teaching in a discrete trial format and reinforcement for correct responses, and for the off-computer activities the techniques used followed the principles of pivotal response training. The computer lessons aimed to improve receptive language (including vocabulary, school readiness such as play and classroom vocabulary, semantics and community life such as body parts and environmental sounds), social understanding (including knowledge of eye gaze, joint attention, face matching and emotion recognition), life skills (including awareness and regulation, functional skills such as time telling and self-awareness such as food and clothing vocabulary), and academic/cognitive skills (including maths, reading, categorisation and problem solving). Off-computer activities additionally targeted expressive language, play, imitation, social interaction, motor skills and daily living skills. This study found no evidence for a statistically significant effect of the TeachTown computer-assisted instruction on social skills as measured by the Brigance Inventory of Early Development and no evidence for any differential treatment effects by age/school year (see Table 46).

Table 46: Evidence summary table for effects of educational interventions on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	LEAP training versus manual-only control	**Combined TeachTown and IBI versus IBI-only**
Outcome	Social skills	Social skills
Outcome measure	SSRS: total	Brigance Inventory of Early Development: social skills
Study ID	STRAIN2011	WHALEN2010
Effect size (CI; p value)	SMD 0.76 (0.52, 1.00; p <0.00001)	(1) *Preschool* SMD -0.18 (-1.00, 0.64; p = 0.68) (2) *Kindergarten and first grade* SMD -0.03 (-0.85, 0.79; p = 0.94) (1)+(2) SMD -0.10 (-0.68, 0.48; p = 0.73)
Heterogeneity (chi²; p value; I²)	Not applicable	Test for subgroup differences: Chi² = 0.06, df = 1; p = 0.81; I^2 = 0%
Quality of the evidence (GRADE)	Low[1,2]	Very low[1,3]
Number of studies/participants	K = 1; N = 294	K = 1; N = 46
Forest plot	1.2.6; Appendix 13	
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind. In addition, risk of detection bias is unclear/unknown as		

identity and blinding of outcome assessors were not reported.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Parent training for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

The three parent training intervention trials (DREW2002, SOFRONOFF2004, WELTERLIN2012) compared parent training programmes with treatment as usual for children with autism (see Table 47).

Table 47: Study information table for included trials of parent training interventions for the core autism feature of impaired reciprocal social communication and interaction

	Parent training versus treatment as usual
No. trials (N)	3 (95)
Study IDs	(1) DREW2002 (2) SOFRONOFF2004 (3) WELTERLIN2012
Study design	(1)-(3) RCT
% female	(1) 21 (2) Not reported (3) 10
Mean age (years)	(1) 1.9 (2) 9.3 (3) 2.5
IQ	(1) Non-verbal IQ 77.1 (assessed using the D and E subscales of the Griffiths Scale of Infant Development; Griffiths, 1986) (2) Not reported (3) 55.4 (assessed using MSEL – developmental quotient)
Dose/intensity (mg/hours)	(1) Planned intensity was 26 hours (3 hours/6 weeks, equating to 0.5 hours/week) (2) Planned intensity was 1 day (6 hours) for the workshop group and 6 hours over 6 weeks (1 hour/week) for the individual sessions group (3) Planned intensity was 18 hours (1.5 hour/week)
Setting	(1) Home (2) University clinic (3) Home
Length of treatment (weeks)	(1) 52 (2) 1 day for workshop group and 6 weeks for individual sessions group (3) 12
Continuation phase (length in weeks and inclusion criteria)	(1) 52 (2) 19 (including 3-month follow-up) (3) 12

Evidence for the effectiveness of parent training interventions on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence, is presented in Table 49. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

DREW2002 examined effects of parent training relative to treatment as usual on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome. This intervention emphasised the development of joint attention and joint action routines, and included advice about behaviour management. Speech and language therapists described developmental principles to parents and then monitored and provided feedback on implementation. Parents were instructed on how to teach joint attention behaviours such as pointing and gaze switching, including the use of visual supports for spoken language and techniques were implemented in allocated times for activities (for instance, joint play times) but also integrated into everyday routines, such as mealtimes, dressing and bedtimes. Instruction in behaviour management techniques followed a similar structure and included instruction in the principles of reinforcement, interrupting unwanted behaviours and encouraging alternative behaviours through joint action routines. No evidence was found for a statistically significant effect of parent training on reciprocal social interaction or non-verbal communication as measured by the ADI-R (see Table 48).

Table 48: Evidence summary table for effects of parent training interventions on the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

	Parent training versus treatment as usual		
Outcome	Reciprocal social interaction (direct outcome)	Non-verbal communication (direct outcome)	Social skills (indirect outcome)
Outcome measure	ADI-R: Reciprocal social interaction	ADI-R: Non-verbal communication	(1) SSQ: total (2) SIB-R: Social interaction
Study ID	DREW2002		(1) SOFRONOFF2004 (2) WELTERLIN2012
Effect size (CI; p value)	SMD -0.38 (-1.19, 0.43; p = 0.36)	SMD -0.37 (-1.18, 0.44; p = 0.37)	(1)+(2) SMD 0.77 (0.25, 1.28; p = 0.003) (1) *SSQ post-intervention combined workshop + individual sessions* SMD 0.98 (0.34, 1.61; p = 0.003) (2) *SIB-R* SMD 0.37 (-0.52, 1.25; p = 0.42)
Heterogeneity (chi²; p value; I²)	Not applicable		Chi² = 1.20, df = 1; p = 0.27; *I²* = 16%
Quality of the evidence (GRADE)	Very low[1,2]		Low[3,4]
Number of studies/participants	K = 1; N = 24		K = 2; N = 71
Forest plot	1.2.7; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors were non-blind.
[2]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias was high or unclear as either parent-rated and parents were non-blind and involved in the intervention or the identity and blinding of the outcome assessor was not reported.
[4]Downgraded for serious imprecision as N <400.

Two of the parent training intervention studies (SOFRONOFF2004, WELTERLIN2012) examined indirect effects of parent training on the core autism feature of impaired reciprocal social communication and interaction. SOFRONOFF2004 was a three-armed trial that included two active intervention arms involving the same intervention content but in different formats. In one group the parent training was delivered in a one-day group workshop and in the other arm the same parent training content was delivered in individual therapist–parent sessions over 6 weeks. The parent training consisted of six components (and in the individual sessions group these were delivered in a one component per week format): psychoeducation (through video demonstration and discussion of the nature of Asperger's syndrome, the heterogeneity of the disorder and the importance of considering the child's perspective in problem situations were outlined and parents were encouraged to give examples of aspects of the disorder affecting their own child); Comic Strip Conversations (using simple drawings to illustrate a conversation between two people and to emphasise what the people may be thinking; Gray, 1994a); Social Stories (using a short story specifically for a target child in order to illustrate a particular situation including social cues, anticipated actions and information on what is occurring and why; Gray, 1994b); management of problem behaviours (parents were introduced to common problem behaviours for children with Asperger's syndrome, including interrupting, temper tantrums, anger, non-compliance and bedtime problems, and techniques for dealing with these problems were outlined); management of rigid behaviours and special interests (the focus of this component was to emphasise the importance of parents understanding the rigid or repetitive behaviour from their child's perspective in order to understand why their child has a need for routines and also as a potential way of using a special interest as a reward); and management of anxiety (parents were taught that problem behaviours were often the result of anxiety and the importance for parents to recognise and address their child's anxiety were emphasised as a means of not just treating but also preventing anxiety-inducing situations). The two active intervention arms (workshop and individual sessions) were initially compared. However, as there were no statistically significant differences between the two formats at post-intervention (test for overall effect: $Z = 0.83$, $p = 0.41$) or follow-up (test for overall effect: $Z = 1.85$, $p = 0.06$), data from the two groups was combined and entered into meta-analysis. WELTERLIN2012 examined effects of the home TEACCH programme. This intervention incorporated parent training in how to teach specific cognitive, fine motor, and language skills to their child. The intervention began with the clinician teaching the child the specific skills and modelling appropriate prompting behaviour and teaching environment set-up for the parents. Parents were also provided with education about autism and intervention strategies and assigned written homework and requested to practice applying new skills in between intervention sessions. From week 8 onwards, parents

took over the active teaching of their child and the clinician provided coaching and feedback. The meta-analysis with data from both these studies provided evidence for a moderate effect on social skills as measured by the SSQ or SIB-R (see Table 48). However, the quality of this evidence was low because of concerns of risk of bias (non-blind outcome assessment) and small sample size.

Social-communication interventions for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

Six of the social-communication intervention trials compared caregiver- or preschool-teacher- mediated social-communication interventions with treatment as usual (caregiver-mediated: ALDRED2001, CARTER2011, GREEN2010, KASARI2010, SCHERTZ2013; preschool-teacher-mediated: KAALE2012; see Table 49). Two of the social-communication trials compared peer-mediated (and/or therapist-mediated) social-communication interventions with treatment as usual (peer-mediated: ROEYERS1996; peer-mediated and/or therapist-mediated: KASARI2012; see Table 49). Two studies examined the effects of a combined joint attention training intervention and early behavioural intervention (EBI) or EIBI programme only (KASARI2006, LANDA2011; see Table 49). One study compared LEGO® therapy with the Social Use of Language Programme (SULP; OWENS2008). Four of the trials compared social skills groups with treatment as usual (FRANKEL2010, KOENIG2010, LAUGESON2009, LOPATA2010; see Table 49), and one study compared a social skills group specifically modified for individuals with high-functioning autism with a standard social skills group condition (DEROSIER2011; see Table 49).

Evidence for the effectiveness and the quality of evidence is presented in: Table 50 and Table 51 for caregiver- or preschool-teacher-mediated social-communication interventions; Table 52 and Table 53 for peer-mediated (and/or therapist-mediated) social-communication interventions; Table 54 and Table 66 for combined joint attention training and EBI/EIBI; Table 56 for LEGO® therapy; and Table 57, Table 58 and Table 59 for social skills group interventions. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Five studies (ALDRED2001, CARTER2011, GREEN2010, KASARI2010, SCHERTZ2013) examined effects of caregiver-mediated social-communication interventions relative to treatment as usual, and one study (KAALE2012) examined effects of preschool-teacher-mediated social-communication intervention relative to treatment as usual, on direct measures of social interaction and communication, and on joint attention and engagement, which may be regarded as proximal measures of the core autism feature of impaired reciprocal social communication and interaction. The specific models of intervention were variable but the content and target of interventions were comparable. In ALDRED2001 the Child's Talk intervention was used (see Section 6.2.3 for further detail). CARTER2011 used Hanen's More Than Words programme. This intervention is delivered by speech and language therapists and involves group-based parent training and individualised in-home parent–child

sessions focused on improving the child's social communication through teaching parents to use techniques including using joint action routines, using visual supports, supporting peer interactions, responding to the child's communicative attempts and following their lead, and using books and play to elicit and to reward communication.

Table 49: Study information table for included trials of social-communication interventions for the core autism feature of impaired reciprocal social communication and interaction

	Caregiver-mediated or preschool-teacher-mediated social-communication intervention versus treatment as usual	Peer-mediated (and/or therapist-mediated) social-communication intervention versus treatment as usual	Joint attention training and EBI/EIBI versus EBI/EIBI only	LEGO® therapy versus SULP	Social skills group versus treatment as usual	Social skills group modified for autism versus standard social skills group
No. trials (N)	6 (364)	2 (145)	2 (87)	1 (31)	4 (192)	1 (55)
Study IDs	(1) ALDRED2001 (2) CARTER2011 (3) GREEN2010 (4) KAALE2012 (5) KASARI2010 (6) SCHERTZ2013	(1) KASARI2012 (2) ROEYERS1996	(1) KASARI2006 (2) LANDA2011	OWENS2008	(1) FRANKEL2010 (2) KOENIG2010 (3) LAUGESON2009 (4) LOPATA2010	DEROSIER2011
Study design	(1)-(6) RCT	(1)-(2) RCT	(1)-(2) RCT	RCT	(1)-(4) RCT	RCT
% female	(1) 11 (2) Not reported (3) 9 (4) 21 (5) 24 (6) Not reported	(1) 10 (2) 32	(1) 19 (2) 21	3	(1) 15 (2) 23 (3) 15 (4) 6	2
Mean age (years)	(1) Median 4-4.3 (2) 1.8 (3) 3.8 (4) 4.1 (5) 2.6 (6) 2.2	(1) 8.1 (2) 9.3	(1) 3.6 (2) 2.4	8.2	(1) 8.5 (2) 9.2 (3) 14.6 (4) 9.5	10
IQ	(1)-(2) Not reported (3) Non-verbal IQ age equivalent: 26.2 months (assessed using the MSEL) (4) 56.2 (assessed using	(1) 90.97 (assessed using the WISC-IV) (2) Not reported (categorical data: 24% IQ>69; 26% IQ 50-69; 51% IQ<50)	(1) 55.4 (assessed using the MSEL) (2) Not reported	110.5 (IQ test not reported)	(1) Verbal IQ: 103.8 (assessed using the WISC-III) (2) 96.2 (assessed using school records or clinic assessment	Not reported (but inclusion criteria IQ ≥85)

	the MSEL) (5) 62.3 (assessed using the MSEL) (6) Not reported				completed within past 2 years) (3) Verbal IQ: 92.3 (assessed using KBIT-2) (4) 103 (assessed using the WISC-IV Short form)	
Dose/ intensity (mg/hours)	(1) Not reported (parents and children attended monthly intervention sessions for 6 months, followed by a further 6 months of less frequent maintenance sessions) (2) Hours of three individualised parent–intervention not reported (intervention consisted of eight group parent-training sessions and three individualised parent–child sessions) (3) 28 (4) 25 (5) 12 (three times 0.5 hour/week) (6) Not reported	(1) Planned intensity of 4 hours (0.67 hour/week) (2) Planned intensity of 7.5 hours (0.5-1 hour/week)	(1) Combined joint attention training and EIBI: 194.3 (32 hours/week); EIBI only: 180 hours (30 hours/week) (2) 205.7 hours for experimental group and 196.2 hours for the control group (8 hours/week)	Planned intensity of 18 hours (1 hour/week)	(1) 11.3 (2) Planned intensity of 20 hours (1.25 hours/week) (3) Planned intensity of 18 hours (1.5 hours/week) (4) Planned intensity of 204 hours (41 hours/week, consisting of five 1.2 hour-sessions a day every day for 5 weeks)	15 hours (1 hour/week) for experimental and 10 hours for control
Setting	(1) Not reported (2) Clinic and home (3) Outpatient (4) Educational (preschool) (5) Not reported	(1)-(2) Educational (school)	(1) Outpatient (2) Educational (Kennedy Krieger classroom)	Educational (school)	(1) Outpatient (2) Not reported (3) Outpatient (4) College campus	Private community-based clinic

	(6) Home					
Length of treatment (weeks)	(1) 52 (2) 15 (3) 56 (4) 8 (5) 8 (6) 17-52 (mean: 30)	(1) 6 (2) 15 sessions (children had 1-2 sessions a week)	(1) 5-6 (2) 26	18	(1) 12 (2) 16 (3) 12 (4) 5	15
Continuation phase (length and inclusion criteria)	(1) 52 (2) 39 (with post-intervention assessments at 22 weeks and follow-up assessments at 39 weeks) (3) 56 (4) 8 (5) 52 (assessments were also performed at 52 weeks for the experimental group but as there was no control at this time point data is not extracted) (6) Up to 60 (including 4- and 8-week post-intervention follow-up assessments)	(1) 12 (includes 6-week post-intervention follow-up) (2) 15 sessions (children had 1-2 sessions a week)	(1) 52 (includes 6-month and 1-year post-intervention follow-ups) (2) 52 (includes 6-month post-intervention follow-up)	18	(1) 24 (including 12-week post-intervention follow-up for the experimental group and 12-week intervention for the waitlist control group) (2) 16 (3) 24 (12-week intervention and waitlist control period followed by 12 weeks active intervention for the waitlist control) (4) 6 (post-intervention assessments completed during the 5 days following treatment)	19 (15 weeks of intervention preceded by baseline assessments 2 weeks prior to intervention and post-intervention assessments within 2 weeks following the intervention)

Table 50: Evidence summary table for effects of social-communication interventions (caregiver- or preschool-teacher- mediated) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Caregiver-mediated or preschool-teacher-mediated social-communication intervention versus treatment as usual						
Outcome	Social interaction	Communication	Social interaction and communication	Parent-rated social-communication	Communication acts	Examiner–child joint/shared attention	Parent–child joint/shared attention
Outcome measure	ADOS: Social interaction	ADOS: Communication	ADOS: Social interaction and communication	CSBS-DP: Social composite	Behavioural observation: Child communication acts or Parent-Child Free Play Procedure: Frequency of intentional communication (weighted)	ESCS: Initiating Joint Attention	Behavioural observation
Study ID	(1) ALDRED2001 (2) GREEN2010	GREEN2010	(1) CARTER2011 (2) GREEN2010	GREEN2010	(1) ALDRED2001 (2) CARTER2011 (3) GREEN2010	(1) CARTER2011 (2) KAALE2012	(1) ALDRED2001 (2) GREEN2010 (3) KASARI2010 (4) SCHERTZ2013 (5) KAALE2012
Effect size (CI; p value)	*Caregiver-mediated* SMD -0.29 (-0.59, 0.00; p = 0.05)	*Caregiver-mediated* SMD -0.03 (-0.35, 0.29; p = 0.85)	*Caregiver-mediated* SMD -0.00 (-0.28, 0.27; p = 0.98)	*Caregiver-mediated* SMD 0.39 (0.06, 0.71; p = 0.02)	*Caregiver-mediated* SMD 0.37 (0.10, 0.64; p = 0.006)	(1)+(2) *Caregiver- or preschool-teacher- mediated* SMD -0.06 (-0.43, 0.32; p = 0.76) (1) *Caregiver-mediated* SMD -0.12 (-0.68, 0.43; p = 0.66) (2) *Preschool-teacher-mediated* SMD 0.00 (-0.51,	(1)+(2) *Caregiver- or preschool-teacher-mediated* SMD 0.30 (0.07, 0.53; p = 0.01) (1) *Caregiver-mediated* SMD 0.33 (0.07, 0.59; p = 0.01) (2) *Preschool-teacher-mediated* SMD 0.17 (-0.33,

						0.51; p = 1.00)	0.68; p = 0.50)
Heterogeneity (chi²; p value; I²)	Chi² = 2.14, df = 1; p = 0.14; *I²* = 53%	Not applicable	Chi² = 2.74, df = 1; p = 0.10; *I²* = 63%	Not applicable	Chi² = 4.57, df = 2; p = 0.10; *I²* = 56%	Chi² = 0.11, df = 1; p = 0.75; *I²* = 0%	Heterogeneity: Chi² = 5.51, df = 4; p = 0.24; *I²* = 27% Test for subgroup differences: Chi² = 0.29, df = 1; p = 0.59; *I²* = 0%
Quality of the evidence (GRADE)	Low[1,2]	Low[2,3]	Very low[1,2,3]	Low[2,4]	Low[1,2]	Moderate[2]	Moderate[2]
Number of studies/ participants	K = 2; N = 180	K = 1; N = 152	K = 2; N = 202	K = 1; N = 152	K = 3; N = 223	K = 2; N = 111	K = 5; N = 302
Forest plot	1.2.8; Appendix 13						

Note. [1]Downgraded for serious inconsistency due to moderate to substantial heterogeneity.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as data could not be extracted from ALDRED2001 for the ADOS communication subdomain.
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure was parent-rated and parents were non-blind and involved in the delivery of the intervention.

Table 51: Evidence summary table for effects of social-communication interventions (caregiver- or preschool-teacher- mediated) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome *(continued)*

	Caregiver-mediated or preschool-teacher-mediated social-communication intervention versus treatment as usual							
Outcome	Parent–child joint attention responses	Parent–child joint engagement	Teacher–child joint/shared attention	Teacher–child joint engagement	Behaviour requests	Non-verbal communication	Focusing on faces	Turn-taking
Outcome measure	Behavioural observation				ESCS: Initiating Behavioural Requests	Parent Interview for Autism-Clinical Version: Non-verbal communication	Behavioural observation (PJAM): focusing on faces at: (1) Post-intervention (2) 4-8-week post-intervention follow-up	Behavioural observation (PJAM): turn-taking at: (1) Post-intervention (2) 4-8 week post-intervention follow-up
Study ID	(1) KASARI2010 (2) SCHERTZ2013	(1) KASARI2010 (2) KAALE2012	KAALE2012		CARTER2011		SCHERTZ2013	
Effect size (CI; p value)	*Caregiver-mediated* SMD 2.25 (1.57, 2.93; p <0.00001)	(1)+(2) *Caregiver- or preschool-teacher-mediated* SMD 0.55 (0.14, 0.95; p = 0.008) (1) *Caregiver-mediated* SMD 0.85 (0.18, 1.52; p = 0.01) (2) *Preschool-teacher-mediated* SMD 0.37 (-0.14,	*Preschool-teacher-mediated* SMD 0.57 (0.05, 1.08; p = 0.03)	*Preschool-teacher-mediated* SMD -0.31 (-0.81, 0.20; p = 0.24)	(1) *Caregiver-mediated post-intervention* SMD 0.18 (-0.37, 0.73; p = 0.52) (2) *Caregiver-mediated 4-month post-intervention follow-up* SMD 0.07 (-0.49, 0.63; p = 0.80)	(1) *Caregiver-mediated post-intervention* SMD -0.09 (-0.67, 0.49; p = 0.75) (2) *Caregiver-mediated 4-month post-intervention follow-up* SMD -0.04 (-0.62, 0.53; p = 0.88)	(1) *Caregiver-mediated post-intervention* SMD 1.87 (0.86, 2.88; p = 0.0003) (2) *Caregiver-mediated 4-8 week post-intervention follow-up* SMD 0.91 (0.05, 1.78; p = 0.04)	(1) *Caregiver-mediated post-intervention* SMD 0.73 (-0.12, 1.58; p = 0.09) (2) *Caregiver-mediated 4-8 week post-intervention follow-up* SMD -0.14 (-0.96, 0.68; p = 0.74)

		0.88; p = 0.15)						
Heterogeneity (chi²; p value; I^2)	Chi² = 6.17, df = 1; p = 0.01; I^2 = 84%	Chi² = 1.25, df = 1; p = 0.26; I^2 = 20%	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]	Moderate[1]	Moderate[1]	Low[3]	Low[3]	Very low[3,4]	Moderate[1]	Low[3]
Number of studies/ participants	K = 2; N = 61	K = 2; N = 99	K = 1; N = 61		K = 1; N = 51/49	K = 1; N = 47	K = 1; N = 23	
Forest plot	1.2.8; Appendix 13							

Note. [1]Downgraded for serious imprecision as N <400.
[2]Downgraded for very serious inconsistency due to substantial to considerable heterogeneity.
[3]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure was parent-reported and parents were non-blind and involved in the delivery of the intervention.

In GREEN2010, the Parent-mediated Communication-focused Treatment (PACT) programme was also delivered by speech and language therapists and consisted of one-to-one clinic sessions between therapist and parent (with the child present) and used techniques such as video feedback to increase parental sensitivity and responsiveness to child communication. Strategies such as joint action routines, familiar repetitive language and pauses were also encouraged in order to develop the child's communication. KASARI2010 tested a caregiver-mediated joint engagement intervention. This joint attention training was adapted from Kasari and colleagues (2006, 2008), and in common with the earlier intervention, involved techniques such as following the child's lead and interest in activities, talking about what the child was doing, repeating back and expanding child utterances, giving corrective feedback, sitting close to and making eye-contact with the child, and making environmental adjustments to engage the child. However, in this case the intervention was caregiver-mediated and involved coaching of the caregiver and the child through interactive play in parent–child dyads. Finally, SCHERTZ2013 examined effects of a Joint Attention Mediated Learning intervention. This intervention was delivered via parent-mediation and targets progressed through three phases: the focusing on faces phase where the child was helped to look freely and often to the parent's face; the turn-taking phase where the child and parent engage in reciprocal and repetitive play that acknowledges the other's shared interest by accommodating the parent's turn; and the joint attention phase where triadic engagement is encouraged using toys. Parent–child interactions were recorded and discussed and parents were required to spend 30 minutes a day with the child, integrating what had been learnt into other daily activities. The intervention was 'complete' when children showed three examples of initiating joint attention in multiple sessions. KAALE2012 also examined a joint attention intervention for preschool children with autism but in this case the delivery was preschool-teacher-mediated rather than caregiver-mediated as in the previous studies. Nevertheless, the content of the intervention was very similar to the caregiver-mediated programmes. In fact, this intervention was adapted from Kasari and colleagues (2006) and used techniques such as interactive play with interesting toys, hiding the toys, prompting and modelling to increase child initiation of higher order joint attention (show, point, give) and encourage joint attention initiation. Common features of the interventions tested across these six trials included: interactive play; action routines; and training for carers or teachers who were involved in mediating the delivery of the intervention, including psycho-education, strategies for encouraging joint attention behaviours, strategies for increasing reciprocal communication through sensitivity and responsiveness to child communication and interaction, and instruction in modelling and feedback.

Meta-analysis with two studies found evidence for a small and statistically significant effect of caregiver-mediated social-communication interventions on social interaction as measured by the ADOS (see Table 50) and meta-analysis with three studies found evidence for a small and statistically significant effect of caregiver-mediated social-communication interventions on communication acts as measured through behavioural observations. However, the quality of the evidence from both

meta-analyses was downgraded to low due to moderate to substantial heterogeneity (I^2 values of 53% and 56%, respectively) and sample size (N <400). There was also evidence from a single study for a small effect of a caregiver-mediated social-communication intervention on parent-rated social-communication as measured by the CSBS-DP social composite score (see Table 50). However, evidence was again downgraded to low, this time due to non-blind outcome assessment and sample size. It is important to note, that the effects on communication and composite communication and social interaction as measured by the ADOS were not statistically significant (see Table 50).

For more proximal measures of impaired social communication and interaction such as joint attention measures, there was evidence from five studies for a small effect of caregiver- or preschool-teacher- mediated social-communication interventions on parent–child joint attention (child initiated) as measured by behavioural observation (see Table 50), and evidence from two studies for a moderate effect of caregiver- or preschool-teacher- mediated social-communication interventions on parent–child joint engagement (see Table 51). The evidence from these meta-analyses was of moderate quality (only downgraded due to sample size). There was also evidence from a two-study meta-analysis for a large and statistically significant effect of caregiver-mediated social-communication interventions on parent–child joint attention responses (see Table 51). The quality of this evidence was downgraded to very low due to considerable heterogeneity and small sample size. However, the results from both single studies showed statistically significant large beneficial treatment effects. There was moderate quality evidence from a single caregiver-mediated intervention study for a large and statistically significant effect on the child focusing on the parent's face at both post-intervention and 4-8-week post-intervention follow-up (see Table 51). There was also evidence from the single preschool-teacher-mediated social-communication intervention study for a moderate and statistically significant effect on teacher–child joint attention as measured by behavioural observation (see Table 51) and this evidence was of moderate quality (only downgraded due to sample size). There were, however, non-significant treatment effects of caregiver- or preschool-teacher- mediated social-communication interventions on examiner–child joint attention as measured by behavioural observation (see Table 51) and non-significant effects of a caregiver-mediated social-communication intervention on behaviour requests or non-verbal communication as measured by the ESCS at post-intervention and follow-up and on turn-taking as measured by behavioural observation (coded using PJAM) at post-intervention and follow-up (see Table 51).

Table 52: Evidence summary table for effects of social-communication interventions (peer-mediated and/or therapist-mediated) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Peer-mediated (and/or therapist-mediated) social-communication intervention versus treatment as usual					
Outcome	Peer–child joint engagement			Child-initiated social interactions	Social network salience	
Outcome measure	Behavioural observations of number of intervals spent in social interaction with unfamiliar typically-developing (TD) peer or % time in joint engagement in playground (Playground Observation of Peer Engagement)	Behavioural observations of % time in joint engagement in playground (Playground Observation of Peer Engagement post-intervention)	Behavioural observations of % time in joint engagement in playground (Playground Observation of Peer Engagement 6-week post-intervention follow-up)	(1) Behavioural observations of number of child-initiated social interactions with familiar TD peer (2) Behavioural observations of number of child-initiated social interactions with unfamiliar TD peer	SNS: Social Network Salience Ratio (post-intervention)	SNS: Social Network Salience Ratio (6-week post-intervention follow-up)
Study ID	(1) KASARI2012 (2) ROEYERS1996	KASARI2012		ROEYERS1996	KASARI2012	
Effect size (CI; p value)	*Peer-mediated* SMD 0.70 (0.31, 1.08; p = 0.0004)	(1) *Therapist-mediated* SMD 0.03 (-0.70, 0.76; p = 0.93) (2) *Peer-mediated* SMD 0.12 (-0.61, 0.84; p = 0.76) (3) *Both therapist- and peer- mediated* SMD 0.00 (-0.73, 0.73; p = 1.00)	(1) *Therapist-mediated* SMD 0.13 (-0.59, 0.85; p = 0.72) (2) *Peer-mediated* SMD 0.75 (-0.00, 1.51; p = 0.05) (3) *Both therapist- and peer- mediated* SMD 0.86 (0.11, 1.62; p = 0.02)	(1) *Familiar TD peer* SMD 0.65 (0.21, 1.09; p = 0.004) (2) *Unfamiliar TD peer* SMD 0.68 (0.24, 1.12; p = 0.003)	(1) *Therapist-mediated* SMD -0.05 (-0.77, 0.66; p = 0.88) (2) *Peer-mediated* SMD 0.42 (-0.30, 1.15; p = 0.25) (3) *Both therapist- and peer- mediated* SMD 1.15 (0.37, 1.93; p = 0.004)	(1) *Therapist-mediated* SMD -0.51 (-1.25, 0.23; p = 0.18) (2) *Peer-mediated* SMD 0.03 (-0.68, 0.75; p = 0.93) (3) *Both therapist- and peer- mediated* SMD 0.32 (-0.40, 1.04; p = 0.39)
Heterogeneity (chi²; p value; I²)	Chi² = 3.38, df = 1; p = 0.07; *I²* = 70%	Not applicable				

Quality of the evidence (GRADE)	Very low[1,2,3]	Low[4]	(1)-(2) Low[4] (3) Moderate[2]	Low[2,3]	(1)-(2) Very low[4,5] (3) Low[2,5]	Very low[4,5]
Number of studies/ participants	K = 2; N = 114	K = 1; N = 29	K = 1; N = 30/29/30	K = 1; N = 85	K = 1; N = 30	K = 1; N = 29/30/30
Forest plot	1.2.8; Appendix 13					

Note. [1]Downgraded for very serious inconsistency due to substantial heterogeneity.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias for ROEYERS1996 as data cannot be extracted for the Social Behaviour Rating Scale which was designed to measure generalisation of gains in social behaviour to larger school setting.
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear as blinding of the typically-developing peer completers was not reported.

Table 53: Evidence summary table for effects of social-communication interventions (peer-mediated and/or therapist-mediated) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome *(continued)*

	Peer-mediated (and/or therapist-mediated) social-communication intervention versus treatment as usual					
Outcome	Number of received friendship nominations		Number of times child identified as someone other children do not like to 'hang out with'		Teacher-rated social skills	
Outcome measure	SNS: indegrees (post-intervention)	SNS: indegrees (6-week post-intervention follow-up)	SNS: rejections (post-intervention)	SNS: rejections (6-week post-intervention follow-up)	TPSS: total (post-intervention)	TPSS: total (6-week post-intervention follow-up)
Study ID	KASARI2012					
Effect size (CI; p value)	(1) *Therapist-mediated* SMD -0.18 (-0.90, 0.54; p = 0.62) (2) *Peer-mediated* SMD 0.96 (0.19, 1.72; p = 0.01) (3) *Both therapist-*	(1) *Therapist-mediated* SMD -0.10 (-0.83, 0.63; p = 0.78) (2) *Peer-mediated* SMD 0.33 (-0.39, 1.05; p = 0.37) (3) *Both therapist-*	(1) *Therapist-mediated* SMD 0.44 (-0.32, 1.21; p = 0.26) (2) *Peer-mediated* SMD 0.94 (0.17, 1.72; p = 0.02) (3) *Both therapist-*	(1) *Therapist-mediated* SMD -0.17 (-0.94, 0.61; p = 0.67) (2) *Peer-mediated* SMD 0.14 (-0.59, 0.87; p = 0.71) (3) *Both therapist-*	(1) *Therapist-mediated* SMD -0.11 (-0.88, 0.66; p =0.77) (2) *Peer-mediated* SMD 0.36 (-0.39, 1.11; p =0.35) (3) *Both therapist-*	(1) *Therapist-mediated* SMD -0.02 (-0.81, 0.77; p =0.97) (2) *Peer-mediated* SMD 0.14 (-0.59, 0.87; p =0.70) (3) *Both therapist-*

	and peer- mediated SMD 0.51 (-0.22, 1.24; p = 0.17)	*and peer- mediated* SMD 0.25 (-0.47, 0.97; p = 0.50)	*and peer- mediated* SMD 0.35 (-0.38, 1.09; p =0.34)	*and peer- mediated* SMD 0.42 (-0.32, 1.15; p = 0.27)	*and peer- mediated* SMD 0.32 (-0.43, 1.06; p = 0.41)	*and peer- mediated* SMD 0.48 (-0.26, 1.22; p =0.20)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	(1) Very low[1,2] (2) Low[1,3] (3) Very low[1,2]	Very low[1,2]	(1) Very low[1,2] (2) Low[1,3] (3) Very low[1,2]	Very low[1,2]	Very low[2,4]	
Number of studies/ participants	K = 1; N = 30	K = 1; N = 29/30/30	K = 1; N = 27/29/29	K = 1; N = 26/29/29	K = 1; N = 26/28/28	K = 1; N = 25/29/29
Forest plot	1.2.8; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear as blinding of the typically-developing peer completers was not reported.
[2]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious imprecision as N <400.
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear as teacher-rated and blinding of teachers was not reported.

Two studies (KASARI2012, ROEYERS1996) examined effects of peer-mediated social-communication interventions relative to treatment as usual, one of which (KASARI2012) also examined effects of therapist-mediated and both therapist- and peer- mediated social-communication interventions relative to treatment as usual, on direct measures of social interaction and communication, and on joint engagement which may be regarded as a proximal measure of the core autism feature of impaired reciprocal social communication and interaction. In ROEYERS1996 the intervention was structured around play sessions with typically-developing peers. Typically-developing peers initially attended a 1.25-hour preparatory session consisting of education about autism and role-playing activities that addressed how to react to aggressive behaviour, how to remain on the same level as the child with autism (for instance sitting or standing), and alternative ways to get the attention of the child with autism when verbal attempts have failed. Subsequent intervention sessions consisted of 0.5-hour free-play sessions between a child with autism and a typically-developing child in a playroom familiar to the child with autism once or twice a week during lunchtime or after school. In KASARI2012 effects of a peer-mediated social skills group programme were examined. The intervention involved three typically-developing children from the target autistic child's classroom attending a social skills group where they were taught strategies for engaging with children with social challenges in the playground. Techniques for teaching the typically-developing peers included social modelling and reinforcement, and homework assignments were set to encourage practice. KASARI2012 also included two additional active intervention arms: a therapist-mediated intervention, individual social-communication intervention; and both a therapist- and peer-mediated intervention condition (both a peer-mediated social skills group programme and an individual social-communication intervention interventions). The therapist-mediated intervention programme taught social communication skills to children with autism based on individualised skill deficits and used techniques including adult coaching, modelling, reinforcement and feedback. Participants were also set homework assignments to practice strategies and skills in social interactions to encourage generalisation.

Meta-analysis with the two peer-mediated intervention studies found evidence for a statistically significant moderate size effect on a proximal measure of the core feature of impaired reciprocal social communication and interaction, peer–child joint engagement as measured by behavioural observations (see Table 52). However, the quality of this evidence was very low due to substantial heterogeneity ($I^2 = 70\%$), small sample size and high risk of selective reporting bias in ROEYERS1996. All other comparisons only involved single study data. There was evidence for moderate and statistically significant effects of a peer-mediated intervention on the frequency of child-initiated social interactions with both the familiar typically-developing peer and an unfamiliar typically-developing peer (see Table 52). However, the quality of the evidence was low due to small sample size and high risk of selective reporting bias as this study (ROEYERS1996) did not report results for the for the Social Behavior Rating Scale which was measured in the trial as an indicator of generalisation of acquired social skills to the larger school setting. There was also

evidence from a single study for large and statistically significant but transient effects on number of received friendship nominations and rejections (see Table 53). However, in addition to showing only short-term benefits the quality of this evidence was low to very low due to unclear blinding of outcome assessors and imprecision. There were also non-significant effects observed for a peer-mediated social-communication intervention on a measure of popularity in school, social network salience as measured by the SNS (see Table 52) and for teacher-rated social skills as measured by the TPSS (see Table 53).

For the combined therapist- and peer-mediated social-communication intervention there was moderate quality evidence (only downgraded for sample size) for a large and statistically significant effect on peer–child joint engagement at 6-week post-intervention follow-up but not at post-intervention assessment (see Table 52). There was also evidence for a large and statistically significant effect on social network salience. However, this effect was transient (significant at post-intervention but not at follow-up; see Table 52) and the quality of the evidence was low to very low due to unclear blinding of outcome assessors and imprecision. Non-significant effects of a combined therapist- and peer-mediated intervention were observed for number of received friendship nominations, rejections and teacher-rated social skills (see Table 53).

Finally, for the therapist-mediated social-communication intervention no statistically significant effects were observed for peer–child joint engagement (see Table 52), social network salience (see Table 52), received friendship nominations (see Table 53), rejections (see Table 53) or teacher-rated social skills (see Table 53).

Table 54: Evidence summary table for effects of social-communication interventions (joint attention training and EBI/EIBI) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Joint attention training and EBI/EIBI versus EBI/EIBI only				
Outcome	Examiner–child joint attention – child-initiated joint attention		Examiner–child joint attention – child responding to joint attention	Examiner–child shared positive affect	Examiner–child joint attention, shared positive affect and utterance
Outcome measure	ESCS subscales: (1) Coordinated joint attention looks (2) Showing (3) Pointing (4) Giving	CSBS-DP: initiating joint attention	ESCS: responding to joint attention	ESCS: joint attention and shared positive affect or CSBS-DP: shared positive affect	ESCS: joint attention and shared positive affect and utterance
Study ID	KASARI2006	LANDA2011	KASARI2006	(1) KASARI2006 (2) LANDA2011	KASARI2006
Effect size (CI; p value)	(1) *Coordinated joint attention looks* SMD -0.09 (-0.74, 0.56; p = 0.79) (2) *Showing* SMD 0.55 (-0.11, 1.21; p = 0.10) (3) *Pointing* SMD 0.69 (0.02, 1.36; p =0.04) (4) *Giving* SMD 0.48 (-0.18, 1.14; p = 0.15)	(1) *Post-intervention* SMD 0.31 (-0.26, 0.88; p = 0.29) (2) *6-month post-intervention follow-up* SMD 0.44 (-0.14, 1.01; p = 0.14)	SMD 1.11 (0.41, 1.81; p = 0.002)	(1) *Post-intervention* SMD 0.04 (-0.39, 0.47; p = 0.85) (2) *6-month post-intervention follow-up* SMD 0.43 (-0.00, 0.87; p = 0.05) (3) *12-month post-intervention follow-up* SMD 0.60 (-0.08, 1.27; p = 0.08)	(1) *Post-intervention* SMD 0.04 (-0.62, 0.70; p = 0.90) (2) *6-month post-intervention follow-up* SMD 0.56 (-0.12, 1.23; p = 0.10) (3) *12-month post-intervention follow-up* SMD 0.77 (0.09, 1.46; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable			(1) Chi² = 0.83, df = 1; p = 0.36; I^2 = 0% (2) Chi² = 0.33, df = 1; p = 0.56; I^2 = 0% (3) Not applicable	Not applicable
Quality of the evidence (GRADE)	(1)-(2) Low[1] (3) Moderate[2] (4) Low[1]	Low[1]	Moderate[2]	(1) Moderate[2] (2)-(3) Low[1]	(1)-(2) Low[1] (3) Moderate[2]

Number of studies/ participants	K = 1; N = 37	K = 1; N = 48	K = 1; N = 37	(1)-(2) K = 2; N = 84 (3) K = 1; N = 36	K = 1; N = 36
Forest plot	1.2.8; Appendix 13				
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded for serious imprecision as N <400.					

Table 55: Evidence summary table for effects of social-communication interventions (joint attention training and EBI/EIBI) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome *(continued)*

	Joint attention training and EBI/EIBI versus EBI/EIBI only				
Outcome	Examiner–child socially engaged imitation	Mother–child joint attention – child-initiated joint attention		Examiner–child and mother–child joint attention: joint attention initiation composite	Examiner–child and mother–child joint attention: joint attention responses composite
Outcome measure	Behavioural observation: socially-engaged intervention	Behavioural observation: mother–child interaction subscales: (1) Coordinated joint attention looks (2) Showing (3) Pointing (4) Giving	Behavioural observation: mother–child interaction – Duration of joint attention (seconds)	ESCS and mother–child interaction observations: joint attention initiation composite	ESCS and mother–child interaction observations: joint attention responses composite
Study ID	LANDA2011	KASARI2006			
Effect size (CI; p value)	(1) *Post-intervention* SMD 0.29 (-0.28, 0.86; p = 0.31) (2) *6-month post-intervention follow-up* SMD 0.73 (0.15, 1.32; p = 0.01)	(1) *Coordinated joint attention looks* SMD 0.48 (-0.18, 1.13; p = 0.15) (2) *Showing* SMD 0.51 (-0.15, 1.16; p = 0.13) (3) *Pointing* SMD -0.39 (-1.04, 0.27; p = 0.25) (4) *Giving* SMD 0.36 (-0.30, 1.01; p = 0.28)	(1) *Post-intervention* SMD 0.77 (0.10, 1.45; p = 0.02) (2) *6-month post-intervention follow-up* SMD 0.19 (-0.46, 0.83; p = 0.57) (3) *12-month post-intervention follow-up*	(1) *Post-intervention* SMD 0.51 (-0.15, 1.17; p = 0.13) (2) *6-month post-intervention follow-up* SMD 0.53 (-0.13, 1.18; p = 0.12) (3) *12-month post-intervention follow-up*	(1) *Post-intervention* SMD 1.11 (0.41, 1.81; p = 0.002) (2) *6-month post-intervention follow-up* SMD 0.80 (0.12, 1.47; p = 0.02) (3) *12-month post-intervention follow-up*

			SMD 0.81 (0.13, 1.50; p = 0.02)	SMD 0.99 (0.29, 1.69; p = 0.006)	SMD 0.17 (-0.49, 0.83; p = 0.61)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	(1) Low[1] (2) Moderate[2]	Low[1]	(1) Moderate[2] (2) Low[1] (3) Moderate[2]	(1)-(2) Low[1] (3) Moderate[2]	(1)-(2) Moderate[2] (3) Low[1]
Number of studies/ participants	K = 1; N = 48	K = 1; N = 37	K = 1; N = 37/37/36		
Forest plot	1.2.8; Appendix 13				

Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious imprecision as N <400.

Two studies (KASARI2006, LANDA2011) examined effects of combined joint attention training and EBI/EIBI relative to EBI/EIBI-only on joint attention which may be regarded as a proximal measure of the core autism feature of impaired reciprocal social communication and interaction. In KASARI2006 all participants in the study (experimental and control groups) were already participating in an EIBI preschool program which was based on ABA principles and followed a typical preschool curriculum but with staff to participant ratios of 1:1 for 6 hours a day. Participants in the experimental group were given an additional joint attention training intervention. This intervention was aimed at increasing joint attention initiation (including coordinated joint looking, showing, giving to share, proximal and distal pointing) and responding to joint attention attempts (including following proximal and distal points). Each session of the joint attention intervention followed the same format with 5 minutes of a direct-instruction table activity where principles of ABA were used to prime the appropriate joint attention response using techniques such as positive reinforcement and hierarchical prompting (verbal prompt, model, physical prompt). The following 20 minutes of the session involved a move to naturalistic milieu instruction on the floor where the same goal was targeted but this time instruction was more child-driven and included techniques such as following the child's lead and interest in activities, talking about what the child was doing, repeating back and expanding child utterances, giving corrective feedback, sitting close to and making eye-contact with the child, and making environmental adjustments to engage the child. In LANDA2011, participants in both the control group and the experimental group received behavioural intervention using the Assessment, Evaluation, and Programming System for Infants and Children (Bricker, 2002) curriculum. This intervention involved techniques such as discrete trial teaching and pivotal response training and AAC techniques (including visual cues and schedules) to target child-initiated intentional communication and diverse object play. The intervention administrator followed the child's lead and expanded language and play behaviour. Both control and experimental interventions also included parent education classes (38 hours) focusing on behavioural strategies for enhancing child development and for behaviour management, and coping and advocacy, and home-based parent training (9 hours) focusing on techniques for improving communication and adaptive behaviour. Both experimental and control interventions included goals for joint attention and imitation. However, the experimental group differed from the control group in the number of orchestrated opportunities to respond to and initiate joint attention and imitate others during social interaction and the number of opportunities afforded by the physical environment for initiating and responding to joint attention and for sharing positive affect, and there was a more discrete breakdown of social targets for the experimental curriculum.

Evidence from the only meta-analysis (with both studies) showed no evidence for statistically significant effects of an additional joint attention training intervention on examiner–child shared positive affect as measured by the ESCS or CSBS-DP at post-intervention or at 6-month post-intervention follow-up (see Table 54). KASARI2006

also included a 12-month post-intervention follow-up assessment for this outcome measure and again treatment effects were non-significant (see Table 54).

KASARI2006 included a range of other outcome measures assessing joint attention. Evidence was found for moderate and statistically significant effects of additional joint attention training on pointing during examiner–child interactions as measured at post-intervention using the ESCS and for examiner–child joint attention, shared positive affect and utterance at 12-month post-intervention follow-up but not for assessments of this outcome at the two earlier time points (see Table 54). In addition, a large effect for the child responding to joint attention was found during examiner–child interactions as measured at post-intervention using the ESCS (see Table 54). This study also found evidence for moderate to large effects of additional joint attention training on the duration of child-initiated joint attention during mother–child interaction at post-intervention and 12-month post-intervention follow-up but not at 6-month post-intervention follow-up, a large but delayed effect on the composite (examiner–child and mother–child) joint attention initiation and large but transient effects on the composite joint attention responses (see Table 55). The quality of the above evidence was moderate (only downgraded for sample size). However, there were also a number of non-significant treatment effects for all but one of the subscales of the ESCS (see Table 54) and for all of the subscales for child-initiated joint attention during mother–child interaction (see Table 55).

LANDA2011 found evidence for a delayed but moderate and statistically significant effect (of moderate quality) of an additional joint attention training intervention on socially engaged imitation as measured using behavioural observation of examiner–child interaction (see Table 55). However, non-significant effects were observed for child-initiated joint attention as measured by the CSBS-DP (see Table 54).

Table 56: Evidence summary table for effects of social-communication intervention (LEGO® therapy) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	LEGO® therapy versus SULP		
Outcome	Social interaction	Frequency of child-initiated social interactions with TD peers	Duration of all social interactions with TD peers
Outcome measure	GARS: Social interaction	Behavioural observation	
Study ID	OWENS2008		
Effect size (CI; p value)	SMD -0.73 (-1.46, -0.00; p = 0.05)	SMD 0.23 (-0.63, 1.09; p = 0.59)	SMD 0.27 (-0.59, 1.13; p = 0.53)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1,2]	Very low[3,4]	
Number of studies/participants	K = 1; N = 31	K = 1; N = 21	
Forest plot	1.2.8; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear as parent-rated and blinding of parents was not reported.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias due to non-blinded behavioural observations which were carried out by the investigator and there was no reliability or validity data reported for observation measures.
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

One study (OWENS2008) examined effects of LEGO® therapy on the core autism feature of impaired reciprocal social communication and interaction. The experimental intervention in this study involved collaborative LEGO play in pairs or small groups (based on a draft manual produced by Dr LeGoff). Typical projects included building a LEGO set in groups of three with each member of the group assigned a different role (for instance, 'engineer', 'supplier' and 'builder') and 'freestyle' LEGO activities in which children designed and built a model in pairs (for instance, a space rocket). The former project type aimed to target joint attention, turn taking, sharing, joint problem solving, listening and general social communication skills. While, the 'freestyle' projects aimed to teach compromise, clear expression of ideas and taking other people's perspectives and ideas into account. During the intervention children were asked to follow 'LEGO Club Rules', which included: 'Build things together'; 'If someone else is using it, don't take it, ask first'; 'Use indoor voices-no yelling'; and 'Use polite words'. The therapists role was to highlight the presence of a problem and help children to come up with their own solutions (or remind them of strategies which they had previously used) rather than pointing out specific social problems or solutions. In this study, the control group also received an active intervention, SULP (Rinaldi, 2004). This control intervention used a direct group-based teaching approach (following the SULP manual) to target eye contact, listening, turn taking, proxemics and prosody. Instruction followed a specified framework, beginning with stories about monster characters who experienced problems with particular social or communication skills, moved on to asking the children to evaluate adult models of good and bad skills, and finally children practised the targeted skill through games and conversation. This study found evidence for a moderate and statistically significant effect (favouring LEGO® therapy) on social interaction as measured by the GARS (see Table 56). However, the quality of the evidence was low due to unclear blinding of parents who were the outcome assessors and small sample size. Moreover, the outcome measures which assessed generalisation of social interaction skills through behavioural observation of social interactions with typically-developing peers in the school playground revealed non-significant treatment effect for both frequency of child-initiated social interactions and duration of all social interactions (see Table 56).

Table 57: Evidence summary table for effects of social-communication interventions (social skills groups) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Social skills group versus treatment as usual						
Outcome	Social skills	Social impairment	Adaptive social behaviour	Capacity for social interactions	Study-specific targeted social skills	Social skills knowledge	Feelings of loneliness
Outcome measure	SSRS Assertion subscale or SSRS standardised social skills score or BASC-2-PRS Social Skills subscale	SRS: total	Social Competence Inventory: pro-social index	Social Competence Inventory: social initiation	ASC: total	(1) Test of Adolescent Social Skills Knowledge: total (2) Skillstreaming Knowledge Assessment: total	Loneliness Scale: total
Study ID	(1) FRANKEL2010 (2) LAUGESON2009 (3) LOPATA2010	LOPATA2010	KOENIG2010		LOPATA2010	(1) LAUGESON2009 (2) LOPATA2010	FRANKEL2010
Effect size (CI; p value)	SMD 0.60 (0.26, 0.95; p = 0.0006)	SMD -0.69 (-1.37, -0.00; p = 0.05)	SMD 0.11 (-0.51, 0.73; p = 0.73)	SMD -0.03 (-0.65, 0.58; p = 0.92)	SMD 0.90 (0.21, 1.59; p = 0.01)	(1)+(2) *Self-rated and researcher-rated* SMD 1.58 (1.03, 2.14; p <0.00001) (1) *Self-rated* SMD 2.17 (1.29, 3.06; p <0.00001) (2) *Researcher-rated* SMD 1.19 (0.48, 1.91; p = 0.001)	SMD -0.67 (-1.16, -0.18; p = 0.008)
Heterogeneity (chi²; p value; I^2)	Chi^2 = 1.40, df = 2; p = 0.50; I^2 = 0%	Not applicable				Chi^2 = 2.87, df = 1; p = 0.09; I^2 = 65%	Not applicable
Quality of the evidence (GRADE)	Low[1,2]	Very low[1,2,3]	Very low[4,5]		Very low[1,2,3]	(1)+(2) Very low[2,6,7] (1)-(2) Low[2,6]	Low[2,8]

Number of studies/ participants	K = 3; N = 137	K = 1; N = 35	K = 1; N = 41	K = 1; N = 36	K = 2; N = 69	K = 1; N = 67
Forest plot	1.2.8; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measures were parent-rated and parents were non-blind and involved in the intervention.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as LOPATA2010 did not report data for the waitlist control group for the staff-rated version of this outcome measure.
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measures were parent-rated and parents were non-blind.
[5]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)
[6]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors (self-completed or researcher) were non-blind.
[7]Downgraded due to very serious inconsistency (I^2 value indicates moderate to substantial heterogeneity).
[8]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as self-rated.

Table 58: Evidence summary table for effects of social-communication interventions (social skills groups) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome *(continued)*

	Social skills group versus treatment as usual						
Outcome	Popularity	Number of times child invited to a play date	Time spent in interactive activities	Time spent in minimally interactive activities	Quality of friendships	Positive treatment response	Emotion recognition
Outcome measure	Piers-Harris Self-Concept Scale: Popularity	QPQ: Guest	QPQ: Engage	QPQ: Disengage	Friendship Qualities Scale: total	Dichotomous measure of number of participants 'much improved/very improved' on CGI-I	Diagnostic Analysis of Non-verbal Accuracy 2: Child Faces
Study ID	FRANKEL2010	(1) FRANKEL2010 LAUGESON2009 (2) LAUGESON2009	FRANKEL2010		LAUGESON2009	KOENIG2010	LOPATA2010
Effect size (CI; p value)	SMD 0.56 (0.07, 1.04; p = 0.02)	(1) *Parent-rated* SMD 0.36 (-0.04, 0.77; p=0.08) (2) *Self-rated* SMD -0.26 (-0.95, 0.42; p=0.45)	SMD 0.20 (-0.31, 0.70; p = 0.44)	SMD -1.31 (-1.87, -0.75; p <0.00001)	SMD 0.14 (-0.55, 0.82; p = 0.70)	RR 26.13 (1.67, 407.99; p = 0.02)	SMD 0.44 (-0.22, 1.10; p = 0.19)
Heterogeneity (chi²; p value; I^2)	Not applicable	(1) Chi^2 = 0.01, df = 1; p = 0.94; I^2 = 0% (2) Not applicable	Not applicable				
Quality of the evidence (GRADE)	Low[1,2]	(1) Very low[3,4] (2) Very low[1,4]	Very low[3,4]	Low[2,3]	Very low[1,4]	Low[5,6]	Very low[4,7]

Number of studies/ participants	K = 1; N = 68	(1) K = 2; N = 97 (2) K = 1; N = 33	K = 1; N = 62	K = 1; N = 33	K = 1; N = 41	K = 1; N = 36
Forest plot	1.2.8; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as self-rated.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measures were parent-rated and parents were non-blind and involved in the intervention.
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrator and participants were non-blind, and high risk of detection bias as although the rater of the CGI was blind this measure was based on interview with parents who were non-blind
[6]Downgraded for serious imprecision as number of events <300.
[7]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors (researchers) were non-blind and high levels of variability for this outcome measure were dealt with by administering the test twice at each time point and taking the average score.

Four studies (FRANKEL2010, KOENIG2010, LAUGESON2009, LOPATA2010) examined effects of social skills group interventions relative to treatment as usual on the core autism feature of impaired reciprocal social communication and interaction. The specific models of intervention were variable but the content and target of interventions were comparable. In FRANKEL2010 the parent-assisted Children's Friendship Training (CFT; Frankel & Myatt, 2003) intervention was examined**.** This group-based social skills intervention involved individuals with autism being integrated into a mixed clinical group (18.6% adjustment disorder, 46% ADHD, 2.7% ADHD and ODD, 0.5% ODD alone, 0.7% fetal alcohol spectrum disorder, 4.9% anxiety disorder, 1.3% mood disorder, 1.3% learning disabilities and 25.2% no diagnosis) and children were taught social skills in terms of rule-based procedures using techniques including instruction, modelling, rehearsal and performance feedback. Homework assignments were also used to try and increase generalisation, including calling another member of the class, parent-supported play dates, and practicing 'making fun of the teasing' with a child who was teasing them. Children and parents were seen at the same time in separate sessions and the aim of the parent sessions was to increase generalisation through training in the organisation and implementation of play dates. LAUGESON2009 tested a very similar intervention but with specific adaptations to the manual to be appropriate for adolescents. In this modified intervention trial (Program for the Education and Enrichment of Relational Skills social skills group), concurrent parent and teen sessions addressed: reciprocal conversational skills (and how parents could identify activities which might lead to potential friendships); appropriate use of electronic communication in developing pre-existing friendships (and parents taught the social structure of school peer groups); how to choose appropriate friends by pursuing extracurricular activities and identifying groups they might fit in with; how to join (and exit) conversations with peers; how to organise and host a get-together with friends; how to be a good sportsman during games and sports; strategies for handling teasing and bullying appropriately and for changing a bad reputation; and strategies for handling disagreements with peers. Each session involved didactic instruction, role-play by the intervention administrators of the appropriate social skill, rehearsal of the social skill by the teen with accompanying performance feedback, and a homework assignment for the next session (parents were instructed on how to overcome obstacles associated with their child completing the upcoming homework assignment). The social skills group intervention (Lopata et al., 2008) examined in LOPATA2010 also involved a parent training component. The social skills group intervention was delivered to children (grouped by age) and targeted outcomes were social skills, emotion recognition and interpretation of non-literal language. Teaching techniques included direct instruction, modelling, role play, performance feedback, team-working to complete task or solve problem, a response-cost reinforcement system, and homework assignments. The weekly concurrent parent training sessions focused on increasing understanding of autism and of the intervention that their child was taking part in, and on teaching parents strategies to encourage generalisation. Finally, in KOENIG2010 the social skills groups were made up of four to five autistic participants and two typically-developing peer tutors and teaching techniques were based on social learning theory and principles

of behaviour theory. Each group session involved two activities that required group members to socialize with peers, including playing cooperatively, taking turns, listening to one another, solving a problem or tolerating frustration and change.

Meta-analysis with three studies found evidence for a moderate and statistically significant effect of social skills group interventions on social skills as measured by the SSRS or BASC-2-PRS and meta-analysis with two studies found evidence for a large and statistically significant effect of social skills group interventions on social skills knowledge as measured by the Test of Adolescent Social Skills Knowledge or Skillstreaming Knowledge Assessment (see Table 57). However, the quality of the evidence from the first meta-analysis was downgraded to low due to non-blind outcome assessment (outcome measures were parent-rated and parents were involved in the intervention) and small sample size and to very low for the latter meta-analysis, again due to small sample size and non-blind outcome assessment (self- or parent-completed) but also for inconsistency (with an I^2 value of 65% indicating moderate to substantial heterogeneity). A non-significant effect was found (in meta-analysis with two studies) for the number of times child invited on a play date as measured by the parent-rated QPQ and the single study that reported data for the self-rated QPQ also failed to find significant treatment effects for this outcome measure (see Table 58).

There was evidence from single studies for large and statistically significant effects of a social skills group intervention on study-specific targeted social skills as measured by the ASC (see Table 57) and on time spent in minimally interactive activities as measured using the QPQ (see Table 58). There was also single study data for moderate treatment effects on social impairment measured using the SRS (see Table 57), feelings of loneliness (see Table 57) and self-rated popularity as measured using the Piers-Harris Self-Concept Scale (see Table 58). However, the quality of this single-study evidence was downgraded to low or very low due to non-blind outcome assessment (parent- or self-rated) and small sample size and one study also showed a high risk of selective reporting bias as data could not be extracted for staff-rated outcome measures. A single study also provided evidence for a large effect of a social skills group on a dichotomous measure of positive treatment response (see Table 58) with the participants receiving the social skills group intervention being over 26 times more likely to show improvement in two individualised social behaviour targets (measured using CGI-I) than participants in the waitlist control group. However, the quality of the evidence is low due to non-blind outcome assessment (although the rater of the CGI was blind this measure was based on interview with parents who were non-blind) and the small number of events (less than 300). Non-significant treatment effects were observed for: adaptive social behaviour and capacity for social interactions as measured by the Social Competence Inventory (see Table 57); time spent in interactive activities as measured by the QPQ (see Table 58); self-rated quality of friendships as measured by the Friendship Qualities Scale (see Table 58); and emotion recognition as measured by the Diagnostic Analysis of Non-verbal Accuracy 2 (see Table 58).

Table 59: Evidence summary table for effects of social-communication interventions (autism-specific social skills group) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Social skills group modified for autism versus standard social skills group		
Outcome	Social skills	Social self-efficacy	Feelings of loneliness
Outcome measure	SRS subscales (standardised change scores): (1) Social Awareness (2) Social Cognition (3) Social Communication (4) Social Motivation (5) Autistic Mannerisms	Social Self-efficacy Scale: total (standardised change score)	Social Dissatisfaction Questionnaire: total (standardised change score)
Study ID	DEROSIER2011		
Effect size (CI; p value)	(1) SMD -0.68 (-1.26, -0.11; p =0.02) (2) SMD -0.33 (-0.89, 0.23; p = 0.24) (3) SMD -0.93 (-1.52, -0.34; p = 0.002) (4) SMD -0.66 (-1.23, -0.08; p = 0.02) (5) SMD -0.67 (-1.24, -0.10; p = 0.02)	SMD -0.12 (-0.67, 0.42; p =0.65)	SMD 0.15 (-0.40, 0.69; p = 0.60)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	(1) Low[1,2] (2) Very low[1,3] (3)-(5) Low[1,2]	Very low[3,4]	Very low[3,4]
Number of studies/participants	K = 1; N = 50	K = 1; N = 52	
Forest plot	1.2.8; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as parent-completed and parents were non-blind and involved in the intervention.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure self-rated.

One study (DEROSIER2011) examined effects of a social skills group intervention that was modified for children with autism relative to a standard social skills group intervention on the core autism feature of impaired reciprocal social communication and interaction. The experimental intervention (social skills group intervention – high functioning autism) was an autism-specific adaptation of a standard social skills group intervention that used cognitive-behavioural and social learning techniques to build social skills and peer relationships. The specific adaptations included the progressive introduction of skills, a focus on socially relevant goals, varied learning opportunities, and structure and predictability. The intervention consisted of three modules: Communication (including verbal communication, non-

verbal communication and listening skills); working with others (including consequences and stop and think, perspective taking, cooperation and compromise); and friendship skills (including making and keeping friends, initiation, social problem solving and coping with bullying and teasing). This adaptation also differed from standard social skills group intervention in the involvement of parents, with parents of children in the experimental group attending an extra four sessions (orientation to the group, and review of each module) and involved through at-home practice. The control group in this trial received a standard social skills group intervention (DeRosier, 2007) developed to build social skills and peer relationships for typically-developing children who were socially at-risk. This study found evidence for moderate to large and statistically significant effects on all but one (social cognition) of the SRS subscales as a measure of social skills (see Table 59). However, the quality of this evidence was low due to non-blind outcome assessment (parent-completed and parents were involved in the intervention) and small sample size. Non-significant treatment effects were observed for self-rated measures of social self-efficacy and feelings of loneliness (see Table 59).

6.2.6 Clinical evidence summary – effect of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction

Many studies have examined the effects of psychosocial interventions on the core autism feature of impaired reciprocal social communication and interaction. However, due to differences in comparators and outcome measures, very little meta-analysis was possible. From the few meta-analyses possible with better quality evidence, there was small to moderate effects in favour of caregiver- or preschool-teacher-mediated social-communication interventions on social interaction (as measured by the ADOS), communication acts, parent–child joint attention and parent–child joint engagement, for young children with autism (mean ages of 1-4 years). There was also very low quality evidence from a meta-analysis for a moderate effect of peer-mediated social-communication interventions on peer–child joint engagement for older children (mean ages of 8-9 years). Based on low to very low quality evidence it was not possible to draw conclusions about the relative benefit of parent training, AAC, animal-based, arts-based, behavioural or cognitive interventions.

6.2.7 Clinical evidence –effect of psychosocial interventions on the core autism feature of restricted interests and rigid and repetitive behaviours

Behavioural interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

One of the behavioural intervention trials (DAWSON2010) compared ESDM with treatment as usual and the other behavioural intervention trial (ROGERS2012) compared P-ESDM with treatment as usual in preschool children with autism (see

Table 60). See section 6.2.3 for further information about the ESDM intervention and see section 6.2.5 for further information about the P-ESDM intervention.

Table 60: Study information table for included trials of behavioural interventions for the core autism feature of restricted interests and rigid and repetitive behaviours

	ESDM versus treatment as usual	**P-ESDM versus treatment as usual**
No. trials (N)	1 (48)	1 (98)
Study IDs	DAWSON2010	ROGERS2012
Study design	RCT	RCT
% female	29	31
Mean age (years)	2.0	1.7
IQ	60.2 (assessed using the MSEL: early-learning composite score; Mullen, 1995)	Not reported (inclusion criteria developmental quotient >35 as measured by MSEL)
Dose/intensity (mg/hours)	1,581 hours with a trained therapist (20 hours/week) Parents reported spending 1,695 hours using ESDM strategies	Planned intensity of 12 hours (1 hour/week) and weekly mean intensity of all intervention was 1.48 hours
Setting	Academic research (university) and home	Three university clinics
Length of treatment (weeks)	104	12
Continuation phase (length and inclusion criteria)	104	12

Evidence for the effectiveness of ESDM and P-ESDM on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 61. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 61: Evidence summary table for effects of behavioural intervention on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	ESDM or P-ESDM versus treatment as usual
Outcome	Repetitive behaviour
Outcome measure	(1) RBS: total (2) ADOS-T: Restricted, Repetitive Behaviours
Study ID	(1) DAWSON 2010 (2) ROGERS2012
Effect size (CI; p value)	(1)+(2) SMD -0.06 (-0.39, 0.27; p = 0.72) (1) *ESDM* SMD -0.35 (-0.95, 0.24; p = 0.24) (2) *P-ESDM* SMD 0.07 (-0.32, 0.47; p = 0.72)
Heterogeneity (chi²; p value; I^2)	Test for subgroup differences: Chi² = 1.38, df = 1; p = 0.24; I^2 = 27.4%
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 2; N = 143
Forest plot	1.3.1; Appendix 13

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and unclear/unknown risk of detection bias as blinding of outcome assessors was either not reported or the outcome measure was parent-completed and parents were non-blind and involved in the intervention. [2]Downgraded for serious imprecision as N <400.

There was no evidence for a statistically significant effect of ESDM or P-ESDM (or any difference between the interventions) on repetitive behaviour as an indirect outcome (see Table 61).

Cognitive interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

The cognitive intervention trial (YOUNG2012) compared enhanced DVD-based ERT with standard DVD-based ERT in children with autism (see Table 39). See section 6.2.5 for further information about the enhanced and standard DVD-based ERT.

Evidence for the effectiveness of the one included cognitive intervention on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 62. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 62: Evidence summary table for effects of cognitive intervention on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Enhanced ERT versus standard ERT
Outcome	Stereotyped behaviour
Outcome measure	SCQ: Stereotyped behaviour
Study ID	YOUNG2012
Effect size (CI; p value)	SMD -0.31 (-1.10, 0.48; p = 0.44)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 25
Forest plot	1.3.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and detection bias as parents were non-blind and were intervention administrators and outcome assessors. [2]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence from the single included cognitive intervention trial for a statistically significant effect of enhanced ERT on stereotyped behaviour as an indirect outcome (see Table 62).

Parent training interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

The parent training intervention trial (AMAN2009) compared combined parent training and antipsychotic medication with antipsychotic medication only in children with autism (see Table 63).

Table 63: Study information table for included trial of parent training (as an adjunct to antipsychotics) for the core autism feature of restricted interests and rigid and repetitive behaviours

	Combined parent training and antipsychotic medication versus antipsychotic medication only
No. trials (N)	1 (124)
Study IDs	AMAN2009
Study design	RCT
% female	Not reported
Mean age (years)	7.4
IQ	Not reported (19% mild LD; 24% moderate LD)
Dose/intensity (mg/hours)	Experimental intervention: Risperidone (or aripiprazole) 0.5-3.5 mg/day (mean: 2 mg/day) and 10.8 60-90-minute sessions for parent training Control intervention: Risperidone (or aripiprazole) 0.5-3.5 mg/day (mean: 2.3 mg/day)
Setting	Not reported
Length of treatment (weeks)	24
Continuation phase (length and inclusion criteria)	54-162.5 weeks (mean: 80 weeks; including 1-year post-intervention follow-up)

Evidence for the effectiveness of combined parent training and antipsychotic on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 64. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 64: Evidence summary table for effects of parent training (as an adjunct to antipsychotics) on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Combined parent training and antipsychotic medication versus antipsychotic medication only
Outcome	Compulsions
Outcome measure	Children's Yale-Brown Obsessive-Compulsive Scale-PDD Version (CYBOCS-PDD): Compulsions
Study ID	AMAN2009
Effect size (CI; p value)	SMD -0.42 (-0.83, -0.01; p = 0.04)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 95
Forest plot	1.3.3; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as outcome measure based on interview, but unclear who the interviewee is but if parental interview then non-blind. There was also a high risk of attrition bias due to higher dropout rates in the experimental (combined risperidone and parent training) group (N = 20; 27% attrition) than the control (risperidone only) group (N = 9; 18% attrition). [2]Downgraded for serious imprecision as N <400.	

The single included parent training trial examined indirect effects of parent training as an adjunct to antipsychotics on the core autism feature of restricted interests and rigid and repetitive behaviours. Both experimental and control groups received risperidone (or aripiprazole if risperidone was ineffective). In addition, the experimental group received a parent training intervention delivered by a behaviour therapist. Parent training was based on the Research Units on Pediatric Psychopharmacology (RUPP) manual (Scahill et al., 2009) and involved seven to nine weekly 60-90-minute sessions where parents were taught to use preventative approaches (for example, visual schedules), and were instructed in the effective use of positive reinforcement, and in strategies for teaching compliance, functional communication skills and specific adaptive skills. Parent training teaching techniques included direct instruction, use of video vignettes, practice activities, behaviour rehearsal with feedback, role-playing, and individualised homework assignments. This study found evidence for a small treatment effect of combined parent training and antipsychotic on compulsions as measured by the CYBOCS-PDD (see Table 64). However, the confidence in effect estimate was low due to risk of bias concerns (unclear blinding of outcome assessment and higher dropout in the experimental group) and small sample size.

Social-communication interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

The social-communication intervention trial (GREEN2010) compared a caregiver-mediated social-communication intervention (PACT) with treatment as usual in children with autism (see Table 49). See section 6.2.5 for further information about the PACT intervention.

Evidence for the effectiveness of the one included social-communication intervention on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 65. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 65: Evidence summary table for effects of social-communication intervention on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Caregiver-mediated social-communication intervention (PACT) versus treatment as usual
Outcome	Repetitive behaviours
Outcome measure	ADOS-G: Repetitive behaviours
Study ID	GREEN2010
Effect size (CI; p value)	SMD -0.30 (-0.62, 0.02; p = 0.06)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 152
Forest plot	1.3.4; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence from the single included social-communication intervention trial for a statistically significant effect of a caregiver-mediated social-communication intervention (PACT) on repetitive behaviours as an indirect outcome (see Table 65).

6.2.8 Clinical evidence summary –effect of psychosocial interventions on the core autism feature of restricted interests and rigid and repetitive behaviours

There was very little evidence for psychosocial interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours. Based on a single trial, there was low quality evidence for a small effect of parent training (as an adjunct to antipsychotics) on compulsions. In contrast, the evidence (low to very low quality) for behavioural interventions, cognitive interventions and social-communication interventions was inconclusive.

6.2.9 Health economic evidence –psychosocial interventions aimed at the core features of autism

Systematic literature review

The guideline systematic search of the economic literature identified no studies assessing the cost effectiveness of psychosocial interventions aimed at overall autistic behaviours or the core autism feature of restricted interests and rigid and repetitive behaviours in children and young people. However, one eligible study on psychosocial interventions aimed at the core autism feature of impaired reciprocal social communication and interaction in children and young people with autism was identified (Byford et al., unpublished). In addition, the systematic search identified one modelling study assessing the cost-savings resulting from provision of enhanced speech and language therapy to children and young people with autism (Marsh et al., 2010). The latter study utilised efficacy data from a social-communication intervention trial [GREEN2010] and therefore it is considered in this section.

Details on the methods used for the systematic review of the economic literature are described in Chapter 3; full references to the included studies and evidence tables with the study details are provided in Appendix 16. Completed methodology checklists of the studies are provided in Appendix 15. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 16, accompanying the respective GRADE clinical evidence profiles.

The study by Byford and colleagues (unpublished manuscript), which was conducted in the UK alongside a trial [GREEN2010], evaluated the cost effectiveness of a caregiver-mediated social-communication intervention (PACT) added on treatment as usual relative to treatment as usual alone, in preschool children with autism (aged 2-5 years). Treatment as usual consisted of visits to NHS paediatricians and speech and language therapists, alongside a variety of other health, social care

and education based services provided by local services. The analysis adopted two different perspectives: a 'service' perspective that included statutory and non-statutory hospital, community and school-based health and social services, and a wider, societal perspective, which included all services and associated costs considered under the 'service' perspective plus education and childcare costs, parental out-of-pocket expenses (aids and home adaptations, attendance of training courses etc.), parental productivity losses (time off work due to the child's autism), as well as parental informal (unpaid) care. The primary outcome measure considered in the economic analysis was the proportion of children that demonstrated a clinical improvement expressed by an ADOS-G score improvement of ≥ 4 points. The time horizon of the analysis was 13 months; costs were expressed in 2007 prices.

According to the results of the study, PACT plus treatment as usual was more effective than treatment as usual alone, as a higher proportion of children achieved an ADOS-G score improvement of ≥ 4 points (53% versus 41%, respectively; OR 1.91 with 95% CIs 0.94 to 3.87); the level of significance of this result was slightly above 0.05 (p=0.074). In terms of cost, PACT plus treatment as usual was significantly costlier than treatment as usual alone under the service perspective (total cost £6,539 versus £2,050, respectively; p<0.001). This difference in the total service cost (mean difference £4,489) was attributed to the high intervention cost of the PACT intervention (mean cost £4,105, standard deviation [SD] £2,122) as no significant differences between other service cost categories (including NHS speech and language therapy, other community health and social services, medication and hospital-based health services) were identified between the two strategies. In contrast, when a societal perspective was considered, PACT plus treatment as usual and treatment as usual alone had similar total costs (£57,919 versus £56,534, respectively, p=0.788). It must be noted that, under the societal perspective, PACT plus treatment as usual was costlier than treatment as usual alone in all cost categories other than informal care; however, with the exception of the difference in service costs, which was statistically significant as discussed earlier, all cost differences across other categories of cost (that is, education and childcare costs, parental expenses and parental productivity losses) were non-significant. Regarding informal care costs, PACT plus treatment as usual was less costly than treatment as usual alone (£46,007 versus £49,814, respectively), but this difference was not statistically significant (p=0.459).

Non-parametric bootstrapping was employed to generate joint distributions of incremental mean costs and effects for PACT plus treatment as usual and treatment as usual alone, by random sampling with replacement from the original dataset. This analysis was undertaken to allow estimation of the probability of PACT plus treatment as usual being the cost-effective strategy under different levels of willingness-to-pay per 1% increase in the proportion of children who demonstrate a clinically meaningful improvement on the ADOS-G. According to the results of this analysis, under a service perspective, PACT plus treatment as usual had ≥ 50% probability of being cost-effective when the willingness-to-pay for a 1% increase in

the proportion of children with a clinically meaningful improvement equalled or exceeded £265 (which is equivalent to a willingness-to-pay of £26,500 per extra child improved); under a societal perspective, PACT and treatment as usual had ≥ 50% probability of being cost-effective when the willingness-to-pay for a 1% increase in the proportion of children with a clinically meaningful improvement equalled or exceeded £100 (which is equivalent to a willingness-to-pay of £10,000 per extra child improved).

The results of the analysis are not straightforward to interpret, as the measure of outcome was not expressed in QALYs. The authors justified the use of a different measure of outcome on the basis of absence of a preference-based measure designed specifically for children and appropriate for preschool children with autism that could be used to estimate QALYs. To decide whether the addition of PACT to treatment as usual is a cost-effective strategy, one needs to judge whether the extra benefit (in terms of the proportion of extra children demonstrating a clinically meaningful improvement on ADOS-G scale) achieved by adding PACT to treatment as usual is worth the extra cost associated with PACT and treatment as usual compared with treatment as usual alone. NICE has set a cost effectiveness threshold of £20,000 to £30,000/QALY (NICE, 2008 – social value judgment), which reflects a maximum willingness-to-pay of £30,000 per extra life year in full health. Under the service perspective, PACT plus treatment as usual incurs an extra £26,500 per additional child improved over the 13-month time horizon of the analysis. The improvement of a child with autism, as defined by an ADOS-G score improvement of ≥ 4 points, occurs from a level of health well above death, to a level of health lower than full health, and therefore the gain over 13 months is likely much narrower than an extra year in full health (which is the definition of one QALY); this means that if the extra clinical benefit of PACT plus treatment as usual was possible to translate into QALYs, the resulting incremental cost effectiveness ratio (ICER) of the intervention would most likely exceed the NICE upper cost effectiveness threshold of £30,000/QALY, meaning that the addition of PACT to treatment as usual is very unlikely to be cost-effective under a service perspective. On the other hand, it is more difficult to judge whether PACT plus treatment as usual is cost-effective under a societal perspective. The ICER of £10,000 per extra child improved would fall below the NICE upper cost effectiveness threshold of £30,000/QALY, if the clinical improvement of a child with autism (as defined by an ADOS-G score improvement of ≥ 4 points) over 13 months was equivalent to at least 33% of a QALY (£10,000/£30,000). Thus, if the clinical improvement of a child with autism after receiving PACT intervention reflects an increase in utility of at least 0.31 on a scale 0-1 (a 0.31 change in utility corresponds to a change equivalent to 0.33 QALYs over 13 months), then the addition of PACT to treatment as usual is a cost-effective strategy under a societal perspective within the NICE context.

One limitation of the study, as reported by its authors, is the likely inaccuracy in estimated parental informal care costs, due to the retrospective self-reporting of informal care. In some cases parents provided inconsistent responses, reporting, for example, more than 24 hours of informal care per day. However, informal care data

were crucial in determining the final cost results under the societal perspective, as the reported rates of informal care were substantial for both groups and accounted for the largest part of total societal costs (79% of total societal costs in the PACT plus treatment as usual group and 88% of total societal costs in the treatment as usual group). Moreover, the reduction in the cost difference between the two strategies under the societal perspective resulted exclusively from lower informal care costs associated with PACT plus treatment as usual relative to treatment as usual alone. Therefore, although it is acknowledged that the amount of informal care is generally difficult to measure accurately and problems in retrospective self-reporting may be, up to a point, unavoidable, it should be noted that it is possible that problems in self-reporting of informal care may have affected the results of the analysis under the societal perspective, which should, consequently, be interpreted with caution.

Another limitation of the analysis, which, up to some extent, is inherent to its design (RCT), is its relatively short time horizon that did not allow assessment of longer-term costs and benefits associated with the addition of PACT to treatment as usual. If the clinical benefits and informal care cost savings resulting from the provision of PACT are retained in the future, then the intervention is more cost-effective than estimated within the time frame of the economic study by Byford and colleagues.

Overall, the study is characterised by minor limitations but is only partially applicable to the NICE context due to the lack of use of QALY as the measure of outcome.

One modelling study evaluated the cost-savings associated with enhanced speech and language therapy relative to standard speech and language therapy for children with autism in the UK (Marsh et al., 2010). The study considered the effect of speech and language therapy on child's communication skills, and the impact of the latter on future independence as expressed by the residential status and use of health and social services in adulthood. The perspective of the analysis was societal. Costs included intervention costs (incurred in childhood) and accommodation, hospital services, respite care, day services, other health and social care services, education, treatments for autism-related needs, supported employment, family expenses and parents' lost employment over adulthood (from 18 and up to 65 years of age). Clinical efficacy data for enhanced versus standard speech and language therapy were taken from GREEN2010, which is a trial that evaluated a social-communication intervention focusing on its effects on reciprocal social communication and interaction. The trial reported significant improvement in parental synchronisation, which was a secondary outcome. Marsh and colleagues used this data to estimate the magnitude of expected improvement in children's language age (and therefore IQ) at the age of 7 years, based on the findings of a naturalistic study, according to which an increase in the level of parental synchronisation improves the language abilities of children with autism (Siller & Sigman, 2008). Subsequently, the estimated increase in IQ at the age of 7 years was linked to increased independence in adulthood based on published evidence; more specifically, higher IQ in childhood has been found to result in more adults with autism living in private and supported

accommodation (Howlin et al., 2004), which, in turn, is associated with lower costs (including health and social care costs) compared with adults with autism living in residential accommodation or in hospital (Knapp et al., 2009). Based on their economic analysis, Marsh and colleagues estimated that provision of enhanced speech and language therapy to the current estimate of 8,800 children with autism aged 2-4 years in the UK would result in lifetime cost-savings of £9.8 million (2006 prices).

The model structure appears to be sensible and reflects the nature of autism and the related life events and costs following provision of enhanced speech and language therapy. Nevertheless, the study suffers from serious methodological limitations. First of all, the positive effect of the intervention on parental synchronisation, derived from GREEN2010, is used to estimate the magnitude of improvement in language age based on naturalistic data reported in Siller and Sigman (2008). However, GREEN2010 reports that, although parent synchronisation was improved, the intervention did not have any positive effect on language age. This finding was practically ignored in the analysis by Marsh and colleagues (2010). Moreover, the methodology and formulae used to convert the effect size for parental synchronisation into improvement in language age were arbitrary and not explained by the authors; for example, the formula used to estimate the effect size for parental synchronisation is not commonly used in the literature, and the estimated effect size differs from that reported in GREEN2010. In addition, the estimated effect size for parental synchronisation has been applied several times onto the longitudinal data on language age reported in the study by Siller and Sigman (it has been applied onto different time points including baseline, intermediate points and the endpoint data), without taking into account the time intervals between intermediate time points. In other words, the treatment effect has been added to each of the intermediate time points for which Siller and Sigman reported language age data, thus potentially overestimating the overall treatment effect and therefore the final language age following provision of enhanced speech and language therapy. Finally, Marsh and colleagues used their estimate on the improvement in language age to calculate the increase in the proportion of children with autism that achieve IQ ≥ 30 at age 7 years, as this cut-off point seems to be associated with more independence and private or supported accommodation living in adulthood (Howlin et al., 2004). The study sample used to estimate the increase in the proportion of children with IQ ≥ 30 at age 7 years consisted of 68 children and was also derived by Howlin and colleagues (2004). Marsh and colleagues estimated that one extra child in the study sample would achieve IQ ≥ 30 following enhanced speech and language therapy; due to the small sample size (N = 68), the improvement of IQ in this child would result in an increase in the proportion of children with IQ ≥ 30 from 54.4% to 55.9%. This increase in the proportion of children with IQ ≥ 30 at age 7 years, which was estimated based on the anticipated improvement of one child in the Howlin and colleagues (2004) study sample, was responsible for the £9.8 million savings reported by the authors. Overall, the methodological limitations of this analysis were judged to be very serious; consequently the analysis was excluded from further consideration at formulation of recommendations.

Further economic considerations

The guideline systematic review on psychosocial interventions aimed at the core features of autism suggests that only caregiver- or preschool-teacher-mediated social-communication interventions are likely to be effective for children and young people with autism. However, the studies assessing social-communication interventions used a variety of comparators and reported a wide range of outcomes, which did not allow broad meta-analysis to be conducted. Therefore, an economic analysis assessing the cost effectiveness of social-communication interventions was not possible to undertake. Moreover, the interventions described in the trials included in the review comprised a very diverse set of interventions, in terms of the intended number of sessions (ranging from 12 to 30), the duration of each session (from 20 minutes to 2 hours), and the description of the therapists and mediators in each study. Due to the diversity of these parameters, it was not possible to make an accurate estimate of the intervention cost. Probably the most 'typical' form of social-communication intervention in the UK context is the intervention described in GREEN2010, which was delivered by specially trained speech and language therapists, supervised by senior speech and language therapists with expertise in autism. The intended number of sessions to be provided per child was 18, while the mean number of sessions actually attended per child was 15.57 (SD 4.37) (Byford et al., unpublished). The mean intervention cost per child with autism, uplifted to 2011 prices, was £4,536 (SD £2,345). This cost figure needs to be weighed against the expected benefits of the intervention, in order to judge whether the intervention is cost-effective, that is, whether the benefits accrued are worth the intervention cost. However, it needs to be noted that improvement in reciprocal social communication and interaction may potentially lead to higher levels of future independence, which may result in changes in residential status (more independent adults with autism tend to live in private and supported accommodation settings rather than in residential accommodation or in hospital), which, in turn, may lead to substantial cost-savings to social services (Knapp et al., 2009). Indeed, a small (N = 68) longitudinal study on children with autism aged 7 years showed that higher IQ levels in childhood are associated with higher levels of independence and private or supported accommodation in adulthood (Howlin et al., 2004). Therefore, if social-communication interventions offer longer term benefits including higher levels of independence, it is possible that intervention costs are at least partially offset by future cost-savings relating to shifts in accommodation status and reduced utilisation of health and social services. This hypothesis needs to be taken into account when making judgements on the cost effectiveness of social-communication interventions.

6.3 PHARMACOLOGICAL INTERVENTIONS – CORE FEATURES OF AUTISM

6.3.1 Introduction

Psychopharmacological interventions to reduce aspects of rigid or repetitive behaviours that appear to be associated with irritability and other behaviours that

challenge may be used when the impact of the behaviours is severe on the young person with autism and family. A variety of medications has been tried ranging from naltrexone (favoured because of the hypothesis that excess opiates may have a role in repetitive behaviours), to selective serotonin reuptake inhibitors (SSRIs) and other drugs, for example, clomipramine which address obsessive compulsive behaviours, clonidine (noradrenergic effect and sedative), the antiepileptic medications and the antipsychotics.

6.3.2 Studies considered

Twenty-nine papers from the search met the eligibility criteria for full-text retrieval. Of these, 12 RCTs provided relevant clinical evidence and were included in the review. Five of these studies examined the efficacy of pharmacological interventions on core autism features as a direct outcome (target of intervention), and seven provided data on core autism features as an indirect outcome. All studies were published in peer-reviewed journals between 2001 and 2012. In addition, seventeen studies were excluded from the analysis. The most common reason for exclusion was that the study was a systematic review with no new useable data and any meta-analysis results were not appropriate to extract. Further information about both included and excluded studies with direct outcomes aimed at core autism features can be found in Appendix 12b.

Pharmacological interventions aimed at overall autistic behaviours

Data were extracted from eight studies for direct and indirect effects of pharmacological interventions on overall autistic behaviours.

One trial examined effects of anticonvulsants on overall autistic behaviours as an indirect outcome (HOLLANDER2010[35] [Hollander et al., 2010).

One trial examined effects of antidepressants on overall autistic behaviours as an indirect outcome (HOLLANDER2005[36] [Hollander et al., 2005]).

One trial examined effects of antihistamines and antipsychotics (relative to antipsychotics alone) on overall autistic behaviours as an indirect outcome (AKHONDZADEH2004[37] [Akhondzadeh et al., 2004]).

One trial examined effects of selective noradrenaline reuptake inhibitors (SNRIs) on overall autistic behaviours as an indirect outcome (ELILILLY2009[38]: one trial with two references, results posted on ClinicalTrials.gov [Eli Lilly and Company, 2009]; and peer-reviewed paper [Harfterkamp et al., 2012]).

[35] See Section 7.3.2 for direct outcomes from HOLLANDER2010.
[36] See Section 6.3.7 for direct outcomes from HOLLANDER2005.
[37] See Section 7.3.2 for direct outcomes from AKHONDZADEH2004.
[38] See Section 8.7.5 for direct outcomes from ELILILLY2009.

Three trials examined effects of antipsychotics on overall autistic behaviours as a direct outcome (LUBY2006 [Luby et al., 2006]; MIRAL2008 [Miral et al., 2008]; NAGARAJ2006 [Nagaraj et al., 2006]), and one trial examined effects of antipsychotics on overall autistic behaviours as an indirect outcome (RUPPRISPERIDONE2001 [one trial reported across eight papers: Aman et al., 2008; Anderson et al., 2007; Arnold et al., 2003; Arnold et al., 2010; McDougle et al., 2005; Research Units on Pediatric Psychopharmacology Autism Network, 2002; Research Units on Pediatric Psychopharmacology Autism Network, 2005; Scahill et al., 2001].

Pharmacological interventions aimed at the core autism feature of impaired reciprocal social communication and interaction

One trial examined effects of antioxidants on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome (HARDAN2012[39] [Hardan et al., 2012]).

Pharmacological interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours

Two trials examined effects of antidepressants on the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome (HOLLANDER2005, KING2009 [King et al., 2009]).

One trial examined effects of antioxidants on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (HARDAN2012).

Three trials examined indirect effects of antipsychotics on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome (JOHNSON&JOHNSON2011 [one trial reported on ClinicalTrials.gov: Johnson & Johnson Pharmaceutical Research & Development, 2011; and in peer-reviewed published paper: Kent et al., 2012], MARCUS2009 [one trial reported across two papers: Marcus et al., 2009; Varni et al., 2012], RUPPRISPERIDONE2001).

6.3.3 Clinical evidence –effect of pharmacological interventions on overall autistic behaviours

Anticonvulsants for overall autistic behaviours as an indirect outcome

The anticonvulsant trial (HOLLANDER2010) compared divalproex sodium with placebo in children with autism (see Table 66).

[39] See Section 7.3.2 for direct outcomes from HARDAN2012.

Table 66: Study information table for included trial of anticonvulsants for overall autistic behaviours

	Divalproex sodium versus placebo
No. trials (N)	1 (27)
Study IDs	HOLLANDER2010
Study design	RCT
% female	16
Mean age (years)	9.5
IQ	63.3 (assessed using the LIPS-Revised [LIPS-R; Roid & Miller, 1995, 1997])
Dose/intensity (mg/hours)	Not reported
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of divalproex sodium on overall autistic behaviours and the quality of evidence is presented in Table 67. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 67: Evidence summary table for effects of anticonvulsants on overall autistic behaviours as an indirect outcome

	Divalproex sodium versus placebo
Outcome	Overall autistic behaviours (global improvement)
Outcome measure	Positive treatment response (number of participants 'much improved/very improved' on CGI-I-autism)
Study ID	HOLLANDER2010
Effect size (CI; p value)	RR 3.53 (0.19, 67.10; p = 0.40)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 27
Forest plot	1.4.1; Appendix 13
Note. [1]Downgraded for very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).	

The single included anticonvulsant trial examined indirect effects on overall autistic behaviours. This study found no evidence for a statistically significant effect of divalproex sodium relative to placebo for overall autistic behaviours as assessed by a dichotomous measure of positive treatment response based on the CGI-I-autism (see Table 67). There was also no statistically significant evidence for harms associated with anticonvulsants (see Section 10.3.2 for adverse events associated with anticonvulsants).

Antidepressants for overall autistic behaviours as an indirect outcome

The antidepressant trial (HOLLANDER2005) compared fluoxetine with placebo in children with autism (see Table 68).

Table 68: Study information table for included trial of antidepressants for overall autistic behaviours

	Fluoxetine versus placebo
No. trials (N)	1 (44)
Study IDs	HOLLANDER2005
Study design	RCT (crossover)
% female	23
Mean age (years)	8.2
IQ	63.7 for N = 34 (assessed using the Wechsler Preschool and Primary Intelligence Scale-Revised [WPPSI-R, age 5-7 years], WISC-III, age 7-16 years, the Wechsler Adult Intelligence Scale [3rd edition] [age 17 years], or the LIPS-R [non-verbal])
Dose/intensity (mg/hours)	Mean final dose of fluoxetine = 9.9 mg Mean final dose of placebo = 10.8 mg
Setting	Not reported
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	20 (8-week double-blind trial followed by 4-week washout and 8-week crossover trial)

Evidence for the effectiveness of fluoxetine on overall autistic behaviours and the quality of evidence is presented in Table 69. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 69: Evidence summary table for effects of antidepressants on overall autistic behaviours as an indirect outcome

	Fluoxetine versus placebo
Outcome	Overall autistic behaviours (global improvement)
Outcome measure	Global Autism Composite Improvement (CGI-AD and CYBOCS)
Study ID	HOLLANDER2005
Effect size (CI; p value)	SMD -0.35 (-0.98, 0.28; p = 0.28)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 39
Forest plot	1.4.2; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

The single included antidepressant trial examined indirect effects on overall autistic behaviours. This study found no evidence for a statistically significant effect of fluoxetine relative to placebo for overall autistic behaviours as assessed by a global improvement composite measure based on the CGI-AD and CYBOCS (see Table 69). There was evidence from another study (KING2009 [King et al., 2009]) for statistically significant harms associated with antidepressants (including: increased energy level; disinhibited, impulsive or intrusive behaviour; decreased attention and concentration; hyperactivity; stereotypy; diarrhoea; any insomnia and initial insomnia or difficulty falling asleep; skin or subcutaneous tissue disorder), although this evidence was from a study using a different drug, citalopram (see Section 10.3.2 for adverse events associated with citalopram data).

Antihistamines for overall autistic behaviours as an indirect outcome

The antihistamine trial (AKHONDZADEH2004) compared combined cyproheptadine and haloperidol with combined placebo and haloperidol in children with autism (see Table 70).

Table 70: Study information table for included trial of antihistamines for overall autistic behaviours

	Cyproheptadine and haloperidol versus placebo and haloperidol
No. trials (N)	1 (40)
Study IDs	AKHONDZADEH2004
Study design	RCT
% female	40
Mean age (years)	6.7
IQ	Not reported
Dose/intensity (mg/hours)	Planned final dose of haloperidol = 0.05 mg/kg/day Planned final dose of cyproheptadine = 0.2 mg/kg/day Planned final dose of placebo not reported
Setting	Outpatient
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	8

Evidence for the effectiveness of cyproheptadine on overall autistic behaviours and the quality of evidence is presented in Table 71. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 71: Evidence summary table for effects of antihistamines on overall autistic behaviours as an indirect outcome

	Cyproheptadine and haloperidol versus placebo and haloperidol
Outcome	Overall autistic behaviours
Outcome measure	CARS: total (change score)
Study ID	AKHONDZADEH2004
Effect size (CI; p value)	SMD -0.96 (-1.62, -0.30; p = 0.004)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Moderate[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.4.3; Appendix 13
Note. [1]Downgraded for serious imprecision as N <400.	

The single included antihistamine trial examined indirect effects on overall autistic behaviours. This study found evidence for a large and statistically significant effect of cyproheptadine and haloperidol relative to placebo and haloperidol for overall autistic behaviours as assessed by the CARS total change score (see Table 71). There was no statistically significant evidence for any harm associated with antihistamines (see Section 10.3.2 for adverse events associated with antihistamines).

Antipsychotics for overall autistic behaviours as a direct or indirect outcome

Three antipsychotic trials (LUBY2006, NAGARAJ2006, RUPPRISPERIDONE2001) compared risperidone with placebo in children with autism, and one trial compared risperidone and haloperidol (MIRAL2008) in children with autism (see Table 72).

Table 72: Study information table for included trials of antipsychotics for overall autistic behaviours

	Risperidone versus placebo	**Risperidone versus haloperidol**
No. trials (N)	3 (165)	1 (30)
Study IDs	(1) LUBY2006 (2) NAGARAJ2006 (3) RUPPRISPERIDONE2001	MIRAL2008
Study design	(1)-(3) RCT	RCT
% female	(1) 26 (2) 13 (3) 19	17
Mean age (years)	(1) 4 (2) 5 (3) 8.8	10.5
IQ	(1) Not reported (2) Not reported (28% with mild LD; 28% with moderate LD) (3) Not reported	Not reported
Dose/intensity (mg/hours)	(1) Mean final of risperidone = 1.14 mg/day Mean final dose of placebo = 1.38 mg/day (2) Planned final dose = 1 mg/day (3) Mean final dose of risperidone = 1.8 mg/day Mean final dose of placebo = 2.4 mg/day	Mean dose of risperidone = 2.6 mg/day Mean dose of haloperidol = 2.6 mg/day
Setting	(1)-(2) Outpatient (3) Study was conducted across five university sites	Not reported
Length of treatment (weeks)	(1) 24 (2) 26 (3) 8	10
Continuation phase (length and inclusion criteria)	(1) 24 (2) 26 (3) 8 (in the studies included in RUPPRISPERIDONE2002, an open-label 16-week extension is reported in Aman and colleagues [2005] and 95-week open-label follow-up phase in Anderson and colleagues [2007], but efficacy or safety data is not extractable for this follow-up)	12 (including a 1-2-week screening phase)

Evidence for the effectiveness of risperidone on overall autistic behaviours and the quality of evidence is presented in Table 73. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 73: Evidence summary table for effects of antipsychotics on overall autistic behaviours as a direct or indirect outcome

	Risperidone versus placebo		**Risperidone versus haloperidol**	
Outcome	Overall autistic behaviours (direct outcome)	Overall autistic behaviours (direct or indirect outcome)	Overall autistic behaviours (direct outcome)	
Outcome measure	(1) Positive treatment response (>20% improvement on CARS) (2) Positive treatment response (>20% improvement on CGAS)	(1) CARS (direct outcome) (2) RF-RLRS (indirect outcome)	Turgay DSM-IV PDD Rating Scale	Overall autistic behaviours (RF-RLRS) (1) Social subscale (2) Motor subscale (3) Affective subscale (4) Sensory subscale (5) Language subscale
Study ID	NAGARAJ2006	(1) LUBY2006 (2) RUPPRISPERI-DONE2001	MIRAL2008	
Effect size (CI; p value)	(1) *CARS* RR 26.25 (1.66, 414.57; p = 0.02) (2) *CGAS* RR 8.95 (2.38, 33.62; p = 0.001)	(1)+(2) SMD -0.87 (-1.25, -0.50; p <0.00001) (1) *Direct CARS* SMD 0.31 (-0.51, 1.14; p = 0.46) (2) *Indirect RF-RLRS* SMD -1.19 (-1.61, -0.76; p <0.00001)	SMD -0.35 (-1.10, 0.40; p = 0.36)	(1) SMD -0.26 (-1.00, 0.49; p = 0.50) (2) SMD -0.34 (-1.09, 0.41; p = 0.37) (3) SMD -0.23 (-0.98, 0.52; p = 0.54) (4) SMD -0.17 (-0.92, 0.57; p = 0.65) (5) SMD 0.22 (-0.53, 0.96; p = 0.57)
Heterogeneity (chi²; p value; I²)	Not applicable	Chi² = 10.08, df = 1; p = 0.001; *I²* = 90%	Not applicable	
Quality of the evidence (GRADE)	Low[1,2]	(1)+(2) Very low[1,3] (1) Very low[4,5] (2) Moderate[1]	Very low[5,6]	
Number of studies/ participants	K = 1; N = 39	K = 2; N = 124	K = 1; N = 28	
Forest plot	1.4.4; Appendix 13			
Note. [1]Downgraded for serious imprecision as N <400. [2]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as mean				

and standard deviation data were not reported for continuous scale outcome measures.
[3]Downgraded for very serious inconsistency – substantial to considerable heterogeneity with I^2=90%
[4]Downgraded for serious risk of bias – high risk of selection bias as the allocation was unconcealed and the groups were not comparable at baseline for this outcome measure (the experimental group showed significantly greater severity of autism symptoms as measured by the CARS).
[5]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[6]Downgraded for serious risk of bias – paper states 'double-blind' but gives no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.

NAGARAJ2006 examined effects of risperidone relative to placebo on overall autistic behaviours as a direct outcome and found evidence for large and statistically significant treatment effects with two dichotomous positive treatment response outcome measures, with participants who received risperidone being over 26 times more likely to show a positive treatment response on the CARS relative to participants who received placebo, and nearly nine times more likely to show a positive treatment response on the CGAS (see Table 73). However, the quality was downgraded to low because of sample size (N <400) and risk of publication bias (no data reported for continuous scale outcome measures).

Evidence for effects of risperidone (relative to placebo) on continuous outcome measures of overall autistic behaviours was more inconsistent. LUBY2006 examined direct effects of antipsychotics on overall autistic behaviours using the CARS and RUPPRISPERIDONE2001 examined indirect effects on overall autistic behaviours as measured by the RF-RLRS. When the data from both trials was meta-analysed there was evidence for a large and statistically significant effect of antipsychotics on overall autistic behaviours (see Table 73). However, there was evidence for substantial to considerable heterogeneity (I^2 = 90), with the effect being driven by the RUPPRISPERIDONE2001 data and only this study showing a statistically significant treatment effect (test for overall effect: Z = 5.49, p <0.00001). Moreover, the quality was downgraded to very low for the meta-analysis (based on inconsistency and sample size) and moderate for the RF-RLRS (indirect outcome) subgroup analysis (downgraded based on sample size).

Finally, the single trial comparing risperidone with haloperidol and examining effects on overall autistic behaviours as a direct outcome found no evidence for any statistically differences between the two antipsychotics (see Table 73).

There was also evidence for statistically significant harms associated with antipsychotics as follows: increased risk of any adverse event, increased risk of clinically relevant weight gain, continuous measure of weight gain, increased appetite, constipation, prolactin concentration, leptin change score, pulse change score, somnolence/drowsiness, fatigue, sedation, rhinitis, fever, tachycardia, drooling, and tremor (see Section 10.3.2 for adverse events associated with antipsychotics).

SNRIs for overall autistic behaviours as an indirect outcome

The serotonin and noradrenaline reuptake inhibitor (SNRI) trial (ELILILLY2009) compared atomoxetine with placebo in children with autism (see Table 74).

Table 74: Study information table for included trial of SNRIs for overall autistic behaviours

	Atomoxetine versus placebo
No. trials (N)	1 (97)
Study IDs	ELILILLY2009
Study design	RCT
% female	14
Mean age (years)	9.9
IQ	92.9 (assessed using the WISC-III)
Dose/intensity (mg/hours)	Planned final dose of 1.2 mg/kg/day
Setting	Not reported
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	28 weeks (8-week double-blind phase followed by 20 week open-label continuation phase, however, data only extracted for the double-blind phase as no control group data available for open-label continuation)

Evidence for the effectiveness of atomoxetine on overall autistic behaviours and the quality of evidence is presented in Table 75. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 75: Evidence summary table for effects of SNRIs on overall autistic behaviours as an indirect outcome

	Atomoxetine versus placebo
Outcome	Overall autistic behaviours
Outcome measure	CSBQ: total
Study ID	ELILILLY2009
Effect size (CI; p value)	SMD -0.27 (-0.68, 0.15; p = 0.21)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 89
Forest plot	1.4.5; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

The single included SNRI trial examined indirect effects on overall autistic behaviours. This study found no evidence for a statistically significant effect of atomoxetine relative to placebo for overall autistic behaviours as assessed by the CSBQ total score (see Table 75). This study did, however, find evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo (see Section 10.3.2 for adverse events associated with SNRIs).

6.3.4 Clinical evidence summary – effect of pharmacological interventions on overall autistic behaviours

Evidence was limited for pharmacological interventions aimed at overall autistic behaviours. There was low quality evidence from a single trial for a non-statistically significant treatment effect of anticonvulsant drugs on overall autistic behaviours. There was also no evidence for a significant positive treatment effect of antidepressant drugs on overall autistic behaviours. However, there was evidence for a number of significant adverse events associated with antidepressants. There was moderate quality evidence from a single study for a large and statistically significant effect of cyproheptadine and haloperidol relative to placebo and haloperidol for overall autistic behaviours. Only one meta-analysis (with two trials) was possible and suggested a large positive treatment effect of antipsychotic drugs on overall autistic behaviours based on very low quality evidence. Moreover, there was evidence for significant harms associated with antipsychotic drugs, including increased risk of any adverse event, weight gain, prolactin concentration, leptin level, and tachycardia. Based on low quality evidence there was no statistically significant effect of SNRI drugs (atomoxetine) relative to placebo for overall autistic behaviours.

6.3.5 Clinical evidence for pharmacological interventions aimed at the core autism feature of impaired reciprocal social communication and interaction

Antioxidants for overall autistic behaviours as an indirect outcome

The antioxidant trial (HARDAN2012) compared N-acetylcysteine with placebo in children with autism (see Table 76).

Table 76: Study information table for included trial of antioxidants for the core autism feature of impaired reciprocal social communication and interaction

	N-acetylcysteine versus placebo
No. trials (N)	1 (33)
Study IDs	HARDAN2012
Study design	RCT
% female	6
Mean age (years)	7.1 (based on N = 29)
IQ	Not reported
Dose/intensity (mg/hours)	Final dose of 2,700 mg/day (three doses of 900 mg)
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of N-acetylcysteine on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 77. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 77: Evidence summary table for effects of antioxidants on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	N-acetylcysteine versus placebo
Outcome	Social impairment
Outcome measure	SRS subscales: (1) total (2) Social Awareness (3) Social Cognition (4) Social Communication (5) Social Motivation (6) Autistic Mannerisms
Study ID	HARDAN2012
Effect size (CI; p value)	(1) *Total score* SMD -0.14 (-0.87, 0.59; p = 0.71) (2) *Social Awareness* SMD -0.45 (-1.19, 0.29; p = 0.23) (3) *Social Cognition* SMD -0.02 (-0.74, 0.71; p = 0.97) (4) *Social Communication* SMD -0.09 (-0.82, 0.64; p = 0.81) (5) *Social Motivation* SMD -0.24 (-0.97, 0.49; p = 0.52) (6) *Autistic Mannerisms* SMD -0.64 (-1.39, 0.11; p = 0.09)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 29
Forest plot	1.5.1; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

The single included antioxidant trial examined indirect effects on the core autism feature of impaired reciprocal social communication and interaction. This study found no evidence for a statistically significant effect of N-acetylcysteine relative to placebo for social impairment as assessed by the SRS total score and subscales (see Table 77). This study also found no evidence for statistically significant harms associated with N-acetylcysteine (see Section 10.3.2 for adverse events associated with antioxidants).

6.3.6 Clinical evidence summary for pharmacological interventions aimed at the core autism feature of impaired reciprocal social communication and interaction

Evidence was limited for pharmacological interventions aimed at the core autism feature of impaired reciprocal social communication and interaction. Results from a single small study provided low quality evidence of no significant benefits or harms associated with antioxidant drugs for social impairment as an indirect outcome.

6.3.7 Clinical evidence for pharmacological interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours

Antidepressants for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

Both of the antidepressant trials compared SSRIs with placebo. One of the antidepressant trials (HOLLANDER2005) involved a comparison between fluoxetine and placebo and one involved a comparison between citalopram and placebo (KING2009) in children with autism (see Table 78).

Table 78: Study information table for included trials of antidepressants for the core autism feature of restricted interests and rigid and repetitive behaviours

	SSRI versus placebo
No. trials (N)	2 (193)
Study IDs	(1) HOLLANDER2005 (2) KING2009
Study design	(1) RCT (crossover) (2) RCT
% female	(1) 23 (2) 14
Mean age (years)	(1) 8.2 (2) 9.4
IQ	(1) 63.7 (assessed using the WPPSI-R [age 5-7 years], WISC-III [age 7-16 years], Wechsler Adult Intelligence Scale [3rd edition] [age 17 years], or the LIPS-R [non-verbal]) (2) Not reported (58% IQ>70)
Dose/intensity (mg/hours)	(1) Final dose of fluoxetine 9.9 mg/day; final dose of placebo 10.8 mg/day (2) Final dose of citalopram 16.5 mg/day; final dose of placebo 18.5 mg/day
Setting	(1) Not reported (2) Outpatient
Length of treatment (weeks)	(1) 8 (2) 12
Continuation phase (length and inclusion criteria)	(1) 20 (8-week double-blind trial followed by 4-week washout and 8-week crossover trial) (2) 12

Evidence for the effectiveness of SSRIs on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 79. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 79: Evidence summary table for effects of antidepressants on the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

	SSRI versus placebo			
Outcome	Global positive treatment response		Compulsions	Repetitive behaviour
Outcome measure	Number of participants who were 'much improved/very improved' on CGI-I	Number of participants with >25% improvement on CYBOCS-PDD and 'much improved/very improved' on CGI-I	CYBOCS/CYBOCS-PDD: Compulsions	RBS-R subscales: (1) Compulsive (2) Restrictive (3) Ritualistic (4) Sameness (5) Self-injurious (6) Stereotyped
Study ID	KING2009		(1) HOLLANDER2005 (2) KING2009	KING2009
Effect size (CI; p value)	RR 0.96 (0.61, 1.51; p = 0.86)	RR 1.56 (0.75, 3.25; p = 0.23)	SMD -0.08 (-0.36, 0.21; p = 0.61)	(1) *Compulsive* SMD 0.09 (-0.23, 0.42; p = 0.57) (2) *Restrictive* SMD 0.34 (0.01, 0.66; p = 0.04) (3) *Ritualistic* SMD 0.00 (-0.32, 0.32; p = 1.00) (4) *Sameness* SMD 0.05 (-0.27, 0.37; p = 0.77) (5) *Self-injurious* SMD 0.15 (-0.17, 0.47; p = 0.36) (6) *Stereotyped* SMD 0.13 (-0.20, 0.45; p = 0.44)
Heterogeneity (chi²; p value; I^2)	Not applicable		Chi² = 1.04, df = 1; p = 0.31; I^2 = 3%	Not applicable
Quality of the evidence (GRADE)	Low[1]		Moderate[2]	Moderate[2]
Number of studies/participants	K = 1; N = 149		K = 2; N = 188	K = 1; N = 149
Forest plot	1.6.1; Appendix 13			

Note. [1]Downgraded for very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[2]Downgraded for serious imprecision as N <400.

Two studies (HOLLANDER2005, KING2009) examined effects of SSRIs relative to placebo on the core autism feature of restricted interests and rigid and repetitive behaviours. In HOLLANDER2005 participants received low dose liquid fluoxetine (or matching placebo) and in KING2009 participants received liquid citalopram (Celexa, 10 mg/5 mL) or placebo (matched for smell, taste and viscosity). Only one meta-analysis with both studies was possible and results revealed no evidence for a statistically significant effect of SSRIs on compulsions as measured by the CYBOCS or CYBOCS-PDD (see Table 79). In KING2009 a number of additional outcome measures were examined for potential effects on restricted interests and rigid and repetitive behaviours. However, consistently with the meta-analysis most of these treatment effects were non-significant including effects on global positive treatment response measured using CGI-I or CYBOCS-PDD and CGI-I, and repetitive behaviours as measured by all but one subscale of the RBS (see Table 79). For the restrictive subscale of the RBS there was evidence of moderate quality for a statistically significant effect; however this effect favoured the placebo (see Table 79). Narrative review of this result showed that improvement was made in experimental (mean change = −0.6; standard deviation =2.6) and control (mean change = −0.9; standard deviation =2.5) conditions but change was greater for participants receiving placebo than for those receiving citalopram. Furthermore, there was also evidence from this study for statistically significant harms associated with citalopram including: increased energy level; disinhibited, impulsive or intrusive behaviour; decreased attention and concentration; hyperactivity; stereotypy; diarrhoea; any insomnia and initial insomnia or difficulty falling asleep; skin or subcutaneous tissue disorder (see Section 10.3.2 for adverse events associated with antidepressants data).

Antioxidants for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

The antioxidant trial (HARDAN2012) compared N-acetylcysteine with placebo in children with autism (see Table 76).

Evidence for the effectiveness of N-acetylcysteine on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 80. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 80: Evidence summary table for effects of antioxidants on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	N-acetylcysteine versus placebo
Outcome	Repetitive behaviour
Outcome measure	RBS-R subscales: (1) Compulsive (2) Restrictive (3) Ritualistic (4) Sameness (5) Self-injurious

	(6) Stereotyped
Study ID	HARDAN2012
Effect size (CI; p value)	(1) *Compulsive* SMD -0.68 (-1.43, 0.08; p = 0.08) (2) *Restrictive* SMD -0.42 (-1.15, 0.32; p = 0.27) (3) *Ritualistic* SMD -0.30 (-1.03, 0.44; p = 0.43) (4) *Sameness* SMD -0.46 (-1.20, 0.28; p = 0.23) (5) *Self-injurious* SMD -0.26 (-0.99, 0.48; p = 0.49) (6) *Stereotyped* SMD -0.51 (-1.25, 0.24; p = 0.18)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 29
Forest plot	1.6.2; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

The single included antioxidant trial examined indirect effects on the core autism feature of restricted interests and rigid and repetitive behaviours. This study found no evidence for a statistically significant effect of N-acetylcysteine relative to placebo for repetitive behaviour as assessed by the RBS-R subscales (see Table 80). This study also found no evidence for statistically significant harms associated with N-acetylcysteine (see Section 10.3.2 for adverse events associated with antioxidants).

Antipsychotics for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Two antipsychotic trials (JOHNSON&JOHNSON2011, RUPPRISPERIDONE2001) compared risperidone with placebo in children with autism, and one antipsychotic trial compared aripiprazole with placebo (MARCUS2009) in children with autism (see Table 81). Data from two trials also allowed for a comparison of low dose antipsychotics (0.125-0.175 mg/day risperidone [JOHNSON&JOHNSON2011]; 5 mg/day aripiprazole [MARCUS2009]) with placebo (see Table 81).

Table 81: Study information table for included trials of antipsychotics for the core autism feature of restricted interests and rigid and repetitive behaviours

	Antipsychotic versus placebo
No. trials (N)	3 (415)
Study IDs	(1) JOHNSON&JOHNSON2011 (2) MARCUS2009 (3) RUPPRISPERIDONE2001
Study design	(1)-(3) RCT
% female	(1) 13 (2) 11 (3) 19
Mean age (years)	(1) 9.3 (2) 9.7 (3) 8.8
IQ	(1)-(3) Not reported
Dose/intensity (mg/hours)	(1) Low dose risperidone:0.125 mg (if <45 kg) or 0.175 mg (if ≥45 kg); High dose risperidone: 1.25 mg (if <45 kg) or 1.75 mg (if ≥45 kg) (2) Fixed doses of 5 mg/day or 10 mg/day or 15 mg/day (3

	active treatment arms) (3) Final daily dose of 1.8 mg of risperidone and 2.4 mg of placebo
Setting	(1) Not reported (2) Research setting (3) Five university sites
Length of treatment (weeks)	(1) 6 (2) 8 (3) 8
Continuation phase (length and inclusion criteria)	(1) 26 (includes open-label phase, however, data cannot be extracted for follow-up as all participants received risperidone resulting in no control group for 6-month outcome measures) (2) 8 (3) 8 (in the studies included in RUPPRISPERIDONE2002, an open-label 16-week extension is reported in Aman and colleagues [2005] and 95-week open-label follow-up phase in Anderson and colleagues [2007] but efficacy or safety data is not extractable for this follow-up)

Evidence for the effectiveness of antipsychotics on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 82. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 82: Evidence summary table for effects of antipsychotics on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Antipsychotic versus placebo	**Low dose antipsychotic versus placebo**
Outcome	Compulsions	
Outcome measure	CYBOCS: Compulsions	
Study ID	(1) JOHNSON&JOHNSON2011 RUPPRISPERIDONE2001 (2) MARCUS2009	(1) JOHNSON&JOHNSON2011 (2) MARCUS2009
Effect size (CI; p value)	(1)+(2) SMD -0.42 (-0.64, -0.20; p = 0.0002) (1) *Risperidone* SMD -0.49 (-0.79, -0.20; p = 0.0009) (2) *Aripiprazole* SMD -0.31 (-0.65, 0.03; p = 0.07)	(1)+(2) SMD -0.27 (-0.59, 0.04; p = 0.09) (1) *Risperidone* SMD -0.29 (-0.79, 0.21; p = 0.26) (2) *Aripiprazole* SMD -0.27 (-0.68, 0.15; p = 0.21)
Heterogeneity (chi²; p value; I²)	Test for subgroup differences: Chi² = 0.65, df = 1; p = 0.42; I^2 = 0%	Test for subgroup differences: Chi² = 0.00, df = 1; p = 0.95; I^2 = 0%
Quality of the evidence (GRADE)	Moderate[1]	Low[2]
Number of studies/participants	K = 3; N = 385	K = 2; N = 193
Forest plot	1.6.3; Appendix 13	
Note. [1]Downgraded for serious imprecision as N <400. [2]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

All of the three included antipsychotic trials examined indirect effects on the core autism feature of restricted interests and rigid and repetitive behaviours. The meta-analysis showed evidence, of moderate quality, for a small and statistically significant effect of antipsychotics on compulsions as measured by the CYBOCS (see Table 82). Subgroup analysis revealed no significant differences between risperidone and aripiprazole for this outcome measure (see Table 82). Two of the studies included in the meta-analysis included more than one active intervention treatment arms with low, high (JOHNSON&JOHNSON2011, MARCUS2009) and moderate (MARCUS2009) dose groups. For the aforementioned meta-analysis these groups were combined, additional analysis examined the effects of low dose against placebo and found no evidence for a statistically significant treatment effect of low dose antipsychotics on compulsions as measured by the CYBOCS and no evidence for risperidone relative to aripiprazole differences (see Table 82).

There was evidence for statistically significant harms associated with antipsychotics as follows: increased risk of any adverse event, increased risk of clinically relevant weight gain, continuous measure of weight gain, increased appetite, constipation, prolactin concentration, leptin change score, pulse change score, somnolence/drowsiness, fatigue, sedation, rhinitis, fever, tachycardia, drooling, and tremor (see Section 10.3.2 for adverse events associated with antipsychotics).

6.3.8 Clinical evidence summary for pharmacological interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours

Evidence was limited for pharmacological interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours. Evidence from the antidepressant meta-analysis revealed no clear evidence for positive treatment effects and significant harms associated with antidepressant drugs. There was also moderate quality evidence from a single study for a placebo effect with antidepressant drugs on restrictive behaviours. Conversely, there was evidence from three trials of antipsychotic drugs, of moderate quality, for a small effect of risperidone or aripiprazole on compulsions. However, there was also evidence for significant harms associated with antipsychotic drugs, including increased risk of any adverse event, weight gain, prolactin concentration, leptin level and tachycardia.

6.3.9 Health economic evidence for pharmacological interventions aimed at the core features of autism

No studies assessing the cost effectiveness of pharmacological interventions aimed at the core features of autism were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

6.4 BIOMEDICAL INTERVENTIONS – CORE FEATURES OF AUTISM

6.4.1 Introduction

The notion of biomedical interventions for neurodevelopmental disorders is intuitively attractive—a disorder of brain function requires treatment that might influence the brain. Unfortunately there are no causative –as opposed to associated- medical conditions, apart from phenyltketonuria, that lend themselves currently to biologically plausible treatments but many biomedical treatments have been tried.

6.4.2 Studies considered

Sixty-nine papers from the search met the eligibility criteria for full-text retrieval. Of these, 27RCTs provided relevant clinical evidence and were included in the review. Nineteen of these studies examined the efficacy of biomedical interventions on core autism features as a direct outcome (target of intervention), and eight provided data on core autism features as an indirect outcome. All studies were published in peer-reviewed journals between 1992 and 2013. In addition, 42 studies were excluded from the analysis. The most common reasons for exclusion were that the study was a systematic review with no new useable data and any meta-analysis results not appropriate to extract, non-randomised group assignment, efficacy data could not be extracted (and authors did not respond to data request) and small sample size (less than ten participants per arm). Further information about both included and excluded studies with direct outcomes aimed at core autism features can be found in Appendix 12b.

Biomedical interventions aimed at overall autistic behaviours

Data were extracted from 24 studies for direct and indirect effects of biomedical interventions on overall autistic behaviours.

Three trials examined effects of complementary therapies on overall autistic behaviours as a direct outcome (CHAN2009 [Chan et al., 2009]; WONG2002 [Wong & Sun, 2002]; WONG2008 [Wong, 2008]). One of these papers was a conference abstract (WONG2002) and one was a dissertation (WONG2008); however, data and study characteristics were extracted from a systematic review (Cheuk et al., 2011). Four trials examined effects of complementary therapies on overall autistic behaviours as an indirect outcome (SILVA2009 [Silva et al., 2009], SILVA2011B[40] [Silva et al., 2011b], WONG2010A [Wong & Sun, 2010], WONG2010B [Wong et al., 2010][41]).

Four trials examined effects of hormones on overall autistic behaviours as a direct outcome (CONIGLIO2001 [Coniglio et al., 2001], DUNNGEIER2000 [Dunn-Geier et al., 2000], MOLLOY2002 [Molloy et al., 2002], SANDLER1999 [Sandler et al., 1999]),

[40] See Section 8.5.6 for direct outcomes from SILVA2009 and SILVA2011B.
[41] See and Section 8.4.7 for direct outcomes from WONG2010A and WONG2010B.

and two trials examined indirect effects of hormones on overall autistic behaviours (OWLEY1999[42] [one trial reported across two papers: Owley et al., 1999; Owley et al., 2001]; UNIS2002 [Unis et al., 2002]).

Two trials examined effects of medical procedures on overall autistic behaviours as a direct outcome (ADAMS2009A [one trial reported across two papers: Adams et al., 2009a; Adams et al., 2009b], SAMPANTHAVIVAT2012 [Sampanthavivat et al., 2012]), and two trials examined indirect effects of medical procedures on overall autistic behaviours (GRANPEESHEH2010 [Granpeesheh et al., 2010] and ROSSIGNOL2009 [Rossignol et al., 2009][43]).

Four trials examined direct effects of nutritional interventions on overall autistic behaviours as a direct outcome (ADAMS2011 [Adams et al., 2011], CHEZ2002 [Chez et al., 2002], FAHMY2013 [Fahmy et al., 2013], KNIVSBERG2002 [one trial reported across two papers: Knivsberg et al., 2002, 2003]), and one trial examined indirect effects of a nutritional intervention on overall autistic behaviours (JOHNSON2010[44] [Johnson et al., 2010]).

Finally, one trial examined direct effects of a sensory intervention on overall autistic behaviours as a direct outcome (KOUIJZER2010 [Kouijzer et al., 2010]), and one trial examined indirect effects of a sensory intervention on overall autistic behaviours (BETTISON1996[45] [Bettison, 1996]).

Biomedical interventions aimed at the core autism feature of impaired reciprocal social communication and interaction

Data were extracted from 12 studies for direct and indirect effects of biomedical interventions on the core autism feature of impaired reciprocal social communication and interaction.

One trial (WONG2008) examined effects of a complementary intervention on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome.

Two studies (OWLEY1999, UNIS2002) examined effects of hormones on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome.

One trial (GRANPEESHEH2010) examined effects of medical procedures on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome, and one trial (ADAMS2009A) examined indirect effects of medical procedures on this core autism feature.

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[42] See Section 6.4.5 for direct outcomes from OWLEY1999.
[43] See Section 6.4.5 for direct outcomes from GRANPEESHEH2010 and Section 7.4.2 for direct outcomes from ROSSIGNOL2009.
[44] See Section 7.4.2 for direct outcomes from JOHNSON2010.
[45] See Section 8.5.6 for direct outcomes from BETTISON1996.

One trial (WHITELEY2010 [Whiteley et al., 2010]) examined direct effects and five trials (ADAMS2011, BENT2011 [Bent et al., 2011], CHEZ2002, JOHNSON2010, KNIVSBERG2002) examined indirect effects of nutritional interventions on the core autism feature of impaired reciprocal social communication and interaction.

Finally, one trial examined indirect effects of a sensory intervention (KOUIJZER2010) on the core autism feature of impaired reciprocal social communication and interaction.

Biomedical interventions aimed at the core autism feature of restricted interests and rigid and repetitive behaviours

Data were extracted from eight studies for direct and indirect effects of biomedical interventions on the core autism feature of restricted interests and rigid and repetitive behaviours.

One trial (OWLEY1999) examined effects of hormones on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome.

Two trials (ADAMS2009A, GRANPEESHEH2010) examined effects of medical procedures on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome.

One trial (BAHRAMI2012 [Bahrami et al., 2012]) examined effects of a motor intervention on the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome.

Three trials (CHEZ2002, KNIVSBERG2002, WHITELEY2010) examined indirect effects of nutritional interventions on the core autism feature of restricted interests and rigid and repetitive behaviours.

Finally, one trial (KOUIJZER2010) examined indirect effects of a sensory intervention on the core autism feature of restricted interests and rigid and repetitive behaviours.

6.4.3 Clinical evidence – effect of biomedical interventions on overall autistic behaviours

Complementary therapies for overall autistic behaviours as a direct or indirect outcome

One of the complementary therapies trials (CHAN2009) compared acupressure with waitlist control, two trials compared acupuncture/electro-acupuncture and a conventional educational programme with a conventional educational programme only (WONG2002, WONG2008), two trials compared acupuncture/electro-acupuncture with sham acupuncture/electro-acupuncture (WONG2010A; WONG2010B) and two trials compared Qigong massage training with waitlist control (SILVA2009, SILVA2011B) (see Table 83).

Evidence for the effectiveness of complementary therapies on overall autistic behaviours and the quality of evidence is presented in Table 84, Table 85 and Table 86. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 83: Study information table for included trials of complementary therapies for overall autistic behaviours

	Acupressure versus waitlist	Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only	Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture	Qigong massage training versus waitlist
No. trials (N)	1 (32)	2 (66)	2 (109)	2 (112)
Study IDs	CHAN2009	(1) WONG2002 (2) WONG2008	(1) WONG2010A (2) WONG2010B	(1) SILVA2009 (2) SILVA2011B
Study design	RCT	(1) RCT (2) RCT (crossover)	(1)-(2) RCT	(1)-(2) RCT
% female	19	(1) 3 (2) 6	(1) 14 (2) 15	(1) 20 (2) 30
Mean age (years)	6.9	(1) 7.2 (2) 7.5	(1) 6.1 (2) 9.3	(1) 5.0 (2) 4.8
IQ	85.4 (assessed using Test of Non-verbal Intelligence, TONI, Brown et al., 1992)	(1)-(2) Not reported	(1) 62.4 (assessed using the Griffiths Mental Developmental Scale [GMDS]; Griffiths, 1954) (2) Not reported	(1)-(2) Not reported
Dose/intensity (mg/hours)	5 hours/30 sessions (0.8 hours/week; 5 sessions/week)	(1) 0.2 hours/40 sessions (0.02 hours/week; 5 sessions/week) (2) 12 hours/24 sessions (1.5 hours/week; 3 sessions/week)	(1) 0.2 hours/40 sessions (0.02 hours/week; 5 sessions/week) (2) 6 hours/12 sessions (1.5 hours week; 3 sessions/week)	(1) Planned intensity: children were to be seen by the therapists 20 times and parents were required to give children daily massages. No information regarding the duration of the massages or actual intensity reported (2) 29.75 hours/119 sessions (1.75 hours/week; 7 sessions/week)
Setting	Not reported	(1)-(2) Not reported	(1) Not reported (2) Hospital	(1) Not reported (2) Home-based

Length of treatment (weeks)	6	(1)-(2) 8	(1) 8 (2) 4	(1) 22 (2) 17
Continuation phase (length and inclusion criteria)	6	(1)-(2) 8	(1) 8 (2) 4	(1) 44 (including 5-month post-intervention follow-up) (2) 17

Table 84: Evidence summary table for effects of complementary therapies (acupuncture) on overall autistic behaviours as a direct or indirect outcome

	Acupressure versus waitlist	**Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only**			**Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture**	
Outcome	Overall autistic behaviours (direct outcome)				Overall autistic behaviours (indirect outcome)	Positive treatment response (indirect outcome)
Outcome measure	Parent's Rating Questionnaire (study-specific) (1) Total score (2) Language (3) Social interaction (4) Stereotyped behaviour (5) Motor functioning	ATEC (1) Total score (2) Speech/ Language/ Communication (3) Sociability (4) Sensory/Cognitive Awareness (5) Health/Physical/ Behavior	RF-RLRS (1) Total score (2) Motor (3) Social (4) Affective (5) Sensory (6) Language	CGI (1) Total score (2) Response to social interaction (3) Social initiation (4) Use of speech (5) Repetitive behaviour (6) Behaviour problem (7) Activity level (8) Sleep problem (9) Digestive problem	RF-RLRS (change scores) (1) Total score (2) Motor (3) Social (4) Affective (5) Sensory (6) Language	Number of participants showing (1) much improvement or (2) minimal improvement in autistic behaviours according to the CGI-I
Study ID	CHAN2009	WONG2008	WONG2002 WONG2008	(1) WONG2008 (2)-(9) WONG2002	WONG2010A WONG2010B	WONG2010B
Effect size (CI; p value)	(1) *Total score* SMD 0.92 (0.19, 1.66; p = 0.01)	(1) *Total score* SMD 0.25 (-0.41, 0.90; p = 0.46) (2) *Speech/Language/*	(1) *Total score* SMD 0.28 (-0.21, 0.77; p = 0.27)	(1) *Total score* SMD -0.90 (-1.58, -0.21; p = 0.01)	(1) *Total score* SMD -0.30 (-0.69, 0.09; p = 0.13)	(1) *Much improvement* RR 5.83 (0.77, 44.28; p =0.09)

	(2) *Language* SMD 1.33 (0.55, 2.10; p =0.0008) (3) *Social interaction* SMD 0.98 (0.24, 1.72; p = 0.009) (4) *Stereotyped behaviour* SMD 0.23 (-0.47, 0.92; p = 0.52) (5) *Motor functioning* SMD 0.45 (-0.25, 1.15; p = 0.21)	*Communication* SMD -0.06 (-0.71, 0.59; p = 0.86) (3) *Sociability* SMD 0.14 (-0.51, 0.80; p = 0.67) (4) *Sensory/Cognitive Awareness* SMD 0.42 (-0.24, 1.08; p =0.21) (5) *Health/Physical/ Behavior* SMD 0.18 (-0.47, 0.84; p =0.59)	(2) *Motor* SMD 0.16 (-0.33, 0.64; p = 0.52) (3) *Social* SMD -0.20 (-0.69, 0.28; p = 0.41) (4) *Affective* SMD 0.17 (-0.32, 0.66; p = 0.49) (5) *Sensory* SMD 0.12 (-0.36, 0.61; p = 0.62) (6) *Language* SMD 0.35 (-0.13, 0.84; p = 0.15)	(2) *Response to social interaction* SMD -0.20 (-0.91, 0.52; p = 0.59) (3) *Social initiation* SMD -0.10 (-0.81, 0.62; p = 0.79) (4) *Use of speech* SMD Not estimable (5) *Repetitive behaviour* SMD -1.11 (-1.88, -0.33; p = 0.005) (6) *Behaviour problem* SMD Not estimable (7) *Activity level* SMD Not estimable (8) *Sleep problem* SMD Not estimable (9) *Digestive problem* SMD Not estimable	(2) *Motor* SMD -0.11 (-0.49, 0.28; p = 0.58) (3) *Social* SMD -0.16 (-0.55, 0.22; p = 0.41) (4) *Affective* SMD -0.27 (-0.66, 0.11; p = 0.17) (5) *Sensory* SMD -0.10 (-0.48, 0.29; p = 0.62) (6) *Language* SMD -0.32 (-0.70, 0.07; p = 0.11)	(2) *Minimal improvement* RR 1.19 (0.77, 1.83; p = 0.43)
Heterogeneity (chi²; p value; I²)	Not applicable		(1) Chi² = 2.42, df = 1; p = 0.12; I^2 = 59% (2) Chi² = 0.48, df = 1; p = 0.49; I^2 = 0% (3) Chi² = 0.37, df = 1; p = 0.54; I^2 = 0% (4) Chi² = 1.20, df = 1; p = 0.27; I^2 = 17% (5) Chi² = 2.52, df = 1; p = 0.11; I^2 = 60% (6) Chi² = 0.11,	Not applicable	(1) Chi² = 0.37, df = 1; p = 0.54; I^2 = 0% (2) Chi² = 1.83, df = 1; p = 0.18; I^2 = 45% (3) Chi² = 0.22, df = 1; p = 0.64; I^2 = 0% (4) Chi² = 0.33, df = 1; p = 0.57; I^2 = 0% (5) Chi² = 0.00, df = 1; p = 0.99; I^2 = 0% (6) Chi² = 0.01,	Not applicable

			df = 1; p = 0.74; I^2 = 0%		df = 1; p = 0.91; I^2 = 0%	
Quality of the evidence (GRADE)	(1)-(3) Low[1,2] (4)-(5) Very low[1,3]	Very low[3,4]	(1) Very low[3,4,5] (2)-(4) Very low[3,4] (5) Very low[3,4,5] (6) Very low[3,4]	(1) Low[2,4] (2)-(3) Very low[3,4] (4) Not applicable (5) Low[2,4] (6)-(9) Not applicable	(1) Very low[3,6] (2) Very low[2,5,6] (3)-(4) Very low[3,6] (5) Low[2,6] (6) Very low[3,6]	Very low[6,7]
Number of studies/participants	K = 1; N = 32	K = 1; N = 36	(1) K = 2; N = 65 (2)-(6) K = 2; N = 66	(1) K = 1; N = 36 (2)-(9) K = 1; N = 30	K = 2; N = 105	K = 1; N = 55
Forest plot	1.7.1; Appendix 13					

Note. SMDs were not estimable where either group standard deviation was zero.
[1]Downgraded for serious risk of bias – high risk of performance and response bias as participants and intervention administrators were non-blind, and high risk of detection bias as outcome measure was parent-rated and parents were non-blind.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and potential for care confounds as the conventional education programme differed for each participant which may introduce bias. There was also an unclear risk of detection bias as although all outcomes were measured by blinded assessors, some outcomes involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report.
[5]Downgraded for serious inconsistency due to moderate to substantial heterogeneity.
[6]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported.
[7]Downgraded for very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 85: Evidence summary table for effects of complementary therapies (acupuncture) on overall autistic behaviours as a direct or indirect outcome *(continued)*

	Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture					
Outcome	Positive treatment response for social relatedness (indirect outcome)	Positive treatment response for non-verbal and verbal communication (indirect outcome)	Positive treatment response for stereotypy interest and behaviour (indirect outcome)	Positive treatment response for cognition (indirect outcome)	Positive treatment response for motor abnormalities (indirect outcome)	Positive treatment response for other parent-reported changes (indirect outcome)
Outcome measure	Number of participants rated 'better than before' based on parental report (study-specific)					
Study ID	WONG2010B					
Effect size (CI; p value)	(1) *Social response* RR 0.67 (0.20, 2.22; p = 0.51) (2) *Social initiation* RR 12.58 (0.75, 209.98; p = 0.08) (3) *Eye contact* RR 1.46 (0.48, 4.42; p =0.50) (4) *Share* RR 0.28 (0.01, 6.58; p = 0.43) (5) *Curiosity* RR 0.28 (0.01, 6.58; p = 0.43) (6) *Patience* RR 2.52 (0.11, 59.18; p = 0.57)	(1) *Expressive language* RR 1.26 (0.58, 2.75; p =0.57) (2) *Receptive language* RR 2.83 (1.22, 6.59; p = 0.02) (3) *Pointing* RR 2.52 (0.11, 59.18; p =0.57) (4) *Imitation* RR 2.52 (0.11, 59.18; p = 0.57)	(1) *Temper* RR 1.33 (0.50, 3.56; p = 0.57) (2) *Compulsive behaviour* RR 0.83 (0.05, 12.66; p = 0.90) (3) *Adaptation to change* RR 0.28 (0.01, 6.58; p = 0.43)	(1) *Memory* RR 0.42 (0.04, 4.33; p = 0.46) (2) *Learning ability* RR 0.83 (0.13, 5.50; p = 0.85)	(1) *Motor skill* RR 9.23 (0.53, 159.14; p =0.13) (2) *Coordination* RR 3.33 (0.78, 14.29; p =0.11) (3) *Drooling* RR 1.67 (0.16, 17.32; p = 0.67)	(1) *Appetite* RR 2.50 (0.28, 22.56; p =0.41) (2) *Attention span* RR 15.94 (0.97, 260.91; p = 0.05) (3) *Sleeping pattern* RR 1.94 (0.56, 6.75; p = 0.29) (4) '*Crafty*' RR 1.67 (0.16, 17.32; p =0.67)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]	(1) Very low[1,2] (2) Low[2,3] (3)-(4) Very low[1,2]	Very low[1,2]			
Number of studies/	K = 1; N = 55	(1) K = 1; N = 54	K = 1; N = 55			

participants		(2)-(4) K = 1; N = 55	
Forest plot	1.7.1; Appendix 13		
Note. [1]Downgraded for very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [2]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported. [3]Downgraded for serious imprecision as number of events <300.			

Three studies (CHAN2009, WONG2002, WONG2008) examined direct effects of acupuncture on overall autistic behaviours and two studies (WONG2010A, WONG2010B) examined effects of acupuncture on overall autistic behaviours as an indirect outcome. The specific models of intervention and choice of comparators varied. CHAN2009 examined direct effects on overall autistic behaviours of acupressure relative to a waitlist control group. The intervention in CHAN2009 involved seven-star needle stimulation (without penetrating the skin) delivered using a dermatoneural medical hammer (with the head holding the seven blunt needles in the shape of a seven-pointed star) to various parts of the back, body and head. Two studies (WONG2002, WONG2008) examined direct effects on overall autistic behaviours of acupuncture or electro-acupuncture (as an adjunct to a comprehensive education programme). In WONG2002 acupuncture was delivered with Hwato needles to five acupoints on the tongue, the acupuncture sessions lasted for less than fifteen seconds and parents were present throughout. In WONG2008 five acupoints were stimulated for 30 minutes per session. However, for both these studies participants in experimental and control groups were also receiving a conventional educational programme and no detail is reported about this adjunctive intervention. Finally, two studies (WONG2010A, WONG2010B) examined indirect effects on overall autistic behaviours of acupuncture or electro-acupuncture (relative to sham acupuncture or sham electro-acupuncture). In WONG2010A, acupuncture was applied to the tongue using an acupuncture needle via five acupoints for approximately 15 seconds; sham acupuncture was applied to the tongue via the same five acupoints as the intervention group but involved the acupuncturist touching the five points with the blunt rather than the sharp end of the needle. In WONG2010B electro-acupuncture was delivered via eight acupoints using an electro-acupuncture machine that provided electrical spacing-density stimulation for 30 minutes, and sham acupuncture was delivered in the same way but with needles only inserted to a superficial level.

Meta-analysis with two studies found no evidence for a statistically significant effect of acupuncture or electro-acupuncture (as an adjunct to a conventional educational programme) on overall autistic behaviours (as a direct outcome) as measured by the RF-RLRS (see Table 84). In addition, meta-analysis with two studies found no evidence for a statistically significant indirect effect of acupuncture or electro-acupuncture (relative to sham acupuncture/electro-acupuncture) on overall autistic behaviours as measured by the RF-RLRS (see Table 84).

Single study data showed evidence for large and statistically significant effects of acupressure on overall autistic behaviours as a direct outcome as measured by a study-specific parent-rated questionnaire for total score, language subscale and social interaction subscale, but not for stereotyped behaviour or motor functioning subscales (see Table 84). The quality of the evidence for statistically significant effects was downgraded to low due to non-blind parent-rated outcome and small sample size.

Single study data also showed evidence for a large effect of acupuncture/electro-acupuncture (as an adjunct to a conventional education programme) on total score for the CGI and the repetitive behaviour subscale of the CGI, but not for response to social interaction or social initiation subscales of the CGI (see Table 84). The confidence in the effect estimates for the statistically significant effects was low due to unclear blinding of outcome assessors and small sample size. Moreover, single study data showed non-significant effects on the ATEC (see Table 84).

A single study that examined dichotomous measures of positive treatment response with electro-acupuncture (relative to sham electro-acupuncture) found non-significant effects for much or minimal improvement on the CGI (see Table 84) and for positive treatment responses in social relatedness, expressive language, non-verbal communication, stereotypy interest and behaviour, cognition, motor abnormalities and other parent-reported changes (see Table 85). This study did find evidence for a large indirect effect of electro-acupuncture on the receptive language subscale of the parent-reported positive treatment responses (see Table 85), with participants who received the electro-acupuncture being almost three times more likely to be 'better than before' as judged by parents in receptive language than participants receiving sham electro-acupuncture. However, the quality of the evidence is low due to the small number of events (less than 300) and the risk of selective reporting bias (follow-up assessment data was not reported). Moreover, given the number of outcome measures reported, there is also the possibility that this effect was spurious and a result of multiple comparisons.

Table 86: Evidence summary table for effects of complementary therapies (massage) on overall autistic behaviours as an indirect outcome

	Qigong massage training versus waitlist		
Outcome	Overall autistic behaviours	Social, language, and communication abilities	Maladaptive behaviour
Outcome measure	(1) Teacher-rated Autism Behavior Checklist: total score (2) Parent-rated PDDBI: Autism composite	(1) Teacher-rated PDDBI: Social, language, and communication abilities (2) Parent-rated PDDBI: Social, language, and communication abilities	(1) Teacher-rated PDDBI: Maladaptive behaviour (2) Parent-rated PDDBI: Maladaptive behaviour
Study ID	(1) SILVA2009 (2) SILVA2011B	(1) SILVA2009 (2) SILVA2009 SILVA2011B	
Effect size (CI; p value)	(1)+(2) SMD -0.85 (-1.32, -0.39; p = 0.0003) (1) *Teacher-rated*	(1) *Teacher-rated PDDBI* SMD 0.82 (0.22, 1.43; p =0.008)	(1) *Teacher-rated PDDBI* SMD -0.56 (-1.16, 0.03; p =0.06)

	Aberrant Behavior Checklist (ABC) SMD -0.91 (-1.52, -0.30; p = 0.004) (2) *Parent-rated PDDBI* SMD -0.77 (-1.49, -0.06; p = 0.03)	(2) *Parent-rated PDDBI* SMD 0.53 (0.07, 1.00; p =0.02)	(2) *Parent-rated PDDBI* SMD -1.03 (-1.50, -0.55; p <0.0001)
Heterogeneity (chi²; p value; I²)	Test for subgroup differences: Chi² = 0.08, df = 1; p = 0.78; *I²* = 0%	(1) Not applicable (2) Chi² = 8.35, df = 1; p = 0.004; *I²* = 88%	(1) Not applicable (2) Chi² = 0.13, df = 1; p = 0.71; *I²* = 0%
Quality of the evidence (GRADE)	Very low[1,2]	(1) Low[2,3] (2) Very low[1,2,4]	(1) Very low[3,5] (2) Very low[1,2]
Number of studies/participants	K = 2; N = 79	(1) K = 1; N = 46 (2) K = 2; N = 79	
Forest plot	1.7.1; Appendix 13		

Note. [1]Downgraded for very serious risk of bias – high risk of selection bias in SILVA2009 as groups were assigned using a random number generator but there were caveats to the randomisation (five sets of siblings were co-assigned due to parental involvement in the treatment and different geographical areas were assigned separately to meet the 'therapist to participant requirements'), groups were also not comparable at baseline for measures of parent rated social communication and autism composite and teacher rated sensory problems. There was also a high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias was high for the parent-rated outcome measure as parents were non-blind and involved in the intervention.
[2]Downgraded for serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of selection bias in SILVA2009 as groups were assigned using a random number generator but there were caveats to the randomisation (five sets of siblings were co-assigned due to parental involvement in the treatment and different geographical areas were assigned separately to meet the 'therapist to participant requirements'), groups were also not comparable at baseline for measures of parent rated social communication and autism composite and teacher rated sensory problems.
[4]Downgraded for very serious inconsistency due to substantial to considerable heterogeneity.
[5]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Both of the Qigong massage training intervention studies (SILVA2009, SILVA2011B) examined effects on overall autistic behaviours as an indirect outcome. Qigong massage is an intervention based in Chinese medicine. In SILVA2009, trained therapists administered qigong massage treatment to the child, and parents were trained in how to administer the massage for daily massage at home and in SILVA2011B the intervention was solely based on parent training of Qigong massage techniques. Meta-analysis with both studies found evidence for a large and statistically significant effect of Qigong massage training on overall autistic behaviours as measured by the teacher-rated ABC total score or the parent-rated PDDBI autism composite score (see Table 86). There was also evidence from both studies for moderate to large and statistically significant effects of Qigong massage training on parent-rated subscales of the PDDBI (see Table 86). However, the confidence in these effect estimates was very low due to the high risk of selection bias in SILVA2009, the lack of blinding for the parent-rated outcome measures, the small sample size and substantial to considerable heterogeneity for the social, language, and communication abilities subscale of the PDDBI (I^2=88%). There was also single study evidence for a large and statistically significant effect of Qigong

massage on the teacher-rated social, language, and communication abilities subscale of the PDDBI, but a non-significant effect on the teacher-rated maladaptive behaviour subscale of the PDDBI (see Table 86). Although the teacher-rated outcomes were blinded measures, the quality of evidence for the significant effect on the social, language, and communication abilities subscale was still low due to a high risk of selection bias and small sample size.

Hormones for overall autistic behaviours as a direct or indirect outcome

All of the six included hormone trials (CONIGLIO2001, DUNNGEIER2000, MOLLOY2002, OWLEY1999, SANDLER1999, UNIS2002) compared secretin with placebo (see Table 87). CONIGLIO2001, DUNNGEIER2000 and OWLEY1999compared porcine secretin with placebo, and MOLLOY2002 and SANDLER1999 compared synthetic human secretin with placebo. UNIS2002 was a three-armed trial comparing porcine secretin, synthetic porcine secretin and placebo. For data analysis with this study, initial comparisons tested for significant differences between the two active intervention arms (porcine secretin and synthetic porcine secretin) and as there were no significant differences between these two groups data was combined for meta-analysis.

Table 87: Study information table for included trials of hormones for overall autistic behaviours

	Secretin versus placebo
No. trials (N)	6 (403)
Study IDs	(1) CONIGLIO2001 (2) DUNNGEIER2000 (3) MOLLOY2002 (4) OWLEY1999 (5) SANDLER1999 (6) UNIS2002
Study design	(1)-(2) RCT (3)-(4) RCT (crossover) (5)-(6) RCT
% female	(1) 25 (2) 7 (3) 12 (4) 14 (5)-(6) Not reported
Mean age (years)	(1) 7.0 (2) 5.1 (3) 6.2 (4) 6.7 (5) 7.5 (6) 6.5
IQ	(1)-(3) Not reported (4) Non-verbal IQ 56.4 (assessed using DAS or MSEL) (5) 62.2 (test not reported) (6) Not reported
Dose/intensity (mg/hours)	(1)-(2) 2 CU/kg (up to 75 CU) (3)-(4) 2 CU/kg (5) 0.4 µg/kg

	(6) 2 CU/kg of porcine secretin or 0.4 µg/kg of synthetic porcine secretin
Setting	(1) Research setting and hospital (2)-(5) Not reported (6) Academic
Length of treatment (weeks)	(1)-(6) Single dose
Continuation phase (length and inclusion criteria)	(1) 6 (assessments at 3 weeks [post-intervention] and 6 weeks [follow-up]) (2) 3 (3) 12 (including crossover period but data were extracted only for 6 week period corresponding to the end of the first phase) (4) 8 (including crossover period but data were extracted only for 4 week period corresponding to the end of the first phase) (5) 4 (assessments at 1 week [post-intervention] and 4 weeks [follow-up]) (6) 4

Evidence for the effectiveness of hormones on overall autistic behaviours and the quality of evidence is presented in Table 88, Table 89, Table 90 and Table 91. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There were no statistically significant effects of secretin on any of the outcome measures for overall autistic behaviours (see Table 88, Table 89, Table 90 and Table 91).

Table 88: Evidence summary table for effects of hormones on overall autistic behaviours as a direct or indirect outcome

	Secretin versus placebo						
Outcome	Positive treatment response (direct outcome)	Overall autistic behaviours (direct outcome)					
Outcome measure	Number of participants showing a decrease of >4.07 points on CARS or 'much/very much improved' on parent-rated CGI at: (1) Post-intervention (2) Follow-up	CARS: total (endpoint or change scores)	Autism Behavior Checklist: total (change score) at: (1) Post-intervention (2) Follow-up	Autism Behavior Checklist: Sensory (change score) at: (1) Post-intervention (2) Follow-up	Autism Behavior Checklist: Social relatedness (change score) at: (1) Post-intervention (2) Follow-up	Autism Behavior Checklist: Body and object use (change score) at: (1) Post-intervention (2) Follow-up	Autism Behavior Checklist: Language (change score) at: (1) Post-intervention (2) Follow-up
Study ID	(1) CONIGLIO2001 (2) CONIGLIO2001 SANDLER1999	(1) DUNN-GEIER2000 (2) MOLLOY2002	(1) DUNNGEIER2000 SANDLER1999 (2) SANDLER1999				
Effect size (CI; p value)	(1) *Post-intervention* RR 1.63 (0.74, 3.60; p = 0.23) (2) *Follow-up* RR 1.24 (0.71, 2.19; p =0.45)	SMD 0.14 (-0.20, 0.48; p =0.41)	(1) *Post-intervention* SMD -0.09 (-0.42, 0.23; p = 0.57) (2) *Follow-up* SMD -0.46 (-1.01, 0.10; p = 0.10)	(1) *Post-intervention* SMD -0.09 (-0.42, 0.25; p =0.61) (2) *Follow-up* SMD -0.52 (-1.08, 0.03; p = 0.06)	(1) *Post-intervention* SMD -0.11 (-0.44, 0.22; p = 0.52) (2) *Follow-up* SMD -0.30 (-0.85, 0.25; p = 0.28)	(1) *Post-intervention* SMD -0.05 (-0.38, 0.28; p = 0.77) (2) *Follow-up* SMD -0.11 (-0.66, 0.43; p = 0.68)	(1) *Post-intervention* SMD -0.01 (-0.35, 0.33; p = 0.96) (2) *Follow-up* SMD -0.32 (-0.87, 0.23; p = 0.26)
Heterogeneity (chi²; p value; I^2)	(1) Not applicable (2) Chi² = 0.02, df = 1; p = 0.88;	Chi² = 0.03, df = 1; p = 0.87; I^2 = 0%	(1) Chi² = 1.36, df = 1; p = 0.24; I^2 = 26% (2) Not	(1) Chi² = 1.17, df = 1; p = 0.28; I^2 = 14% (2) Not	(1) Chi² = 0.95, df = 1; p = 0.33; I^2 = 0% (2) Not	(1) Chi² = 0.28, df = 1; p = 0.60; I^2 = 0% (2) Not	(1) Chi² = 1.70, df = 1; p = 0.19; I^2 = 41% (2) Not

	I^2 = 0%		applicable	applicable	applicable	applicable	applicable
Quality of the evidence (GRADE)	Very low[1,2,3]	Moderate[4]	(1) Moderate[4] (2) Low[5]				(1) Low[4,6] (2) Low[5]
Number of studies/ participants	(1) K = 1; N = 57 (2) K = 2; N = 109	K = 2; N = 137	(1) K = 2; N = 145 (2) K = 1; N = 52	(1) K = 2; N = 140 (2) K = 1; N = 52	(1) K = 2; N = 143 (2) K = 1; N = 52	(1) K = 2; N = 145 (2) K = 1; N = 52	(1) K = 2; N = 136 (2) K = 1; N = 52
Forest plot	1.7.2; Appendix 13						

Note. [1]Downgraded for serious risk of bias – risk of detection bias is unclear/unknown in CONIGLIO2001 as the paper reports that it was 'double-blind study' but it is not clear whether outcome assessors were blinded.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias in CONIGLIO2001 as data could not be extracted for the CARS (continuous measure), GARS or Preschool Language Scales (PLS).
[4]Downgraded due to serious imprecision as N <400
[5]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)
[6]Downgraded for serious inconsistency due to moderate heterogeneity

Table 89: Evidence summary table for effects of hormones on overall autistic behaviours as a direct or indirect outcome *(continued)*

	Secretin versus placebo						
Outcome	Overall autistic behaviours (direct outcome)	Overall autistic behaviours (direct or indirect outcome)	Overall autistic behaviours (indirect outcome)	Overall autistic behaviours (direct outcome)			
Outcome measure	Autism Behavior Checklist: Socialisation (change score) at: (1) Post-intervention (2) Follow-up	GARS: Autism quotient	CGI: total	CGI (change score): Response to social interaction at: (1) Post-intervention (2) Follow-up	CGI (change score): Social initiation at: (1) Post-intervention (2) Follow-up	CGI (change score): Use of speech at: (1) Post-intervention (2) Follow-up	CGI (change score): Types of repetitive behaviour at: (1) Post-intervention (2) Follow-up
Study ID	(1) DUNN-GEIER2000 SANDLER1999	MOLLOY2002 OWLEY1999	OWLEY1999	SANDLER1999			

	(2) SANDLER1999						
Effect size (CI; p value)	(1) *Post-intervention* SMD -0.05 (-0.39, 0.28; p = 0.76) (2) *Follow-up* SMD -0.25 (-0.80, 0.30; p = 0.37)	SMD 0.34 (-0.06, 0.74; p = 0.10)	SMD 0.23 (-0.29, 0.76; p = 0.39)	(1) *Post-intervention* SMD 0.00 (-0.54, 0.54; p =1.00) (2) *Follow-up* SMD -0.34 (-0.90, 0.23; p = 0.24)	(1) *Post-intervention* SMD -0.09 (-0.64, 0.45; p = 0.74) (2) *Follow-up* SMD 0.00 (-0.56, 0.56; p = 1.00)	(1) *Post-intervention* SMD -0.20 (-0.74, 0.35; p = 0.48) (2) *Follow-up* SMD 0.00 (-0.56, 0.56; p = 1.00)	(1) *Post-intervention* SMD -0.18 (-0.72, 0.37; p = 0.52) (2) *Follow-up* SMD -0.26 (-0.82, 0.30; p = 0.37)
Heterogeneity (chi²; p value; I^2)	(1) Chi² = 0.06, df = 1; p = 0.81; I^2 = 0% (2) Not applicable	Chi² = 0.04, df = 1; p = 0.84; I^2 = 0% (2)-(4) Not applicable	Not applicable				
Quality of the evidence (GRADE)	(1) Moderate[1] (2) Low[2]	Low[2]					
Number of studies/ participants	(1) K = 2; N = 139 (2) K = 1; N = 52	K = 2; N = 98	K = 1; N = 56	(1) K = 1; N = 52 (2) K = 1; N = 49			
Forest plot	1.7.2; Appendix 13						

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 90: Evidence summary table for effects of hormones on overall autistic behaviours as a direct or indirect outcome *(continued)*

	Secretin versus placebo						
Outcome	Overall autistic behaviours (direct outcome)				Overall autistic behaviours (indirect outcome; porcine + synthetic groups combined)		
Outcome measure	CGI (change score): Behaviour problems at: (1) Post-intervention (2) Follow-up	CGI (change score): Activity level at: (1) Post-intervention (2) Follow-up	CGI (change score): Sleep problems at: (1) Post-intervention (2) Follow-up	CGI (change score): Digestive problems at: (1) Post-intervention (2) Follow-up	SOS-M (change score): total (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Social (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Communication (1) Parent-rated (2) Teacher-rated

Study ID	SANDLER1999				UNIS2002		
Effect size (CI; p value)	(1) *Post-intervention* SMD 0.40 (-0.15, 0.95; p = 0.16) (2) *Follow-up* SMD 0.42 (-0.14, 0.99; p = 0.14)	(1) *Post-intervention* SMD 0.32 (-0.23, 0.87; p = 0.25) (2) *Follow-up* SMD 0.08 (-0.48, 0.64; p = 0.77)	(1) *Post-intervention* SMD 0.16 (-0.41, 0.72; p = 0.59) (2) *Follow-up* SMD -0.23 (-0.79, 0.34; p = 0.44)	(1) *Post-intervention* SMD -0.18 (-0.74, 0.37; p = 0.52) (2) *Follow-up* SMD 0.00 (-0.57, 0.57; p = 1.00)	(1) *Parent-rated* SMD -0.10 (-0.56, 0.35; p = 0.66) (2) *Teacher-rated* SMD 0.17 (-0.37, 0.71; p = 0.53)	(1) *Parent-rated* SMD 0.07 (-0.38, 0.53; p = 0.75) (2) *Teacher-rated* SMD 0.25 (-0.28, 0.79; p = 0.36)	(1) *Parent-rated* SMD 0.25 (-0.20, 0.71; p =0.28) (2) *Teacher-rated* SMD 0.50 (-0.05, 1.04; p = 0.07)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Low[1]						
Number of studies/ participants	(1) K = 1; N = 52 (2) K = 1; N = 49		(1) K = 1; N = 49 (2) K = 1; N = 48	(1) K = 1; N = 50 (2) K = 1; N = 48	(1) K = 1; N = 78 (2) K = 1; N = 56		
Forest plot	1.7.2; Appendix 13						
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).							

Table 91: Evidence summary table for effects of hormones on overall autistic behaviours as a direct or indirect outcome *(continued)*

	Secretin versus placebo						
Outcome	Overall autistic behaviours (indirect outcome; porcine + synthetic groups combined)						
Outcome measure	SOS-M (change score): Repetitive behaviour (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Digestive (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Mood (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Sensory (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Hyperactivity (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Lethargy (1) Parent-rated (2) Teacher-rated	SOS-M (change score): Sleep Parent-rated
Study ID	UNIS2002						
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.20 (-0.65, 0.25; p = 0.39) (2) *Teacher-rated* SMD 0.18 (-0.36,	(1) *Parent-rated* SMD 0.08 (-0.37, 0.54; p = 0.72) (2) *Teacher-rated* SMD 0.28 (-0.39,	(1) *Parent-rated* SMD -0.06 (-0.51, 0.40; p = 0.80) (2) *Teacher-rated* SMD 0.33 (-0.26,	(1) *Parent-rated* SMD -0.39 (-0.85, 0.07; p = 0.09) (2) *Teacher-rated* SMD 0.00 (-0.59,	(1) *Parent-rated* SMD -0.05 (-0.51, 0.40; p = 0.82) (2) *Teacher-rated* SMD 0.14 (-0.48,	(1) *Parent-rated* SMD 0.09 (-0.37, 0.55; p = 0.70) (2) *Teacher-rated* SMD 0.31 (-0.33,	*Parent-rated* SMD 0.02 (-0.44, 0.48; p = 0.94)

	0.72; p = 0.51)	0.96; p = 0.41)	0.93; p = 0.27)	0.59; p = 1.00)	0.76; p = 0.66)	0.95; p = 0.35)	
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Low[1]						Moderate[2]
Number of studies/ participants	(1) K = 1; N = 78 (2) K = 1; N = 56	(1) K = 1; N = 78 (2) K = 1; N = 35	(1) K = 1; N = 77 (2) K = 1; N = 47	(1) K = 1; N = 77 (2) K = 1; N = 46	(1) K = 1; N = 77 (2) K = 1; N = 43	(1) K = 1; N = 76 (2) K = 1; N = 41	K = 1; N = 76
Forest plot	1.7.2; Appendix 13						
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to serious imprecision as N <400.							

Medical procedures for overall autistic behaviours as a direct or indirect outcome

One of the included medical procedure trials (ADAMS2009A) compared long-term chelation (seven rounds of dimercaptosuccinic acid [DMSA] therapy) and short-term chelation (one round of DMSA therapy and six rounds of placebo). The other three included medical procedure trials (GRANPEESHEH2010, ROSSIGNOL2009, SAMPANTHAVIVAT2012) compared hyperbaric oxygen therapy (HBOT) and attention-placebo control condition (see Table 92). In ADAMS2009A, participants received one screening round of DMSA (a round consisted of three doses/day for 3 days, followed by 11 days off) and children who met criteria for Phase 2 (in particular those excreting significant heavy metals) were randomised to receive continued DMSA (six subsequent rounds) or placebo (six subsequent rounds of methyl cellulose). DMSA was compounded individually for each child from pharmaceutical grade DMSA (over 99% pure) supplied by Spectrum Chemical. To control for the strong smell of DMSA the bottles of placebo included a small slotted container that contained DMSA so that the medication smell was present. In GRANPEESHEH2010 and ROSSIGNOL2009, experimental group participants were delivered 1.3 atmosphere (atm) and 24% oxygen in a HBOT chamber, while control participants in GRANPEESHEH2010 were provided with free airflow through the HBOT chamber at ambient pressure and control participants in ROSSIGNOL2009 were provided with slightly pressurised room air (1.03 atm and 21% oxygen). In SAMPANTHAVIVAT2012, HBOT was delivered to experimental participants through a multiplace chamber at 153 kilopascals (kPa) or 1.5 atm absolute with 100% oxygen was delivered to participants, and for control participants sham HBOT was delivered with air pressured at 116 kPa (1.15 atm absolute).

Table 92: Study information table for included trials of medical procedures for overall autistic behaviours

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)	HBOT versus attention-placebo
No. trials (N)	1 (49)	3 (168)
Study IDs	ADAMS2009A	(1) GRANPEESHEH2010 (2) ROSSIGNOL2009 (3) SAMPANTHAVIVAT2012
Study design	RCT	(1)-(3) RCT
% female	7	(1) Not reported (2) 16 (3) 17
Mean age (years)	6.6	(1) 6.2 (2) 4.9 (3) 5.9
IQ	Not reported	(1)-(3) Not reported
Dose/intensity (mg/hours)	Planned intensity for the experimental group of	(1) Planned intensity of 80 hours (6-10 hours/week)

	180 mg/day (l-glutathione) and seven rounds of DMSA (each round consists of 3 days of DMSA [10 mg/kg-dose, nine doses over 3 days], followed by 11 days off [no treatment], and then repeating). For the control group one round of DMSA and six rounds of placebo planned	(2) Planned intensity of 40 hours (10 hours/week) (3) Planned intensity of 20 hours (5 hours/week)
Setting	Outpatient	(1) Outpatient (2)-(3) Not reported
Length of treatment (weeks)	17	(1) 10-15 (2)-(3) 4
Continuation phase (length and inclusion criteria)	17	(1) 34 (ClinicalTrials.gov reports 1-month and 3-month follow-ups but paper does not report follow-up data) (2)-(3) 4

Evidence for the effectiveness of medical procedures on overall autistic behaviours and the quality of evidence is presented in Table 93 and Table 94. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There were no statistically significant effects of chelation on overall autistic behaviours as measured by the ATEC, PDDBI (autism composite) or the Severity of Autism Scale (see Table 93).

Table 93: Evidence summary table for effects of medical procedures (chelation) on overall autistic behaviours as a direct outcome

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)		
Outcome	Overall autistic behaviours		
Outcome measure	ATEC (1) Total score (2) Speech/Language/ Communication (3) Sociability (4) Sensory/Cognitive Awareness (5) Health/Physical/ Behavior	PDDBI: Autism composite	Severity of Autism Scale: total
Study ID	ADAMS2009A		
Effect size (CI; p value)	(1) *Total score* SMD 0.25 (-0.57, 1.06; p = 0.55) (2) *Speech/Language/ Communication* SMD 0.01 (-0.63, 0.65; p = 0.97) (3) *Socialiability* SMD 0.14 (-0.51, 0.78; p = 0.68)	SMD 0.24 (-0.41, 0.88; p = 0.47)	SMD -0.13 (-0.80, 0.54; p = 0.70)

	(4) *Sensory/Cognitive Awareness* SMD 0.28 (-0.36, 0.93; p = 0.39) (5) *Health/Physical/ Behavior* SMD 0.33 (-0.49, 1.14; p = 0.43)		
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2]		
Number of studies/participants	(1) K = 1; N = 24 (2)-(4) K = 1; N = 40 (5) K = 1; N = 24	K = 1; N = 40	K = 1; N = 36
Forest plot	1.7.3; Appendix 13		
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as efficacy data cannot be extracted for the PGI scale as no measure of variability reported.			

Table 94: Evidence summary table for effects of medical procedures (HBOT) on overall autistic behaviours as director indirect outcome

	HBOT versus attention-placebo					
Outcome	Positive treatment response	Overall autistic behaviours			Global severity	Global improvement
Outcome measure	Number of participants showing an improvement in ADOS diagnostic classification based on total score	ADOS: total	Parent-rated ATEC (1) Total score (2) Speech/Language/ Communication (3) Sociability (4) Sensory/Cognitive Awareness (5) Health/Physical/ Behavior	Clinician-rated ATEC (1) Total score (2) Speech/Language/ Communication (3) Sociability (4) Sensory/Cognitive Awareness (5) Health/Physical/ Behavior	CGI-S (1) Parent-rated (2) Clinician-rated	CGI-I (1) Parent-rated (2) Clinician-rated
Study ID	GRANPEESHEH2010	ROSSIGNOL2009	ROSSIGNOL2009 SAMPANTHAVIVAT2012	SAMPANTHAVIVAT2012		
Effect size (CI; p value)	RR 1.11 (0.36, 3.44; p = 0.85)	SMD -0.16 (-0.69, 0.37; p = 0.55)	(1) *Total score* SMD -0.05 (-0.42, 0.32; p = 0.78) (2) *Speech/Language/ Communication* SMD 0.10 (-0.27, 0.47; p = 0.59) (3) *Sociability* SMD -0.02 (-0.39, 0.35; p = 0.93) (4) *Sensory/Cognitive Awareness* SMD -0.25 (-0.62, 0.13; p = 0.20) (5) *Health/Physical/ Behavior* SMD 0.02 (-0.35, 0.39; p = 0.91)	(1) *Total score* SMD -0.03 (-0.54, 0.49; p = 0.91) (2) *Speech/Language/ Communication* SMD -0.04 (-0.55, 0.48;p =0.89) (3) *Sociability* SMD 0.27 (-0.25, 0.79;p = 0.30) (4) *Sensory/Cognitive Awareness* SMD -0.07 (-0.59, 0.44;p =0.78) (5) *Health/Physical/ Behavior* SMD -0.20 (-0.72, 0.31; p = 0.44)	(1) *Parent-rated* SMD 0.03 (-0.48, 0.55;p = 0.90) (2) *Clinician-rated* SMD -0.34 (-0.86, 0.18; p = 0.20)	(1) *Parent-rated* SMD -0.28 (-0.80, 0.23; p = 0.28) (2) *Clinician-rated* SMD -0.57 (-1.10, -0.05; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable		(1) Chi² = 0.72, df = 1; p = 0.40; *I²* = 0% (2) Chi² = 0.20, df = 1; p = 0.65; *I²* = 0% (3) Chi² = 1.14, df = 1;	Not applicable		

			p = 0.28; I^2 = 13% (4) Chi^2 = 4.28, df = 1; p = 0.04; I^2 = 77% (5) Chi^2 = 0.07, df = 1; p = 0.79; I^2 = 0%		
Quality of the evidence (GRADE)	Low[1]	Low[2]	(1)-(3) Moderate[3] (4) Very low[2,4] (5) Moderate[3]	Low[2]	(1) Low[2] (2) Moderate[3]
Number of studies/participants	K = 1; N = 34	K = 1; N = 56	K = 2; N = 114	K = 1; N = 58	
Forest plot	1.7.3; Appendix 13				

Note. [1]Downgraded for very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[2]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious imprecision as N <400.
[4]Downgraded due to very serious inconsistency as the I^2 value indicates substantial to considerable heterogeneity.

There was moderate quality, single-study evidence, for a moderate effect of HBOT on clinician-rated global improvement as measured by the CGI-I (see Table 94). However, non-significant effects were observed for overall autistic behaviours as measured by the ATEC (parent-rated and clinician-rated) and dichotomous or continuous ADOS outcome measures and for parent- and clinician-rated global severity as measured by the CGI-S (see Table 94). There was also evidence for statistically significant adverse events associated with HBOT with participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotraumas than participants who received sham HBOT (see Chapter 10, Section 10.4.2, for adverse events associated with HBOT).

Nutritional interventions for overall autistic behaviours as a direct or indirect outcome

One of the nutritional intervention trials (ADAMS2011) compared a multivitamin and mineral supplement with placebo. Two of the included studies (CHEZ2002, FAHMY2013) compared an L-carnosine/L-carnitine supplement with placebo. One of the trials (JOHNSON2010) compared an omega-3 fatty acid supplement with a healthy diet control. Finally, one (KNIVSBERG2002) compared a gluten- and casein-free diet with treatment as usual (see Table 95). In ADAMS2011 the multivitamin and mineral supplement included most vitamins and minerals (with the exception of vitamin K, copper and iron) and was provided as a liquid (with a cherry flavour). Dosage levels of nutrients in the supplement were selected to be significantly higher than recommended daily allowance levels, but were either at or below the Tolerable Upper Limit. In CHEZ2002 the L-carnosine and placebo pills were contained by a gelatin capsule and parents were instructed to mix the powder with food or drink. In FAHMY2013 the L-carnitine was administered to participants in liquid form, in the morning and evening, dosing instructions were explained to parents by the pharmacist and printed on the packaging and the placebo was matched on appearance and taste (containing 5% glucose syrup). In JOHNSON2010 the omega-3 fatty acid supplement was docosahexaonic acid (DHA; Martek Biosciences product) capsules. Finally, in KNIVSBERG2002, a dietician visited parents and provided oral and written information about gluten- and casein-free diets. Parents were also able to contact the dietician by telephone during the trial period.

Evidence for the effectiveness of nutritional interventions on overall autistic behaviours and the quality of evidence is presented in Table 96, Table 97, Table 98 and Table 99. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 95: Study information table for included trials of nutritional interventions for overall autistic behaviours

	Multivitamin/mineral supplement versus placebo	L-carnosine/L-carnitine supplement versus placebo	Omega-3 fatty acids versus healthy diet control	Gluten- and casein-free diet versus treatment as usual
No. trials (N)	1 (141)	2 (61)	1 (23)	1 (20)
Study IDs	ADAMS2011	(1) CHEZ2002 (2) FAHMY2013	JOHNSON2010	KNIVSBERG2002
Study design	RCT			
% female	11	(1) 32 (2) 17	Not reported	
Mean age (years)	10.8	(1) 7.5 (2) Mean not reported (median: 5.7/5.8)	3.4	7.4
IQ	Not reported			PIQ 82.8 (assessed using the LIPS)
Dose/intensity (mg/hours)	One dose a day at lunchtime (formulation of vitamin/mineral supplement based on 60 lb which was adjusted up or down according to body weight up to a maximum of 100 lb: 1000 IU vitamin A; 600 mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70 mg mixed tocopherols; 20 mg B1, 20 mg B2, 15 mg niacin and 10 mg niacinamide B3; 15 mg B5; 40 mg B6; 500 mcg B12; 100 mcg folic acid; 550 mcg folinic acid; 150 mcg biotin; 250 mcg choline; 100 mcg inositol; 3.6 mg mixed carotenoids; 50 mg coenzyme Q10; 50 mg N-acetylcysteine;	(1) Planned intensity of 800 mg/day (in two daily doses of 400 mg) (2) Planned intensity of 100 mg/kg a day (in two daily doses)	Planned intensity of 400 mg/day (in two daily doses)	Unknown (compliance not recorded)

	100 mg calcium; 70 mcg chromium; 100 mcg iodine; 500 mcg lithium; 100 mg magnesium; 3 mg manganese; 150 mcg molybdenum; 50 mg potassium; 22 mcg selenium; 500 mg sulphur; 12 mg zinc)			
Setting	Outpatient			Home
Length of treatment (weeks)	13	(1) 8 (2) 26	13	52
Continuation phase (length and inclusion criteria)	13	(1) 8 (2) 26	13	52

Table 96: Evidence summary table for effects of nutritional interventions (multivitamin) on overall autistic behaviours as a direct outcome

	Multivitamin/mineral supplement versus placebo			
Outcome	Overall autistic behaviours			
Outcome measure	PGI-R: (1) Average improvement (2) Overall improvement	ATEC: total	Severity of Autism Scale: total	PDDBI: Autism composite
Study ID	ADAMS2011			
Effect size (CI; p value)	(1) *Average improvement* SMD 0.55 (0.16, 0.94; p = 0.006) (2) *Overall improvement* SMD 0.49 (0.10, 0.88; p = 0.01)	SMD 0.04 (-0.34, 0.43; p = 0.83)	SMD -0.04 (-0.43, 0.34; p = 0.83)	SMD 0.02 (-0.37, 0.40; p = 0.93)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Moderate[1]			
Number of studies/participants	K = 1; N = 104			
Forest plot	1.7.4; Appendix 13			
Note. [1]Downgraded due to serious imprecision as N <400.				

There was moderate quality, single-study evidence, for small to moderate effects of a multivitamin/mineral supplement on average improvement and overall improvement as measured by the PGI-R. However, non-significant effects were observed for all other outcome measures of overall autistic behaviours, the ATEC, Severity of Autism Scale and PDDBI (see Table 96). There was also no statistically significant evidence for harms associated with the multivitamin/mineral supplement (see Chapter 10, Section 10.4.2, for adverse events associated with the multivitamin/mineral supplement).

Table 97: Evidence summary table for effects of nutritional interventions (L-carnosine/L-carnitine) on overall autistic behaviours as a direct outcome

	L-carnosine/L-carnitine supplement versus placebo		
Outcome	Overall autistic behaviours		
Outcome measure	CGI-I (parent-rated): Overall improvement	CARS: total	GARS: Autism quotient
Study ID	CHEZ2002	(1) CHEZ2002 (2) FAHMY2013	CHEZ2002
Effect size (CI; p value)	SMD 0.47 (-0.25, 1.19; p = 0.20)	SMD -0.12 (-0.65, 0.42; p = 0.67)	SMD -0.34 (-1.05, 0.38; p = 0.35)
Heterogeneity (chi²; p value; I²)	Not applicable	Chi² = 3.18, df = 1; p = 0.07; *I²* = 69%	Not applicable
Quality of the evidence (GRADE)	Low[1]	Very low[1,2]	Low[1]
Number of studies/participants	K = 1; N = 31	K = 2; N = 56	K = 1; N = 31
Forest plot	1.7.4; Appendix 13		
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to very serious inconsistency as the I² value indicates substantial heterogeneity.			

There was no evidence for a statistically significant effect of an L-carnosine/L-carnitine supplement on overall autistic behaviours as measured by a parent-rated CGI-I scale, the CARS or the GARS (see Table 97).

Table 98: Evidence summary table for effects of nutritional interventions (omega-3) on overall autistic behaviours as an indirect outcome

	Omega-3 fatty acids versus healthy diet control
Outcome	Overall autistic behaviours
Outcome measure	CBCL/1.5-5: PDD
Study ID	JOHNSON2010
Effect size (CI; p value)	SMD -0.98 (-1.86, -0.10; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 23
Forest plot	1.7.4; Appendix 13
Note. [1]Downgraded due to serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded. [2]Downgraded due to serious imprecision as N <400.	

There was single-study evidence for a large effect of an omega-3 fatty acid supplement on overall autistic behaviours as measured by the PDD subscale of the CBCL/1.5-5 (see Table 98). However, the quality of the evidence was downgraded to low due to non-blind outcome assessment and small sample size. There was no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo by another study, Bent et al., 2011 (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

There was single-study evidence for a large effect of a gluten- and casein-free diet on overall autistic behaviours as measured by the DIPAB total score (see Table 99). However, the quality of this evidence was low due to non-blind outcome assessment (parents were intervention administrators and involved in outcome assessment) and small sample size.

Table 99: Evidence summary table for effects of nutritional interventions (gluten- and casein-free diet) on overall autistic behaviours as a direct outcome

	Gluten- and casein-free diet versus treatment as usual
Outcome	Overall autistic behaviours
Outcome measure	DIPAB: total
Study ID	KNIVSBERG2002
Effect size (CI; p value)	SMD -1.37 (-2.36, -0.37; p = 0.007)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 20
Forest plot	1.7.4; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind. There was also a high risk of detection bias for the DIPAB as although the investigator was blinded to group assignment, this outcome measure was based on parental interview and parents were non-blind to group assignment and other potentially confounding factors. [2]Downgraded due to serious imprecision as N <400.	

Sensory interventions for overall autistic behaviours as a direct or indirect outcome

One study (KOUIJZER2010) examined direct effects of neurofeedback relative to treatment as usual on overall autistic behaviours. While, the other included sensory intervention study (BETTISON1996) compared auditory integration training with an attention-placebo condition and examined effects on overall autistic behaviours as an indirect outcome (see Table 100). In KOUIJZER2010, the neurofeedback intervention involved recording participants' electroencephalographic activity, showing them their oscillatory brain activity as it is recorded (using bar graphs to reflect the amplitude of a particular frequency) and training the participant to 'move up or down' their brain activity while observing the amplitude of their own brain waves. The targeted oscillatory activity was to reduce theta activity over frontal and central electrodes. In BETTISON1996, the auditory integration training was based on the method of Berard (1993). Experimental group participants listened to filtered and modulated music that was specially modified for each participant based on their

pretest audiogram. While participants in the control group listened to the same music for the same number of sessions as the experimental group, for the control group the music was unmodified (structured listening condition).

Table 100: Study information table for included trials of sensory interventions for overall autistic behaviours

	Neurofeedback versus treatment as usual	**Auditory integration training versus attention-placebo (structured listening)**
No. trials (N)	1 (20)	1 (80)
Study IDs	KOUIJZER2010	BETTISON1996
Study design	RCT	RCT
% female	15	18
Mean age (years)	9.3	Not reported
IQ	Not reported (but inclusion criteria IQ ≥80)	PIQ 76 (as assessed using the LIPS)
Dose/intensity (mg/hours)	Planned intensity was an estimated 18.7 hours (40 sessions; 0.9 hour/week)	10 hours (7 hours/week)
Setting	Educational (specialist)	Educational
Length of treatment (weeks)	20	1.4
Continuation phase (length and inclusion criteria)	46 (but data cannot be extracted for 6-month post-intervention follow-up)	52 (follow-up assessments at 1 month, 3 months, 6 months and 1 year)

Evidence for the effectiveness of sensory interventions on overall autistic behaviours and the quality of evidence is presented in Table 101 and Table 102. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 101: Evidence summary table for effects of sensory interventions (neurofeedback) on overall autistic behaviours as a direct outcome

	Neurofeedback versus treatment as usual
Outcome	Overall autistic behaviours
Outcome measure	SCQ: total (1) Parent-rated (2) Teacher-rated
Study ID	KOUIJZER2010
Effect size (CI; p value)	(1) *Parent-rated* SMD -1.85 (-2.94, -0.77; p = 0.0008) (2) *Teacher-rated* SMD -0.29 (-1.18, 0.59; p = 0.51)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2) Very low[1,3,4]
Number of studies/participants	K = 1; N = 20
Forest plot	1.7.5; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial. [2]Downgraded for serious imprecision as N <400.	

[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for 6-month follow-up.
[4]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

There was single-study evidence for a large effect of neurofeedback on overall autistic behaviours as measured by the parent-rated SCQ (see Table 101). However, the quality of the evidence is very low due to non-blind outcome assessment, small sample size and selective reporting bias (no data reported for 6-month follow-up). In addition, the effects on the teacher-rated version of this scale were non-significant (see Table 101).

Table 102: Evidence summary table for effects of sensory interventions (auditory integration training) on overall autistic behaviours as an indirect outcome

	Auditory integration training versus attention-placebo (structured listening)
Outcome	Overall autistic behaviours
Outcome measure	Autism Behavior Checklist: total (1) 1-month follow-up (2) 3-month follow-up (3) 6-month follow-up (4) 12-month follow-up
Study ID	BETTISON1996
Effect size (CI; p value)	(1) *1-month follow-up* SMD 0.10 (-0.34, 0.54; p = 0.64) (2) *3-month follow-up* SMD 0.22 (-0.22, 0.66; p = 0.33) (3) *6-month follow-up* SMD 0.25 (-0.19, 0.69; p = 0.27) (4) *12-month follow-up* SMD 0.27 (-0.17, 0.71; p = 0.24)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 80
Forest plot	1.7.5; Appendix 13
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of auditory integration training on overall autistic behaviours at any of the time points assessed (see Table 102).

6.4.4 Clinical evidence summary – effect of biomedical interventions on overall autistic behaviours

Evidence was limited for biomedical interventions aimed at overall autistic behaviours. There was low to very low quality evidence from small single trials for acupuncture, massage, multivitamin/mineral supplement, omega-3 fatty acid supplement, gluten- and casein-free diet and neurofeedback. There was one trial that examined effects of chelation on overall autistic behaviours that found no evidence for any statistically significant effects.

6.4.5 Clinical evidence – effect of biomedical interventions on the core autism feature of impaired reciprocal social communication and interaction

Complementary therapies for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

The one included complementary intervention trial (WONG2008) involved a comparison between electro-acupuncture and conventional educational programme and conventional educational programme only (see Table 103).

Table 103: Study information table for the included trial of a complementary intervention for the core autism feature of impaired reciprocal social communication and interaction

	Electro-acupuncture and conventional educational programme versus conventional educational programme only
No. trials (N)	1 (36)
Study IDs	WONG2008
Study design	RCT (crossover)
% female	6
Mean age (years)	7.5
IQ	Not reported
Dose/intensity (mg/hours)	12 hours/24 sessions (1.5 hours/week; 3 sessions/week)
Setting	Not reported
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	8

Evidence for the effectiveness of complementary therapies on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 104. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 104: Evidence summary table for the effects of a complementary intervention on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	Electro-acupuncture and conventional educational programme versus conventional educational programme only	
Outcome	Communication	Social interaction
Outcome measure	ADOS: Communication (change score)	ADOS: Social interaction (change score)
Study ID	WONG2008	
Effect size (CI; p value)	SMD -0.19 (-0.85, 0.46; p = 0.56)	SMD 0.00 (-0.65, 0.65; p = 1.00)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 36	
Forest plot	1.8.1; Appendix 13	
Note. [1]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect		

and measure of appreciable benefit or harm (SMD -0.5/0.5).

There was no evidence for statistically significant effects of electro-acupuncture (as an adjunct intervention) on the core autism feature of impaired reciprocal social interaction and communication (see Table 104).

Hormones for the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

The two included hormone trials (OWLEY1999, UNIS2002) compared secretin with placebo (see Table 105). See Section 6.4.3 for intervention details. UNIS2002 involved two active intervention arms (porcine secretin and synthetic porcine secretin) and initial data analysis compared these two active treatment arms, however as there were no significant differences data from these two groups was combined and compared with placebo.

Table 105: Study information table for included trials of hormones for the core autism feature of impaired reciprocal social communication and interaction

	Secretin versus placebo
No. trials (N)	2 (146)
Study IDs	(1) OWLEY1999 (2) UNIS2002
Study design	(1) RCT (crossover) (2) RCT
% female	(1) 14 (2) Not reported
Mean age (years)	(1) 6.7 (2) 6.5
IQ	(1) Non-verbal IQ 56.4 (assessed using DAS or MSEL) (2) Not reported
Dose/intensity (mg/hours)	(1) 2 CU/kg (2) 2 CU/kg of porcine secretin or 0.4 µg/kg of synthetic porcine secretin
Setting	(1) Not reported (2) Academic
Length of treatment (weeks)	(1)-(2) Single dose
Continuation phase (length and inclusion criteria)	(1) 8 (including crossover period but data were extracted only for 4 week period corresponding to the end of the first phase) (2) 4

Evidence for the effectiveness of hormones on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 106. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 106: Evidence summary table for effects of hormones on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	Secretin versus placebo		
Outcome	Communication	Social interaction	Communication and social interaction
Outcome measure	(1) ADOS: Communication (endpoint and change scores) (2) GARS: Communication	(1) ADOS: Social interaction (endpoint and change scores) (2) GARS: Social interaction	ADOS: Communication + Social interaction (change score)
Study ID	(1) OWLEY1999 UNIS2002 (2) OWLEY1999		OWLEY1999
Effect size (CI; p value)	(1) *ADOS* SMD -0.10 (-0.44, 0.24; p = 0.56) (2) *GARS* SMD 0.38 (-0.15, 0.90; p = 0.16)	(1) *ADOS* SMD 0.46 (0.12, 0.80; p = 0.008) (2) *GARS* SMD 0.42 (-0.11, 0.95; p = 0.12)	SMD 0.55 (0.02, 1.09; p = 0.04)
Heterogeneity (chi²; p value; I²)	(1) Chi² = 0.94, df = 1; p = 0.33; *I²* = 0% (2) Not applicable	(1) Chi² = 2.93, df = 1; p = 0.09; *I²* = 66% (2) Not applicable	Not applicable
Quality of the evidence (GRADE)	(1) Moderate[1] (2) Low[2]	(1) Very low[1,3] (2) Low[2]	Moderate[1]
Number of studies/participants	(1) K = 2; N = 141 (2) K = 1; N = 56		K = 1; N = 56
Forest plot	1.8.2; Appendix 13		

Note. [1]Downgraded for serious imprecision as N <400.
[2]Downgraded for very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for very serious inconsistency due to moderate to substantial heterogeneity.

There was no evidence for statistically significant effects of secretin on communication as measured by the ADOS and the GARS, or social interaction as measured by the GARS. However, statistically significant small to moderate effects in favour of the placebo were observed for social interaction and composite communication and social interaction score as measured by the ADOS (see Table 106). Narrative review of this placebo effect reveals improvement in both groups but greater improvement in the placebo group.

Medical procedures for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

One of the included medical procedures trials (GRANPEESHEH2010) compared HBOT with attention-placebo and the other included trial (ADAMS2009A) for medical procedures intervention compared long-term chelation with short-term chelation (see Table 92). See Section 6.4.3 for intervention details.

Evidence for the effectiveness of medical procedures on the core autism feature of impaired reciprocal social communication and interaction, and the quality of

evidence is presented in Table 107 and Table 108. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was no evidence for any statistically significant effects of HBOT on the core autism feature of impaired reciprocal social communication and interaction as measured by positive treatment responses based on improvement on the ADOS, the SRS or behavioural observation of appropriate vocalisation (see Table 107). There was also evidence from another trial (SAMPANTHAVIVAT2012) for statistically significant adverse events associated with HBOT with participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotraumas than participants who received sham HBOT (see Chapter 10, Section 10.4.2, for adverse events associated with HBOT).

There was no evidence for any statistically significant indirect effects of chelation on the core autism feature of impaired reciprocal social communication and interaction as measured by the PDDBI, social pragmatic and social approach behaviours (see Table 108). It was not possible to extract any data from the paper for adverse events.

Table 107: Evidence summary table for effects of medical procedures (HBOT) on the core autism feature of impaired reciprocal social communication and interaction as a direct outcome

	HBOT versus attention-placebo			
Outcome	Communication	Social interaction	Social impairment	Appropriate vocalisation
Outcome measure	Positive treatment response (number of participants showing improvement in ADOS diagnostic classification based on Communication domain)	Positive treatment response (number of participants showing improvement in ADOS diagnostic classification based on Socialisation domain)	SRS subscales (change scores): (1) Social awareness (2) Social cognition (3) Social communication (4) Social motivation (5) Autistic mannerisms	Behavioural observation: Appropriate vocalisation (change score)
Study ID	GRANPEESHEH2010			
Effect size (CI; p value)	RR 1.33 (0.25, 7.00; p = 0.73)	RR 1.40 (0.20, 9.66; p = 0.73)	(1) *Social awareness* SMD -0.11 (-0.84, 0.62; p = 0.76) (2) *Social cognition* SMD 0.53 (-0.21, 1.27; p = 0.16) (3) *Social communication* SMD -0.32 (-1.05, 0.41; p = 0.39) (4) *Social motivation* SMD 0.06 (-0.67, 0.79; p = 0.87) (5) *Autistic mannerisms* SMD 0.36 (-0.38, 1.09; p = 0.34)	SMD 0.17 (-0.51, 0.84; p = 0.62)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Low[1]		Low[2]	
Number of studies/ participants	K = 1; N = 34		K = 1; N = 29	K = 1; N = 34
Forest plot	1.8.3; Appendix 13			

Note. [1]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 108: Evidence summary table for effects of medical procedures (chelation) on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)	
Outcome	Social pragmatic problems	Social approach behaviours
Outcome measure	PDDBI: Social Pragmatic	PDDBI: Social Approach
Study ID	ADAMS2009A	
Effect size (CI; p value)	SMD 0.52 (-0.13, 1.17; p =0.12)	SMD -0.08 (-0.72, 0.56; p = 0.81)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	
Number of studies/participants	K = 1; N = 40	
Forest plot	1.8.3; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as efficacy data cannot be extracted for the ADOS Communication, Sociability, and Communication + Sociability or the PGI scale as no measure of variability reported.		

Nutritional interventions for the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

Two of the included nutritional intervention studies compared a gluten- and casein-free diet with treatment as usual, one examined effects on social interaction and communication as a direct outcome (WHITELEY2010) and one as an indirect outcome (KNIVSBERG2002). Two studies examined effects of an omega-3 fatty acid supplement on the core autism feature of impaired reciprocal social communication and interaction, one study (BENT2011) examined effects relative to placebo and one trial used a healthy-diet control comparator (JOHNSON2010). One study (ADAMS2011) compared a multivitamin/mineral supplement with placebo, and one study (CHEZ2002) compared an L-carnosine supplement with placebo (see Table 109). In WHITELEY2010, a strict gluten- and casein-free diet was introduced over the course of two weeks and nutritionists monitored the experimental group for the trial duration to ensure dietary compliance and nutritional intake. Participants in the experimental group were also advised to take a multivitamin supplement including calcium for the trial duration to compensate for any nutritional deficiency during the intervention. In BENT2011, the omega-3 fatty acid supplement was provided as an orange-flavoured pudding packet (Coromega®, Vista, CA) and placebo pudding packets had the same orange flavour with an identical appearance and taste, but included safflower oil which has a similar texture to omega-3 fatty acids and is comprised of non-omega-3 fatty acids. See Section 6.4.3 for intervention details for KNIVSBERG2002, JOHNSON2010, ADAMS2011 and CHEZ2002.

Evidence for the effectiveness of nutritional interventions on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 110, Table 111, Table 112 and Table 113. The full

evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was evidence for a moderate effect of a gluten- and casein-free diet on social interaction as a direct outcome as measured by the GARS, and large indirect effects on communication and interaction, resistance to communication and interaction, and social isolation as measured by the DIPAB (see Table 110). However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind or unclear blinding of outcome assessment) and small sample size. In addition, non-significant effects were observed for a gluten- and casein-free diet on social communication and interaction as a direct outcome when a blinded outcome measure (ADOS) was used (see Table 110). WHITELEY2010 reported adverse events associated with a gluten- and casein-free diet and found no participants in either group reported side effects associated with the diet (see Chapter 10, Section 10.4.2, for adverse events associated with gluten- and casein-free diet).

Table 109: Study information table for included trials of nutritional interventions for the core autism feature of impaired reciprocal social communication and interaction

	Gluten-and casein-free diet versus treatment as usual	Omega-3 fatty acids versus placebo	Omega-3 fatty acids versus healthy diet control	Multivitamin/mineral supplement versus placebo	L-carnosine supplement versus placebo
No. trials (N)	2 (92)	1 (27)	1 (23)	1 (141)	1 (31)
Study IDs	(1) KNIVSBERG2002 (2) WHITELEY2010	BENT2011	JOHNSON2010	ADAMS2011	CHEZ2002
Study design	(1)-(2) RCT	RCT			
% female	(1) Not reported (2) 11	11	Not reported	11	32
Mean age (years)	(1) 7.4 (2) 8.2	5.8	3.4	10.8	7.5
IQ	(1) PIQ 82.8 (assessed using the LIPS) (2) Not reported	77.5 (assessed using the Stanford-Binet Intelligence Scales)	Not reported		
Dose/intensity (mg/hours)	(1)-(2) Unknown (compliance not recorded)	1.3 g of omega-3 fatty acids per day (with 1.1 g of eicosapentanoic acid [EPA] and DHA) administered as two daily doses (with 650 mg of omega-3 fatty acids, 350 mg of EPA and 230 mg of DHA per dose)	Planned intensity of 400 mg/day (in two daily doses)	One dose a day at lunchtime (formulation of vitamin/mineral supplement based on 60 lb which was adjusted up or down according to body weight up to a maximum of 100 lb: 1000 IU vitamin A; 600 mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70 mg mixed tocopherols; 20 mg B1, 20 mg B2, 15 mg niacin and 10 mg niacinamide B3; 15 mg B5; 40 mg B6; 500 mcg	Planned intensity of 800 mg/day (in two daily doses of 400 mg)

				B12; 100 mcg folic acid; 550 mcg folinic acid; 150 mcg biotin; 250 mcg choline; 100 mcg inositol; 3.6 mg mixed carotenoids; 50 mg coenzyme Q10; 50 mg N-acetylcysteine; 100 mg calcium; 70 mcg chromium; 100 mcg iodine; 500 mcg lithium; 100 mg magnesium; 3 mg manganese; 150 mcg molybdenum; 50 mg potassium; 22 mcg selenium; 500 mg sulphur; 12 mg zinc)	
Setting	(1)-(2) Home	Outpatient			
Length of treatment (weeks)	(1) 52 (2) 35 (data extracted for 8-month intervention as after this point duration was variable across participants)	12	13		8
Continuation phase (length and inclusion criteria)	(1) 52 (2) 104 (experimental group received diet and control group received treatment as usual for 8 months, at 8 months interim assessment of change in scores for the experimental group on one of several measures	12	13		8

	[ADOS, GARS, Vineland Adaptive Behavior Scale: VABS, ADHD Rating Scales-IV] against predefined statistical thresholds as evidence of improvement, if threshold exceeded both groups allocated to receive diet and re-assessed at 20 months, if threshold not exceeded experimental and control group continued to receive their respective interventions and then re-assessed at 12 months, if experimental group exceeded threshold at 12 months both groups received diet intervention and re-assessed at 24 months, if threshold not exceed then both groups stopped trial)			

Table 110: Evidence summary table for effects of nutritional interventions (gluten- and casein-free diet) on the core autism feature of impaired reciprocal social communication and interaction as a direct or indirect outcome

	Gluten- and casein-free diet versus treatment as usual				
Outcome	Communication (direct outcome)	Social interaction (direct outcome)	Communication and interaction (indirect outcome)	Resistance to communication and interaction (indirect outcome)	Social isolation (indirect outcome)
Outcome measure	(1) ADOS: Communication (change score) (2) GARS: Communication (change score)	(1) ADOS: Social interaction (change score) (2) GARS: Social interaction (change score)	DIPAB: Communication and interaction (K-scores)	DIPAB: Resistance to communication and interaction (M-scores)	DIPAB: Social interaction or isolation (I-scores)
Study ID	WHITELEY2010		KNIVSBERG2002		
Effect size (CI; p value)	(1) *ADOS* SMD -0.42 (-0.95, 0.12; p = 0.13) (2) *GARS* SMD -0.34 (-0.87, 0.19; p = 0.21)	(1) *ADOS* SMD -0.01 (-0.54, 0.52; p = 0.96) (2) *GARS* SMD -0.67 (-1.22, -0.13; p = 0.02)	SMD 1.19 (0.22, 2.15; p = 0.02)	SMD -1.58 (-2.61, -0.55; p = 0.003)	SMD -1.35 (-2.34, -0.35; p = 0.008)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	(1) Very low[1,2] (2) Very low[2,3]	(1) Very low[1,2] (2) Low[3,4]	Low[4,5]		
Number of studies/participants	K = 1; N = 55		K = 1; N = 20		
Forest plot	1.8.4; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group).
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind, and unclear/unknown risk of detection bias as the identity and blinding of outcome assessors not reported. Also high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group).
[4]Downgraded for serious imprecision as N <400.
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind. There was also a high risk of detection bias for the DIPAB as although the investigator was blinded to group assignment, this outcome measure was based on parental interview and parents were non-blind to group assignment and other potentially confounding factors.

Table 111: Evidence summary table for effects of nutritional interventions (omega-3) on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	Omega-3 fatty acids versus placebo	**Omega-3 fatty acids versus healthy diet control**	
Outcome	Social impairment	Frequency of positive vocalisations	Frequency of social initiations
Outcome measure	SRS: total	Behavioural observation	
Study ID	BENT2011	JOHNSON2010	
Effect size (CI; p value)	SMD 0.06 (-0.77, 0.90; p = 0.88)	SMD 0.21 (-0.62, 1.03; p = 0.63)	SMD 0.44 (-0.40, 1.27; p = 0.31)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]		
Number of studies/participants	K = 1; N = 22	K = 1; N = 23	
Forest plot	1.8.4; Appendix 13		
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).			

There was no evidence for statistically significant effects of an omega-3 fatty acid supplement (relative to placebo or healthy diet control) on social impairment as measured by the SRS, or frequency of positive vocalisations and frequency of social initiations as measured by behavioural observation (see Table 111). There was no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

Table 112: Evidence summary table for effects of nutritional interventions (multivitamin) on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	Multivitamin/mineral supplement versus placebo	
Outcome	Sociability	Eye contact
Outcome measure	PGI-R: Socialiability improvement	PGI-R: Eye contact improvement
Study ID	ADAMS2011	
Effect size (CI; p value)	SMD 0.14 (-0.24, 0.53; p = 0.46)	SMD 0.28 (-0.11, 0.67; p = 0.15)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 104	
Forest plot	1.8.4; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for statistically significant effects of a multivitamin/mineral supplement on sociability or eye contact improvement as measured by the PGI-R (see Table 112). There was also no statistically significant evidence for harms

associated with the multivitamin/mineral supplement (see Chapter 10, Section 10.4.2, for adverse events associated with the multivitamin/mineral supplement).

Table 113: Evidence summary table for effects of nutritional interventions (L-carnosine) on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	L-carnosine supplement versus placebo	
Outcome	Communication	Social interaction
Outcome measure	GARS: Communication	GARS: Social interaction
Study ID	CHEZ2002	
Effect size (CI; p value)	SMD 0.19 (-0.52, 0.90; p = 0.60)	SMD -0.51 (-1.23, 0.21; p = 0.16)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 31	
Forest plot	1.8.4; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for statistically significant effects of an L-carnosine supplement on communication or social interaction as measured by the GARS (see Table 113). Data could not be extracted from this paper for adverse events.

Sensory interventions for the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

The one included sensory intervention trial (KOUIJZER2010) compared neurofeedback with treatment as usual (see Table 100). See Section 6.4.3 for intervention details.

Evidence for the effectiveness of sensory interventions on the core autism feature of impaired reciprocal social communication and interaction, and the quality of evidence is presented in Table 114 and Table 115. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was evidence for large and statistically significant treatment effects on a number of parent-rated outcome measures of the core autism feature of impaired reciprocal social communication and interaction, including the reciprocal social interaction and communication subscales of the SCQ, the social cognition and autistic mannerisms subscales of the SRS, and the interests, inappropriate initialisation, context use, non-verbal communication and pragmatics subscales of the CCC-2. However, the confidence in these effect estimates was very low due to risk of bias concerns (non-blind outcome assessment), small sample size, and selective reporting bias (no data reported for 6-month follow-up). There were also a large number of non-significant effects observed for parent-rated social impairment and communication as measured using the SRS and CCC-2 total scores, and some subscales of the SRS (social awareness, social communication, and social motivation) and CCC-2 (social relations, and stereotyped conversation), and all of the teacher-rated outcome measures were non-significant (see Table 114 and Table 115).

Table 114: Evidence summary table for effects of sensory interventions on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome

	Neurofeedback versus treatment as usual							
Outcome	Reciprocal social interaction	Communication		Social impairment	Social awareness	Social cognition	Social communication	Social motivation
Outcome measure	SCQ: Reciprocal social interaction (1) Parent-rated (2) Teacher-rated	SCQ: Communication (1) Parent-rated (2) Teacher-rated	CCC-2: total (1) Parent-rated (2) Teacher-rated	SRS: total (1) Parent-rated (2) Teacher-rated	SRS: Social awareness (1) Parent-rated (2) Teacher-rated	SRS: Social cognition (1) Parent-rated (2) Teacher-rated	SRS: Social communication (1) Parent-rated (2) Teacher-rated	SRS: Social motivation (1) Parent-rated (2) Teacher-rated
Study ID	KOUIJZER2010							
Effect size (CI; p value)	(1) *Parent-rated* SMD -1.54 (-2.57, -0.52; p = 0.003) (2) *Teacher-rated* SMD -0.39 (-1.28, 0.49; p = 0.38)	(1) *Parent-rated* SMD -1.14 (-2.10, -0.18; p = 0.02) (2) *Teacher-rated* SMD -0.19 (-1.07, 0.69; p = 0.68)	(1) *Parent-rated* SMD -0.88 (-1.81, 0.04; p =0.06) (2) *Teacher-rated* SMD -0.05 (-0.93, 0.83; p = 0.91)	(1) *Parent-rated* SMD -0.92 (-1.85, 0.02; p = 0.05) (2) *Teacher-rated* SMD 0.01 (-0.87, 0.88; p = 0.99)	(1) *Parent-rated* SMD -0.64 (-1.55, 0.26; p = 0.16) (2) *Teacher-rated* SMD 0.22 (-0.66, 1.10; p = 0.62)	(1) *Parent-rated* SMD -1.38 (-2.38, -0.38; p = 0.007) (2) *Teacher-rated* SMD 0.35 (-0.53, 1.24; p = 0.43)	(1) *Parent-rated* SMD -0.78 (-1.70, 0.14; p = 0.10) (2) *Teacher-rated* SMD 0.49 (-0.40, 1.38; p = 0.28)	(1) *Parent-rated* SMD -0.54 (-1.43, 0.36; p = 0.24) (2) *Teacher-rated* SMD 0.45 (-0.44, 1.34; p = 0.33)
Heterogeneity (chi²; p value; I²)	Not applicable							
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2) Very low[1,3,4]		Very low[1,3,4]			(1) Very low[1,2,3] (2) Very low[1,3,4]	Very low[1,3,4]	
Number of studies/participants	K = 1; N = 20							
Forest plot	1.8.5; Appendix 13							
Note. [1]Downgraded due to serious risk of bias – high risk of performance, response and detection bias as intervention administrators, participants and								

outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for 6-month follow-up.
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 115: Evidence summary table for effects of sensory interventions on the core autism feature of impaired reciprocal social communication and interaction as an indirect outcome *(continued)*

	Neurofeedback versus treatment as usual							
Outcome	Autistic mannerisms	Social relations	Interests	Inappropriate initialisation	Stereotyped conversation	Context use	Non-verbal communication	Pragmatics
Outcome measure	SRS: Autistic mannerisms (1) Parent-rated (2) Teacher-rated	CCC-2: Social relations (1) Parent-rated (2) Teacher-rated	CCC-2: Interests (1) Parent-rated (2) Teacher-rated	CCC-2: Inappropriate initialisation (1) Parent-rated (2) Teacher-rated	CCC-2: Stereotyped conversation (1) Parent-rated (2) Teacher-rated	CCC-2: Context use (1) Parent-rated (2) Teacher-rated	CCC-2: Non-verbal communication (1) Parent-rated (2) Teacher-rated	CCC-2: Pragmatics (1) Parent-rated (2) Teacher-rated
Study ID	KOUIJZER2010							
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.98 (-1.92, -0.04; p = 0.04) (2) *Teacher-rated* SMD -0.41 (-1.30, 0.48; p = 0.37)	(1) *Parent-rated* SMD -0.37 (-1.26, 0.51; p = 0.41) (2) *Teacher-rated* SMD 0.00 (-0.88, 0.88; p = 1.00)	(1) *Parent-rated* SMD -1.18 (-2.15, -0.21; p = 0.02) (2) *Teacher-rated* SMD 0.00 (-0.88, 0.88; p = 1.00)	(1) *Parent-rated* SMD -1.08 (-2.03, -0.13; p = 0.03) (2) *Teacher-rated* SMD -0.15 (-1.03, 0.73; p = 0.74)	(1) *Parent-rated* SMD -0.56 (-1.45, 0.34; p = 0.22) (2) *Teacher-rated* SMD 0.31 (-0.58, 1.19; p = 0.50)	(1) *Parent-rated* SMD -1.00 (-1.94, -0.06; p = 0.04) (2) *Teacher-rated* SMD 0.29 (-0.60, 1.17; p = 0.52)	(1) *Parent-rated* SMD -1.05 (-2.00, -0.10; p = 0.03) (2) *Teacher-rated* SMD 0.33 (-0.55, 1.22; p = 0.46)	(1) *Parent-rated* SMD -0.98 (-1.92, -0.04; p = 0.04) (2) *Teacher-rated* SMD 0.24 (-0.64, 1.13; p = 0.59)
Heterogeneity (chi²; p value; I²)	Not applicable							
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2) Very low[1,3,4]	Very low[1,3,4]	(1) Very low[1,2,3] (2) Very low[1,3,4]		Very low[1,3,4]	(1) Very low[1,2,3] (2) Very low[1,3,4]		
Number of studies/participants	K = 1; N = 20							
Forest plot	1.8.5; Appendix 13							

Note. [1]Downgraded due to serious risk of bias – high risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for 6-month follow-up.
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

6.4.6 Clinical evidence summary – effect of biomedical interventions on the core autism feature of impaired reciprocal social interaction and communication

There was low to very low quality evidence from single small studies for effects of a gluten- and casein-free diet or neurofeedback on the core autism feature of impaired reciprocal social communication and interaction. There was also evidence for small to moderate placebo effects of secretin on communication and social interaction consistent with improvement across both groups but greater improvement in the placebo group. Based on low quality evidence, the results were inconclusive regarding complementary interventions, medical procedures (HBOT), nutritional interventions and sensory interventions.

6.4.7 Clinical evidence – effect of biomedical interventions on the core autism feature of restricted interests and rigid and repetitive behaviours

Hormones for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

The one included hormone trial (OWLEY1999) compared secretin with placebo (see Table 116). See Section 6.4.3 for intervention details.

Table 116: Study information table for included trial of hormones for the core autism feature of restricted interests and rigid and repetitive behaviours

	Secretin versus placebo
No. trials (N)	1 (56)
Study IDs	OWLEY1999
Study design	RCT (crossover)
% female	14
Mean age (years)	6.7
IQ	Non-verbal IQ 56.4 (assessed using DAS or MSEL)
Dose/intensity (mg/hours)	2 CU/kg
Setting	Not reported
Length of treatment (weeks)	Single dose
Continuation phase (length and inclusion criteria)	8 (including crossover period but data were extracted only for 4-week period corresponding to the end of the first phase)

Evidence for the effectiveness of hormones on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 117. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 117: Evidence summary table for effects of hormones on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Secretin versus placebo
Outcome	Stereotyped behaviour/interests
Outcome measure	(1) ADOS: Repetitive behaviours (2) GARS: Stereotyped behaviours
Study ID	OWLEY1999
Effect size (CI; p value)	(1) *ADOS* SMD 0.36 (-0.17, 0.89; p = 0.19) (2) *GARS* SMD 0.17 (-0.36, 0.69; p = 0.53)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 56
Forest plot	1.9.1; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for statistically significant effects of secretin on the core autism feature of restricted interests and rigid and repetitive behaviours as measured by the ADOS and the GARS (see Table 117). Data could not be extracted from this study for adverse events associated with secretin.

Medical procedures for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

One of the included medical procedures trials (ADAMS2009A) involved a comparison between long-term and short-term chelation, and the other included medical procedures trial (GRANPEESHEH2010) involved a comparison between HBOT and attention-placebo (see Table 118). See Section 6.4.3 for intervention details.

Table 118: Study information table for included trials of medical procedures for the core autism feature of restricted interests and rigid and repetitive behaviours

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)	**HBOT versus attention-placebo**
No. trials (N)	1 (49)	1 (46)
Study IDs	ADAMS2009A	GRANPEESHEH2010
Study design	RCT	RCT
% female	7	Not reported
Mean age (years)	6.6	6.2
IQ	Not reported	Not reported
Dose/intensity (mg/hours)	Planned intensity for the experimental group of 180 mg/day (l-glutathione) and seven rounds of DMSA (each round consists of 3 days of DMSA [10 mg/kg-dose, nine doses over 3 days], followed by	Planned intensity of 80 hours (6-10 hours/week)

	11 days off [no treatment], and then repeating). For the control group one round of DMSA and six rounds of placebo planned	
Setting	Outpatient	Outpatient
Length of treatment (weeks)	17	10-15
Continuation phase (length and inclusion criteria)	17	34 (ClinicalTrials.gov reports 1-month and 3-month follow-ups but paper does not report follow-up data)

Evidence for the effectiveness of medical procedures on the core autism feature of restricted interests and rigid and repetitive behaviours and the quality of evidence is presented in Table 119 and Table 120. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 119: Evidence summary table for effects of medical procedures (chelation) on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)	
Outcome	Sensory/Perceptual approach behaviours	Ritualisms/Resistance to change
Outcome measure	PDDBI: Sensory/Perceptual Approach Behaviours	PDDBI: Ritualisms/Resistance to Change
Study ID	ADAMS2009A	
Effect size (CI; p value)	SMD 0.29 (-0.35, 0.94; p = 0.37)	SMD -0.18 (-0.83, 0.46; p = 0.57)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 40	
Forest plot	1.9.2; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for any statistically significant effects of chelation on the core autism feature of restricted interests and rigid and repetitive behaviours as measured by the PDDBI (see Table 119). Data could not be extracted from this paper for adverse events.

Table 120: Evidence summary table for effects of medical procedures (HBOT) on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	HBOT versus attention-placebo	
Outcome	Vocal stereotypy	Physical stereotypy
Outcome measure	Behavioural observation: Vocal stereotypy (change score)	Behavioural observation: Physical stereotypy (change score)
Study ID	GRANPEESHEH2010	
Effect size (CI; p value)	SMD -0.29 (-0.97, 0.39; p = 0.40)	SMD -0.42 (-1.10, 0.26; p = 0.23)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	
Number of studies/participants	K = 1; N = 34	
Forest plot	1.9.2; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for the RBS.		

There was no evidence for any statistically significant effects of HBOT on the core autism feature of restricted interests and rigid and repetitive behaviours as measured by behavioural observations of vocal and physical stereotypy (see Table 120). Data could not be extracted from this study for adverse events but there was evidence from another study (SAMPANTHAVIVAT2012) for statistically significant adverse events associated with HBOT with participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotraumas than participants who received sham HBOT (see Chapter 10, Section 10.4.2, for adverse events associated with HBOT).

Motor interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

The only included motor intervention trial (BAHRAMI2012) compared Kata exercise training with treatment as usual (see Table 121). Participants were trained in a modified form of Heian Shodan (shotokan) Kata techniques (including techniques from karate). Kata techniques which were trained included logical arrangements of blocking, punching, sticking, and kicking techniques in a set sequence. A number of autism-specific modifications were made to Kata training, including an initial 20-hour training course for instructors in autism, the use of video to model a specific technique at the beginning of each training session, and techniques to help keep participants engaged including reinforcement, inclusion of play activities, visual demonstration/modelling, visual cues (pictures, line, and spots drawings on the floor), and practice.

Table 121: Study information table for included trial of motor intervention for the core autism feature of restricted interests and rigid and repetitive behaviours

	Kata exercise training versus treatment as usual
No. trials (N)	1 (30)
Study IDs	BAHRAMI2012
Study design	RCT
% female	13
Mean age (years)	9.1
IQ	Not reported
Dose/intensity (mg/hours)	Planned intensity estimated at 52 hours (56 sessions; 2 hours/week up to week 8 and 6 hours/week for weeks 9-14)
Setting	Educational (specialist)
Length of treatment (weeks)	14
Continuation phase (length and inclusion criteria)	19 (including one-month post-intervention follow-up)

Evidence for the effectiveness of a motor intervention on the core autism feature of restricted interests and rigid and repetitive behaviours and the quality of evidence is presented in Table 122. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 122: Evidence summary table for effects of motor intervention on the core autism feature of restricted interests and rigid and repetitive behaviours as a direct outcome

	Kata exercise training versus treatment as usual
Outcome	Stereotyped behaviour
Outcome measure	GARS: Stereotyped behaviour at: (1) Post-intervention (2) 1-month post-intervention follow-up
Study ID	BAHRAMI2012
Effect size (CI; p value)	(1) *Post-intervention* SMD -0.90 (-1.66, -0.15; p = 0.02) (2) *1-month follow-up* SMD -0.76 (-1.51, -0.02; P =0.04)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 30
Forest plot	1.9.3; Appendix 13
Note. [1]Downgraded due to serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind. The risk of detection bias was also high as the outcome measure was based on interview with carers and teachers who were non-blind and blinding of examiner not reported. [2]Downgraded due to serious imprecision as N <400.	

There was single-study evidence for moderate to large effects of Kata exercise training on the core autism feature of restricted interests and rigid and repetitive behaviours as measured by the GARS at post-intervention and at 1-month follow-up (see Table 122). However, the quality of the evidence is low due to risk of bias concerns (non-blind outcome assessment) and sample size.

Nutritional interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

Two of the included nutritional intervention studies compared a gluten- and casein-free diet and treatment as usual (KNIVSBERG2002, WHITELEY2010). One study (CHEZ2002) compared an L-carnosine supplement with placebo (see Table 109). See Section 6.4.3 for intervention details for KNIVSBERG2002 and CHEZ2002 and Section 6.4.5 for intervention details for WHITELEY2010.

Evidence for the effectiveness of nutritional interventions on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 123 and Table 124. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 123: Evidence summary table for effects of nutritional interventions (gluten- and casein-free diet) on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Gluten- and casein-free diet versus treatment as usual		
Outcome	Unusual or bizarre behaviour	Repetitive behaviours	Stereotyped behaviour
Outcome measure	DIPAB: Unusual or Bizarre Behavior (B-scores)	ADOS: Repetitive Behaviors (change score)	GARS: Stereotyped Behavior (change score)
Study ID	KNIVSBERG2002	WHITELEY2010	
Effect size (CI; p value)	SMD -0.96 (-1.90, -0.02; p = 0.04)	SMD -0.33 (-0.86, 0.20; p = 0.23)	SMD -0.08 (-0.61, 0.45; p = 0.76)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1,2]	Very low[3,4]	Very low[4,5]
Number of studies/participants	K = 1; N = 20	K = 1; N = 55	
Forest plot	1.9.4; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind. There was also a high risk of detection bias for the DIPAB as although the investigator was blinded to group assignment, this outcome measure was based on parental interview and parents were non-blind to group assignment and other potentially confounding factors.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group).
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm.
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind, and unclear/unknown risk of detection bias as the identity and blinding of outcome assessors not reported. Also high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group).

There was evidence for a large effect of a gluten- and casein-free diet on unusual or bizarre behaviour as measured by the DIPAB (see Table 123). However, the quality of the evidence was downgraded to low due to risk of bias concerns (non-blind outcome assessment) and small sample size. In addition, non-significant effects were observed for a gluten- and casein-free diet on repetitive behaviours when a blinded outcome measure (ADOS) was used and for stereotyped behaviours as measured by the GARS where blinding of outcome assessment was unclear (see Table 123). WHITELEY2010 reported adverse events associated with a gluten- and casein-free diet and found no participants in either group reported side effects associated with the diet (see Chapter 10, Section 10.4.2, for adverse events associated with gluten- and casein-free diet).

Table 124: Evidence summary table for effects of nutritional interventions (L-carnosine) on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	L-carnosine supplement versus placebo
Outcome	Stereotyped behaviour
Outcome measure	GARS: Stereotyped Behavior
Study ID	CHEZ2002
Effect size (CI; *p* value)	SMD -0.41 (-1.13, 0.30; p = 0.26)
Heterogeneity (chi^2; *p* value; I^2)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 31
Forest plot	1.9.4; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm.	

There was no evidence for a statistically significant effect of an L-carnosine supplement on stereotyped behaviour as measured by the GARS (see Table 124). Data could not be extracted from this paper for adverse events.

Sensory interventions for the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

The one included sensory intervention trial (KOUIJZER2010) involved compared neurofeedback with treatment as usual (see Table 100). See Section 6.4.3 for intervention details.

Evidence for the effectiveness of sensory interventions on the core autism feature of restricted interests and rigid and repetitive behaviours, and the quality of evidence is presented in Table 125. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 125: Evidence summary table for effects of sensory intervention on the core autism feature of restricted interests and rigid and repetitive behaviours as an indirect outcome

	Neurofeedback versus treatment as usual
Outcome	Stereotyped behaviour
Outcome measure	SCQ: Stereotyped Behavior (1) Parent-rated (2) Teacher-rated
Study ID	KOUIJZER2010
Effect size (CI; p value)	(1) *Parent-rated* SMD -1.41 (-2.41, -0.40; p = 0.006) (2) *Teacher-rated* SMD 0.56 (-0.33, 1.46; p = 0.22)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2) Very low[1,3,4]
Number of studies/participants	K = 1; N = 20
Forest plot	1.9.5; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial. [2]Downgraded due to serious imprecision as N <400. [3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for 6-month follow-up. [4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm.	

There was evidence for a large and statistically significant effect of neurofeedback on stereotyped behaviour as measured by the parent-rated SCQ (see Table 125). However, the quality of the evidence is very low due to risk of bias concerns (non-blind outcome assessment), small sample size and high risk of selective reporting bias (data not reported for 6-month follow-up). In addition, results were inconsistent with non-significant treatment effects observed on teacher-rated stereotyped behaviour (see Table 125).

6.4.8 Clinical evidence summary – effect of biomedical interventions on the core autism feature of restricted interests and rigid and repetitive behaviours

There was low quality evidence from a single small trial for effects of an exercise intervention on the core autism feature of restricted interests and rigid and repetitive behaviours. There was also very low quality evidence from a single study for indirect effects of neurofeedback on stereotyped behaviour. There was evidence for a large effect of a gluten- and casein-free diet on unusual or bizarre behaviours; however, evidence was inconsistent and when a blinded outcome measure (ADOS) was examined, no significant effects of a gluten- and casein-free diet were observed. Based on low to very low quality evidence, it was not possible to reach a conclusion about the effect of secretin, medical procedures and sensory interventions.

6.4.9 Health economic evidence – biomedical interventions aimed at the core features of autism

No studies assessing the cost effectiveness of biomedical interventions aimed at the core features of autism in children and young people were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter3.

6.5 FROM EVIDENCE TO RECOMMENDATIONS

There was evidence from meta-analyses with blinded outcome assessment for small to moderate effects of caregiver- or preschool-teacher-mediated social-communication interventions on social interaction (as measured by the ADOS), communication acts, parent–child joint attention and parent–child joint engagement, for young children with autism. There was also evidence from a meta-analysis with a blinded outcome assessor for a moderate effect of peer-mediated social-communication interventions on peer–child joint engagement for older children (mean ages of 8-9 years). Based on this positive evidence, the GDG judged that social-communication programmes may help to address significant issues for children with autism, including social isolation. There were problems with developing an economic model based on this evidence due to the variety of comparators and outcome measures used in the trials, as well as the diversity of the interventions included in the clinical effectiveness systematic review in terms of the number of intervention sessions, duration of each session and descriptions of the intervention administrators. However, the PACT intervention, which included many of the common features for caregiver-mediated social-communication interventions, has been evaluated for its cost effectiveness. On the basis of economic evidence PACT is unlikely to be cost-effective within the NICE decision-making context when a service perspective is adopted. However, the intervention may be cost-effective under a societal perspective. According to the GDG expert opinion, it is possible that the PACT intervention was too intense (and therefore too costly) and that lower intensity of the intervention (that is, lower intervention cost) might result in similar clinical outcomes, thus improving its cost effectiveness relative to treatment as usual. Given these considerations the GDG judged that social-communication interventions should be recommended for children with autism and, where they are delivered, should include common core elements of being play-based and including training for the intervention administrator/mediator (caregiver, teacher or peer) on strategies for increasing reciprocal social communication and interaction. In addition, the GDG wished to highlight the need for any social-communication intervention to be pitched at the child or young person's developmental level and for the method of delivery to include modelling and video-interaction feedback by a trained professional.

There was evidence from two trials for the efficacy of risperidone in treating autistic behaviours in children and young people with autism. However, the evidence for positive treatment effects of antipsychotics on overall autistic behaviours was of very

low quality. There was also evidence from three studies of antipsychotics, of moderate quality, for a small effect of risperidone or aripiprazole on compulsions. However, core autism features were an indirect outcome of these trials, where antipsychotics were actually targeted at behaviour that challenges. Considered together with the more robust data for potential harms associated with these drugs, the GDG concluded that antipsychotics should not be used for the management of the core features of autism.

There was no evidence for positive treatment effects on core autism features associated with antidepressants. In fact, there was single study moderate quality data for placebo effects with SSRIs on restrictive behaviours. There was also evidence for significant harms associated with citalopram. Using their expert knowledge and opinion, the GDG concluded that antidepressants should not be used to target core features of autism in children and young people.

There was no evidence for benefits associated with anticonvulsants on overall autistic behaviours. There was also no evidence for significant adverse events associated with anticonvulsants. However, the GDG made the decision based on their knowledge and expertise that anticonvulsants should not be used in the treatment of core features of autism in children and young people, as further research examining the efficacy and safety of divalproex sodium is necessary in order to provide evidence for clinically important treatment effects.

There was some single-study evidence for effects of gluten- and casein-free diets on core features of autism. However, the evidence was inconsistent and when blinded measures of core autism features were examined non-significant effects were observed. On the basis of this evidence the GDG concluded that there was insufficient evidence for the safety and efficacy of exclusion diets and that further randomised and blinded placebo-controlled trials would be required before the use of such interventions could be recommended to treat core autism features in children and adults. The GDG consensus was that based on the current available evidence, exclusion diets should not be used to target the core features of autism in children and young people.

There was no evidence for significant positive treatment effects of single-dose secretin on overall autistic behaviours or repetitive behaviours and rigid and restrictive interests. Moreover, there was evidence for placebo effects with secretin on the core autism feature of impaired reciprocal social communication and interaction. Consequently, the GDG judged that secretin should not be recommended. Moreover, as this was a direct outcome of secretin intervention studies, and based on the clinical opinion of the GDG that secretin would not be used for any other outcome, the consensus judgement was that secretin should not be recommended for children and young people with autism for any target behaviour.

There was no evidence for any benefits associated with chelation for the targeted core autism features. This study did not report any evidence for adverse events; however, the GDG were concerned about potential harms. At present the GDG concluded that there was not sufficient evidence to recommend chelation targeted at core features of autism in children or young people. Moreover, given the clinical opinion of the GDG that chelation would not be targeted at any other outcome it was judged that chelation should not be recommended for any target behaviour in children and young people with autism.

With the exception of single study data for clinician-rated global improvement there was no evidence for beneficial effects of HBOT on core features of autism in children and young people. There was also evidence for increased risk of minor-grade ear barotrauma associated with HBOT. The GDG were mindful of potential risks and decided that HBOT should not be recommended for the core features of autism, or for any other target behaviour, for children and young people.

The GDG considered the results of the LEAP intervention to be potentially promising given the relatively large sample size. However, blinded independent evaluation of effects on core autism features was considered necessary before a treatment recommendation could be made.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

6.6 RECOMMENDATIONS

6.6.1 Clinical practice recommendations

Psychosocial interventions

6.6.1.1 Consider a specific social-communication intervention for the core features of autism in children and young people that includes play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication in the child or young person. Strategies should:

- be adjusted to the child or young person's developmental level
- aim to increase the parents', carers', teachers' or peers' understanding of and sensitivity and responsiveness to the child or young person's patterns of communication and interaction
- include techniques of therapist modelling and video-interaction feedback
- include techniques to expand the child or young person's communication, interactive play and social routines.

The intervention should be delivered by a trained professional. For pre-school children consider parent, carer or teacher mediation. For school-aged children consider peer mediation.

Pharmacological and dietary interventions

6.6.1.2 Do not use the following interventions for the management of core features of autism in children and young people:

- antipsychotics
- antidepressants
- anticonvulsants
- exclusion diets (such as gluten- or casein-free diets).

Interventions for autism that should not be used

6.6.1.3 Do not use the following interventions to manage autism in any context in children and young people:

- secretin
- chelation
- hyperbaric oxygen therapy.

6.6.2 Research recommendations

6.6.2.1 Are comprehensive early interventions that combine multiple elements and are delivered by parents and teachers (for example, the Learning Experiences – an Alternative Program for Preschoolers and Their Parents [LEAP] model) effective in managing the core symptoms of autism and coexisting difficulties (such as adaptive behaviour and developmental skills) in preschool children?

7 INTERVENTIONS AIMED AT BEHAVIOUR THAT CHALLENGES

7.1 INTRODUCTION

The term 'behaviour that challenges' is used to describe a constellation of behaviours that frequently occur in people with developmental disorders, including intellectual disability and autism, but are unusual in other populations. These behaviours include: physical aggression towards self (self-injury); severe levels of 'habitual behaviours' such as rocking and head-banging; physical aggression towards others; destruction of property; temper outbursts; high levels of oppositionality and defiance; and verbal aggression. Patterns of behaviour that challenges are extremely variable; behaviours may be frequent or rare and individual acts can have minor or severe consequences for the person and others.

Impact of behaviour that challenges

Behaviour that challenges usually has a significant impact on individuals themselves, on their parents and carers and those who work with them (Gallagher et al, 2008). This may come about through physical injury to the person or his/her carers, but also through lost opportunities for participation in home, school, work and leisure activities in the wider community or through poor interpersonal relationships. The burden on carers is considerable; behaviour that challenges usually causes high levels of stress and often restricts other opportunities for parents who may have to give up work or reduce their employment to care for their son or daughter because other options are precluded due to the severity of the behaviour. There is frequently significant impact on the wider family, particularly siblings, as they may be the victims of aggression but also because of the impact on their home environment, including decreased attention from parents, lack of opportunity for family activities and concerns about bringing friends home.

Costs of behaviour that challenges

Behaviour that challenges has economic implications for health, education and social care, as well as through lost opportunities for parents/carers. It is a common reason for high-cost, specialist education, over and above that required for a child/young person's communication and learning needs. Behaviour that challenges is a frequent reason for requesting respite care and those providing the care need greater levels of training than would otherwise be required (Allen et al., 2007; Knapp et al., 2005). Health services are frequently involved in assessment and treatment of behaviour that challenges; amongst adults with developmental disorders, behaviour that challenges is often cited as the reason for psychiatric in-patient evaluation and long-term care. Parents may need to reduce or even stop employment because of the demands of looking after their son or daughter (for example because of frequent school exclusions and the difficulty of identifying other carers).

Causes of behaviour that challenges

Behaviour that challenges usually occurs when individuals cannot effectively communicate their wishes, needs or distress directly or more acceptably using verbal or non-verbal means (Emerson & Bromley, 1995; McClintock et al., 2003). The most commonly recognised causes for behaviour that challenges are: a response to mental distress or psychiatric disorder; a reaction to physical discomfort or pain (Oliver et al., 2003); or they may be learned behaviours. 'Maladaptive' learned behaviours of this kind may actually be quite adaptive for the individual concerned if he or she has no other effective means of communication. Typically such behaviours are used to escape from demands or undesired situations or activities and/or as a means of obtaining some form of reward. Reinforcement can be tangible (for example desired food or objects), intangible (for example attention from other people) or have a direct physical consequence (for example head-banging or rocking may reinforce certain sensations). Very often, too, in the case of behaviours that challenge, a dual system of reward is operating. Thus, while the child is receiving positive reinforcement (for example attention; food; escape from disliked activities) the adult, too, is often reinforced in that, by giving the child what he/she wants, the unpleasant behaviour ceases). Thus, over time, behaviours that challenge can become strengthened and more difficult to modify.

Behaviours that challenge may also be triggered by environmental factors; sensory hypersensitivities (for example noise, bright lighting), or by excessive social and physical demands (for example having to take part in games lessons, or cope unaided in the play ground or school dining room). Other causes include restrictions on repetitive or stereotyped behaviours and (particularly in children with severe intellectual or communication impairments) inability to communicate their needs or emotions other than by actions, which may hurt others or be disruptive in nature (Mancil, 2006).

A further cause of behaviour that challenges is mental distress or a psychiatric disorder (Hayes et al., 2011; Moss et al., 2000). People with developmental and communication disorders often find it difficult to express their emotions directly and when they experience conditions such as anxiety and depression, these may be apparent to others only through their impact on behaviour. Hence, anxiety is often associated with high levels of arousal, which can lead to apparently unprovoked explosions of behaviour. Similarly, a common symptom of depression is irritability, which may be apparent when the person becomes angry or aggressive under minor provocation. ADHD is another psychiatric cause of behaviour that challenges, and poor impulse control may be an important mediator (Sayers et al., 2011). Other mental disorders that are less common in children and adolescents, such as psychotic disorders, may also cause behaviour that challenges. The presence of a mental or psychiatric disorder is determined by systematically exploring the entire constellation of behaviours, their onset and timing, the situations in which they occur and their relationship to environmental triggers including negative life events.

Physical conditions causing discomfort or pain are also important to consider. People with underlying medical conditions, which are sometimes causally related to autism, are more likely to experience pain because of these. People with autism may find it difficult to communicate their physical distress; they may also be unaware that it is their bodily sensations that are causing them discomfort or pain and therefore may act out in challenging ways. The role of physical disorders in behaviour that challenges is evaluated through a thorough medical history, appropriate physical examination and laboratory investigations.

None of the above causes of behaviour that challenges is exclusive; they may occur simultaneously as causes or one factor (such as physical pain) may have been the original cause that then led to a maladaptive learned response (that is, attention from others for the behaviour). Because the interventions for the various causes are quite different, a thorough and careful assessment is required. Ideally, intervention should be aimed at the primary cause (s) but even with careful assessment, it is not always possible to be certain of the underlying aetiology. Sometimes interventions need to be trialled and their effectiveness for an individual evaluated as a method for establishing the cause of behaviour that challenges (Oliver, 1995).

Current practice

The presence of behaviours that challenge is one of the principal reasons why children and young people are referred to child health services or CAMHS. Particularly in the case of sudden onset behaviours, a careful physical and mental health examination is needed to exclude these as possible causes and to treat as necessary. If behaviours that challenge appear to be directly related to anxiety and stress in specific situations, then the first line of approach is to modify the situation in which the behaviour occurs (for example by reducing demands or eliminating other factors that appear to be distressing the child or young person).

Very often, however, it does not prove possible immediately to identify any specific cause, and in such situations a more detailed behavioural analysis is conducted. This involves collecting information, either from records kept by parents or teachers and so on, or from direct observation, on when, where, with whom, in what form, and how often the behaviour occurs and how others respond to it. This makes it possible to:

1. *Identify potential causes*
2. *Identify maintaining factors (*for example, do parents/teachers attend to or give-in to the behaviour that challenges to avoid further outbursts; is the child excluded from classroom activities (and hence is able to avoid situations he/she dislikes)?
3. *Identify alternative behaviours*. Behaviours that challenge frequently arise because the child has no other effective means of communication. Strategies such as the prompting, shaping and reinforcement of new skills are often used to teach the child to communicate the same needs but in a different and more acceptable form (for example signs, gestures, electronic aids; Mancil, 2006).

Approaches such as these enable clinicians/ parents/teachers to formulate hypotheses about the causes, functions, and possible means of reducing behaviours that challenge. Sometimes, relatively simple environmental changes can have a significant impact (for example allowing the child to stay in the school library during play times, games lessons, or group assemblies, if these activities cause particular stress). Stress, due to over-expectations or excessive demands at school, can also lead to behaviours that challenge in the home, and again, modifications to the school programme or curriculum may be the first line of approach to intervention. In other cases, specific behavioural strategies are used. Parents/teachers can be helped to encourage more appropriate behaviours, rather than responding to the behaviours that challenge. At the same time the child/young person can be taught alternative behaviours that achieve the same goals. If mental health problems are pervasive, long standing or very severe, then medication may be considered.

Dealing with behaviours that challenge can place great demands on families, school staff or other carers; interventions may take time to have an effect or initial treatment plans may have to be changed if they prove unsuccessful. Thus, clinical services may need to offer considerable support in the home or school environment if intervention is to continue. Parents and siblings may also require individual counselling to help them deal with the physical and emotional demands that the child's challenging behaviours can make. Often, too, if the behaviours that challenge are very severe and/or persistent then a combination of pharmacological behavioural, psychological and environmental strategies may be needed. Thus, if the young person is experiencing severe anxiety or stress, medication may be needed in order for him/her to be able to respond to a behavioural programme. If behaviour that challenges is due to environmental factors such as bullying at school, then the focus will need to be on the school's anti-bullying procedures. Issues such as parental stress, anxiety, lack of sleep, money or housing worries can all have a direct or indirect impact on behaviours that challenge, and again will need support in their own right.

7.1.1 Review protocol – interventions aimed at behaviour that challenges

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 7 (further information about the search strategy can be found in Appendix 7).

Table 126: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s)	**RQ 5.1**: For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for anticipating, preventing or managing behaviour that challenges or poses a risk*, when compared with alternative management strategies? *Subgroup analyses will examine and compare treatment effects on behaviour that challenges when the interventions are specifically aimed at these behaviours (direct outcomes) and when the primary target of the intervention was another outcome but effects on behaviour that challenges are examined (indirect outcomes)
Sub-question(s)	**RQ 5.1.1:** For children and young people with autism, and their families and carers, is the engagement with or effectiveness of interventions aimed at reducing behaviour that challenges or poses a risk different for: • looked-after children? • immigrant groups? • children with regression in skills? **RQ 5.1.2**: For children and young people with autism is the effectiveness of interventions aimed at reducing behaviour that challenges or poses a risk moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)? **RQ 5.1.3**: For children and young people with autism is the effectiveness of interventions aimed at reducing behaviour that challenges or poses a risk mediated by: • the intensity of the intervention? • the duration of the intervention? • the length of follow-up? • programme components?
Objectives	To evaluate the clinical and cost effectiveness of interventions aimed at reducing behaviour that challenges or poses a risk for children and young people with autism.
Criteria for considering studies for the review	
Population	Children and young people (from birth until their 19th birthday) with autism, (across the full range of intellectual ability) and their families and carers. If some, but not all, of a study's participants are eligible for our review, we will ask the study authors for disaggregated data. If we are unable to

	obtain the appropriate disaggregated data, then we will include a study if the majority (at least 51%) of its participants are eligible for our review. If we are unable to determine the exact percent of a study's participants who are eligible, then we will include the study if its participants are eligible on average (for example, the mean participant age is less than 19 years). Consideration will be given to the particular management and support needs of: • looked-after children • immigrant groups • children with regression in skills Excluded groups include: • adults (19 years and older).
Intervention	Psychosocial, biomedical or pharmacological interventions which are aimed at reducing behaviour that challenges or poses a risk as a direct or indirect outcome
Comparison	No treatment or treatment as usual (includes placebo and waitlist control up until receiving intervention), other active interventions
Critical outcomes	• **Challenging behaviour** (as measured by behaviour checklists including the ABC) • **Positive treatment response** (dichotomous measure of positive treatment response where adaptive or challenging behaviour was the direct outcome) • **Global state-challenging behaviour** (as measured by the CGI where challenging behaviour was the direct outcome)
Time points	Some studies may measure outcomes at multiple time points. We will run the following analyses: • Post-intervention (end of treatment) • Longest follow-up
Study design	• RCTs • Systematic reviews Non-English language papers will be excluded, as will books, dissertation abstracts, trade magazines, policy and guidance, and non-empirical research.
Include unpublished data?	Yes but only where: • the evidence was accompanied by a trial report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	No limit
Minimum sample size	• N ≥ 10 per arm (ITT) Exclude studies with >50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
Study setting	• Primary, secondary and tertiary health and social care. This guideline will also be relevant to other health and social care settings (including forensic services and youth justice settings) although they are not explicitly covered.

	• The guideline will also address interventions relevant to early years services and educational settings.
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, HTA, IBSS, MEDLINE, PreMEDLINE, PsycEXTRA, PsycINFO, Social Policy and Practice, Sociological Abstracts, SSA, SSCI
Date searched	Systematic reviews: 1995 up to January 2013. RCTs: inception of database up to January 2013
Searching other resources	Hand-reference searching and citation searches of included studies, hand-searching of the 'Research Autism' website, and searching the ISRCTN and ClinicalTrials.gov website using the term 'autism'
The review strategy	• The initial aim is to conduct a meta-analysis evaluating the clinical effectiveness of the interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. Consider subgroup meta-analyses that takes into account the effectiveness of interventions as moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)?

7.1.2 Outcomes – behaviour that challenges

A large number of outcome measures for behaviour that challenges were reported: those that reported sufficient data to be extractable and were not excluded (see Appendix 12c) are in Table 127.

Table 127: Outcome measures for behaviour that challenges extracted from studies of interventions aimed at behaviour that challenges

Category	Scale
Behaviour that challenges	• ABC (Aman et al., 1985a, 1985b) – Total score and Irritability, Lethargy/Social Withdrawal, Stereotypic Behaviour, Hyperactivity/Non-compliance and Inappropriate Speech subscales • Achenbach CBCL (Achenbach, 1991): Aggression • BASC-2-PRS (Reynolds & Kamphaus, 2004) – Withdrawal subscale • Behavior Screening Questionnaire (BSQ; Richman et al., 1982) – Total score • BASC (cited in Bent et al., 2011 and reference not reported) – Externalizing, Behavioural Symptoms, and Hyperactivity subscales • Behavioural observation ('Toy Play' condition of the standard functional analysis, Iwata et al., 1994) – Challenging Behaviors (that is, aggression, self-injury, property destruction) and Hyperactivity subscales • CBCL/1.5-5 – Total problem score, and Externalizing, Emotional regulation,

	Withdrawn, Attention problems, Aggressive behaviours, and ODD symptoms • CGI (Guy, 1976): CGI-S and CGI-I • Conners' Parent Rating Scales (Conners, 1989) – Conduct problem, Learning problem, Psychosomatic, Impulsivity-hyperactivity, Anxiety, and Hyperactivity subscales • Conners' Teacher Rating Scales (CTRS; Conners, 1989) – Conduct problem, Hyperactivity, Inattention-passivity, and Hyperactivity index subscales • DBC – Total score • DBC (Einfeld & Tonge, 2002) – Total Behaviour Problem Score • Eyberg Child Behaviour Inventory (ECBI; Eyberg & Ross, 1978) – Number of problem behaviours and Intensity of problem behaviours • Home Situations Questionnaire (Barkley et al., 1999) – Severity • Non-compliance index (study-specific, Scahill et al., 2012) – based on VABS (Sparrow et al., 1984) Daily Living Skills subscale • Overt Aggression Scale (OAS; Yudofsky et al., 1986) – Total score • OAS-Modified (OAS-M; see Buitelaar et al., 2001) – Irritability subscale • Parent monitoring of anger (study-specific; Sofronoff et al., 2007) – Parent-reported instances of child anger and Parent confidence in child managing own anger • Parent-defined target symptom (study-specific target symptom ratings on 9-point scale [Arnold et al., 2003]; study-specific visual analogue scale [VAS] for the most troublesome symptom [Shea et al., 2004]) • PDDBI – Maladaptive behaviours composite, Arousal regulation problems, and Aggressiveness subscales • PGI-R – Hyperactivity improvement and Tantrumming improvement subscales • Positive treatment response: Number of participants who were 'much improved/very improved' on CGI-I • Positive treatment response: Number of participants who showed >25% improvement on ABC Irritability with or without 'much improved/very improved' on CGI-I • Positive treatment response: Number of participants who scored <3 'definitely improved' or better on 9-point parent-defined target symptom scale (study-specific scale; Arnold et al., 2003) • Positive treatment response: Parental report of positive response (study-specific; Kern et al., 2001) • Preschool Behavior Checklist (McGuire & Richman, 1988) – Total score • Problem Behavior Questionnaire (study-specific [Carr & Blakeley-Smith, 2006]) – Most serious problem behaviours • Pupil Evaluation Inventory—Teacher (Pekarik et al., 1976) – Aggression and Withdrawal subscales • QPQ (Frankel & Mintz, 2008) – Conflict subscale • Relapse rate after discontinuation: Number of participants showing >25% worsening in ABC Irritability and rated as 'worse/very much worse' on CGI-I • Sensory Profile (Dunn, 1999) – Inattention/distractibility and Sedentary subscales • Sleep Diary (Schreck & Mulick, 2000) – Sleep behaviour • SSRS (Gresham & Elliott, 1990) – Externalising, Internalising, and Problem Behaviours subscales • Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) – Externalizing scale • VABS – Maladaptive behaviour index

7.2 PSYCHOSOCIAL INTERVENTIONS – BEHAVIOUR THAT CHALLENGES

7.2.1 Studies considered

Thirty-two papers from the search met the eligibility criteria for full-text retrieval. Of these, 13 trials provided relevant clinical evidence and were included in the review. Four of these studies examined the efficacy of psychosocial interventions on behaviour that challenges as a direct outcome (target of intervention), and nine provided data on behaviour that challenges as an indirect outcome. All studies were published in peer-reviewed journals between 2000 and 2012. In addition, 19 studies were excluded from the analysis. The most common reasons for exclusion were that group allocation was non-randomised or the study was a systematic review with no new useable data and any meta-analysis results were not appropriate to extract. Further information about both included and excluded studies can be found in Appendix 12c.

One animal-based intervention study examined indirect effects on behaviour that challenges (BASS2009[46]).

One behavioural intervention study examined effects on behaviour that challenges as a direct outcome (CARR2006 [Carr & Blakeley-Smith, 2006]), and one study examined indirect effects of a behavioural intervention on behaviour that challenges (SMITH2000[47] [Smith et al., 2000]).

Two studies examined effects of a cognitive-behavioural intervention on behaviour that challenges, one as a direct outcome of the intervention (SOFRONOFF2007 [Sofronoff et al., 2007]), and one as an indirect outcome (CHALFANT2007[48] [Chalfant et al., 2007]).

Two parent training studies examined effects on behaviour that challenges as a direct outcome (AMAN2009 [one trial reported across three papers: Aman et al., 2009; Arnold et al., 2012; Scahill et al., 2012]; SOFRONOFF2004 [Sofronoff et al., 2004]), and two studies examined indirect effects of a parent training intervention on behaviour that challenges (RICKARDS2007[49] [one trial reported across two papers: Rickards et al., 2007; Rickards et al., 2009]; TONGE2006[50] [one trial reported across two papers: Tonge et al., 2006; Tonge et al., 2012]).

Finally, four studies examined effects of social-communication interventions on behaviour that challenges as an indirect outcome (FRANKEL2010, LAUGESON2009, LOPATA2010, OWENS2008[51]).

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[46] See Chapter 6, Section 6.2.5, for direct outcomes from BASS2009.
[47] See Chapter 8, Section 8.2.3, for direct outcomes from SMITH2000.
[48] See Chapter 8, Section 8.7.3, for direct outcomes from CHALFANT2007.
[49] See Chapter 8, Section 8.2.3, for direct outcomes from RICKARDS2007.
[50] See Chapter 9, Section 9.2.2, for direct outcomes from TONGE2006.
[51] See Section 6.2.5 for direct outcomes from FRANKEL2010, LAUGESON2009, LOPATA2010 and OWENS2008.

7.2.2 Clinical evidence – effect of psychosocial interventions on behaviour that challenges

Animal-based intervention for behaviour that challenges as an indirect outcome

The animal-based intervention trial (BASS2009) compared horseback riding intervention with waitlist control in children with autism (see Table 32). See Section 7.2.1for further details of the intervention.

Table 128: Study information table for included trial of animal-based intervention for behaviour that challenges

	Horseback riding versus waitlist control
No. trials (N)	1 (34)
Study IDs	BASS2009
Study design	RCT
% female	15
Mean age (years)	7.3
IQ	Not reported
Dose/intensity (mg/hours)	12 hours (1 hour/week)
Setting	Equestrian training centre
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of horseback riding on behaviour that challenges and the quality of evidence for each outcome are presented in Table 129. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 129: Evidence summary table for effects of animal-based intervention on behaviour that challenges as an indirect outcome

	Horseback riding versus waitlist control	
Outcome	Inattention/distractibility	Sedentary
Outcome measure	Sensory Profile: Inattention/distractibility	Sensory Profile: Sedentary
Study ID	BASS2009	
Effect size (CI; p value)	SMD 1.20 (0.46, 1.94; p = 0.002)	SMD 1.14 (0.40, 1.88; p = 0.002)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2,3]	
Number of studies/participants	K = 1; N = 34	
Forest plot	1.10.1; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as not all subscales that measure behaviour that challenges are reported, for instance, data are missing for the emotionally reactive subscale.

There was single-study evidence for large and statistically significant effects of horseback riding on behaviour that challenges as an indirect outcome as measured by the Inattention and Sedentary subscales of the Sensory Profile (see Table 129). However, the quality of the evidence was downgraded to very low due to risk of bias concerns (non-blind parent-rated outcome assessment), small sample size and high risk of selective reporting bias (results were not reported for all behaviour that challenges outcome measure subscales).

Behavioural interventions for behaviour that challenges as a direct or indirect outcome

One of the behavioural intervention trials (CARR2006) compared behavioural and medical intervention with medical intervention only in children with autism, and the other included behavioural intervention trial compared EIBI with parent training (see Table 130). In CARR2006, the intervention was aimed at addressing the problem of escape motivated problem behaviour associated with illness. Consistent with the school protocol for illness, children in both the experimental and control groups were taken to the school nurse to receive medical treatment for discomfort or pain. However, children in the experimental group also received a behavioural intervention to target illness-related problem behaviour. Behavioural intervention strategies included: behavioural momentum (Mace et al., 1988; defined as beginning an academic session with a mastered task and then interspersing two to four non-mastered tasks between successive presentations of the mastered tasks); increased choice of and access to reinforcement (Dyer et al., 1990; defined as presenting the student with four to six reinforcers to choose from rather than a single one as was typical and reducing the number of correct responses required to access reinforcement by 30% to 50%); and escape extinction and prompts (Carr et al., 1980; defined as maintaining the presentation of academic demands even after the occurrence of problem behaviour and not allowing the student to escape from completing the task and providing an imitative, gestural or physical prompt to ensure correct responding). In SMITH2000 children received EIBI based on Lovaas and colleagues' (1981) manual and the principles of ABA. The intervention began with one-to-one, discrete trial, treatment delivered by a student therapist in the child's home and with parental involvement. Treatment progressed gradually from relatively simple tasks (for example, responding to basic requests made by an adult) to more complex tasks (such as conversing). Once the child had achieved certain behavioural criteria (speaking in short phrases; cooperating with verbal requests from others; playing appropriately with toys; and had acquired self-care skills such as dressing and toileting) the intervention was implemented away from the home and in group settings such as classrooms. This shift usually occurred approximately 1 year after onset of intervention but there was large variation across children. The control group in SMITH2000 also received an active intervention, parent training. Parent training was also based on Lovaas and colleagues' (1981) manual and parents were trained in the basic principles of discrimination learning, discrete trial formats and functional analyses of maladaptive behaviours and applied these techniques to help their children acquire parent-identified skills.

Table 130: Study information table for included trials of behavioural interventions for behaviour that challenges

	Behavioural and medical intervention versus medical intervention only	**EIBI versus parent training**
No. trials (N)	1 (22)	1 (28)
Study IDs	CARR2006	SMITH2000
Study design	RCT	RCT
% female	14	18
Mean age (years)	7.3	3.0
IQ	Not reported	51 (assessed using the Stanford-Binet Intelligence scale or Bayley Scales of Infant Development)
Dose/intensity (mg/hours)	Variable (intervention was delivered in response to illness-related problem behaviour)	**Experimental group**: 2,137 (intensive treatment was defined as 30 hours/week but the actual intervention intensity was 15 hours/week) **Control group**: No mean reported (range 65-195). Children's families received two sessions per week of parent training, totalling 5 hours per week.
Setting	Educational (school)	Home-based (and educational for the experimental group)
Length of treatment (weeks)	43	**Experimental group**: 145 **Control group**: 39
Continuation phase (length and inclusion criteria)	43 (follow-up for waitlist control group was 56 weeks as the intervention was delivered in the post-treatment period)	Up to 260 (follow-up evaluations occurred when children were aged 7-8 years)

Evidence for the effectiveness of behavioural interventions on behaviour that challenges and the quality of evidence for each outcome are presented in Table 131 and Table 132. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 131: Evidence summary table for effects of behavioural intervention (behavioural and medical) on behaviour that challenges as a direct outcome

	Behavioural and medical intervention versus medical intervention only
Outcome	Illness-related problem behaviour
Outcome measure	Problem Behavior Questionnaire: Most serious problem behaviours
Study ID	CARR2006
Effect size (CI; p value)	SMD -1.65 (-2.64, -0.66; p = 0.001)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 21

Forest plot	1.10.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors were non-blind and the outcome measure was designed specifically for the study and as such lacked formal assessments of reliability and validity. [2]Downgraded due to serious imprecision as N <400.	

Table 132: Evidence summary table for effects of behavioural intervention (EIBI) on behaviour that challenges as a direct outcome

	EIBI versus parent training
Outcome	Aggression
Outcome measure	Achenbach CBCL: Aggression (1) Parent-rated (2) Teacher-rated
Study ID	SMITH2000
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.36 (-1.10, 0.39; p = 0.35) (2) *Teacher-rated* SMD 0.47 (-0.28, 1.23; p = 0.22)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 28
Forest plot	1.10.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure was non-blind parent- or teacher- completed checklist and checklist was not validated in autism population. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was evidence from a single small study for a large effect of a combined behavioural and medical intervention (relative to a medical intervention only) for illness-related problem behaviour (see Table 131). However, the quality of this evidence was low due to risk of bias concerns (non-blind outcome assessment) and small sample size.

There was no evidence for statistically significant effects of EIBI (relative to parent training) on aggression as measured by the parent- or teacher- rated Achenbach CBCL (see Table 132).

Cognitive-behavioural interventions for behaviour that challenges as a direct or indirect outcome

The two included cognitive-behavioural intervention trials (CHALFANT2007, SOFRONOFF2007) compared CBT with waitlist control (see Table 133). In SOFRONOFF2007 the target of the intervention was anger management and the CBT involved group discussion, practice opportunities, the concept of an 'emotional tool box' and social stories and homework assignments to explore positive emotions, feelings of anger, and strategies for 'fixing the feeling' for anger management including taking a break, expending energy in another way, relaxation, thinking about how other people can help and thinking through the consequences of anger. The intervention also included 'parent groups' where parents were taken through

what their children were learning in the intervention and were encouraged to help their child with homework assignments. In CHALFANT2007, the 'Cool Kids' programme (Lyneham et al., 2003) was adapted to meet the needs of children with autism and then applied to target components of anxiety. Topics included recognising the physical symptoms of anxiety, using coping skills such as 'self-talk', simple cognitive restructuring exercises and relapse prevention. Some sessions incorporated the families and involved planning weekly exposure tasks and parents were offered additional sessions and provided with a manual to support their child's learning. Autism-specific adaptations were made to the CBT programme in CHALFANT2007 including: extending the intervention over a longer period of time (6 months); using more visual aids and structured worksheets; devoting the most time to relaxation components (three treatment sessions and two booster sessions) and exposure (four and a half treatment sessions and all booster sessions) because they involve more concrete exercises and place less emphasis on the children's communication skills; simplifying the information included in the cognitive therapy component (one and a half treatment sessions and two booster sessions) and providing children with large lists of possible alternative responses to assist them when required to generate their own helpful and unhelpful thoughts. CHALFANT2007 examined indirect effects on behaviour that challenges of this intervention that was targeted at coexisting anxiety (see Section 8.7.3 for direct effects of intervention).

Table 133: Study information table for included trials of cognitive-behavioural interventions for behaviour that challenges

	CBT versus waitlist control
No. trials (N)	2 (103)
Study IDs	(1) CHALFANT2007 (2) SOFRONOFF2007
Study design	(1)-(2) RCT
% female	(1) 26 (2) 4
Mean age (years)	(1)-(2) 10.8
IQ	(1) Not reported (2) 106.9 (assessed using WISC-III Short-form)
Dose/intensity (mg/hours)	(1) Planned intensity of 24 hours (2 hours/week) (2) Planned intensity of 12 hours (2 hours/week)
Setting	(1) Clinical (no further information reported) (2) Not reported
Length of treatment (weeks)	(1) 12 (2) 6
Continuation phase (length and inclusion criteria)	(1) 12 (2) 12 (including 6-week post-intervention follow-up)

Evidence for the effectiveness of cognitive-behavioural interventions on behaviour that challenges and the quality of evidence for each outcome are presented in Table 134. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 134: Evidence summary table for effects of cognitive-behavioural interventions on behaviour that challenges as a direct or indirect outcome

	CBT versus waitlist control		
Outcome	Anger management (direct outcome)		Hyperactivity and conduct problems (indirect outcome)
Outcome measure	Parent reported instances of child anger at: (1) Post-intervention (2) 6-week follow-up	Parent-reported confidence in their child managing their own anger at: (1) Post-intervention (2) 6-week follow-up	SDQ: Externalising scale (1) Parent-rated (2) Teacher-rated
Study ID	SOFRONOFF2007		CHALFANT2007
Effect size (CI; p value)	(1) *Post-intervention* SMD -0.92 (-1.54, -0.30; p = 0.004) (2) *6-week follow-up* SMD -1.03 (-1.65, -0.40; p = 0.001)	(1) *Post-intervention* SMD 0.61 (0.00, 1.21; p = 0.05) (2) *6-week follow-up* SMD 1.10 (0.47, 1.74; p = 0.0006)	(1) *Parent-rated* SMD-0.62 (-1.22, -0.03; p = 0.04) (2) *Teacher-rated* SMD -0.62 (-1.21, -0.02; p = 0.04)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2,3]		(1) Low[1,2] (2) Low[2,4]
Number of studies/participants	K = 1; N = 45		K = 1; N = 47
Forest plot	1.10.3; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure parent-rated and parents were non-blind.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for the Children's Inventory of Anger – Parent Form as no measure of variability is reported.
[4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as teacher-rated and blinding of teachers is not reported.

There was evidence from a small single study for moderate to large effects of CBT on anger management as a direct outcome as measured by study-specific parent monitoring of instances of child anger (over a week) and parent-reported confidence in their child managing their own anger (see Table 134). However, the quality of the evidence was very low due to risk of bias concerns (non-blind outcome assessment), small sample size, and selective reporting bias (data could not be extracted for the Children's Inventory of Anger – Parent Form scale). There was also evidence from another small study for moderate effects of CBT on hyperactivity and conduct problems as measured by the parent- and teacher-rated SDQ externalising scale (see Table 134). However, the quality of this evidence was downgraded to low due to risk of bias concerns (non-blind outcome assessment or unclear blinding of outcome assessors) and small sample size.

Parent training for behaviour that challenges as a direct or indirect outcome

Two of the included parent training intervention trials compared parent training with treatment as usual, one of which examined effects on behaviour that challenges as a direct outcome (SOFRONOFF2004) and one as an indirect outcome (TONGE2006). One of the parent training intervention studies compared parent training and an antipsychotic with an antipsychotic only (AMAN2009), and one of the trials compared parent training and early intervention centre programme with early intervention centre programme only (RICKARDS2007) (see Table 135).

SOFRONOFF2004 was a three-armed trial that included two active intervention arms involving the same intervention content but in different formats. In one group the parent training was delivered in a 1-day group workshop and in the other arm the same parent training content was delivered in individual therapist–parent sessions over 6 weeks. The parent training consisted of six components (and in the individual sessions group these were delivered in a one component/week format): psychoeducation (through video demonstration and discussion the nature of Asperger's syndrome, the heterogeneity of the disorder and the importance of considering the child's perspective in problem situations were outlined and parents were encouraged to give examples of aspects of the disorder affecting their own child); Comic Strip Conversations (using simple drawings to illustrate a conversation between two people and to emphasise what the people may be thinking; Gray, 1994a); Social Stories (using a short story specifically for a target child in order to illustrate a particular situation including social cues, anticipated actions and information on what is occurring and why; Gray, 1994b); management of problem behaviours (parents were introduced to common problem behaviours for children with Asperger's syndrome, including interrupting, temper tantrums, anger, non-compliance and bedtime problems, and techniques for dealing with these problems were outlined); management of rigid behaviours and special interests (the focus of this component was to emphasise the importance of parents understanding the rigid or repetitive behaviour from their child's perspective in order to understand why their child has a need for routines and also as a potential way of using a special interest as a reward); and management of anxiety (parents were taught that problem behaviours were often the result of anxiety and the importance for parents to recognise and address their child's anxiety were emphasised as a means of not just treating but also preventing anxiety-inducing situations). The two active intervention arms were initially compared and where there were no significant differences the groups were combined and entered into meta-analysis. Where there was a significant difference between active intervention arms the data from each active intervention arm (relative to treatment as usual) was entered into the meta-analysis as subgroups (with the subtotal function disabled).

TONGE2006 examined effects of the 'Preschoolers with Autism' (Brereton & Tonge, 2005) programme relative to treatment as usual on overall autistic behaviours as an indirect outcome. This study also included two active intervention arms, the parent education and behaviour management (PEBM) training intervention and the PEC

intervention. Intervention consisted of both small group parent training sessions and individual family sessions. Group sessions (for both PEBM and PEC) included: education about autism; features of communication, social, play, and behavioural impairments; principles of managing behaviour and change; teaching new skills; improving social interaction and communication; services available; managing parental stress, grief and mental health problems; and sibling, family and community responses to autism. The key 'active' ingredient which differed between PEBM and PEC intervention arms was that in the PEBM individual family sessions the parents were provided with workbooks, modelling, videos, rehearsal (with child when present), homework tasks and feedback, while for the PEC intervention although the educational material in the manual was the same no skills training or homework tasks were set for the individual sessions and the emphasis was on non-directive interactive discussion and counselling. Initially the two active intervention arms (PEBM and PEC) were compared and there were no statistically significant difference between the two arms for behaviour that challenges so data from the two groups were combined and compared with treatment as usual.

AMAN2009 examined effects of parent training as an adjunct to antipsychotics on behaviour that challenges. In this trial, both experimental and control groups received risperidone (or aripiprazole if risperidone was ineffective). In addition, the experimental group received a parent training intervention delivered by a behaviour therapist. Parent training was based on the RUPP manual (Scahill et al., 2009) and involved seven to nine weekly 60- to 90-minute sessions where parents were taught to use preventative approaches (for example, visual schedules), and were instructed in the effective use of positive reinforcement, and in strategies for teaching compliance, functional communication skills and specific adaptive skills. Parent training teaching techniques included direct instruction, use of video vignettes, practice activities, behaviour rehearsal with feedback, role-playing, and individualised homework assignments.

Finally, in RICKARDS2007 both experimental and control group children participated in an early intervention centre programme that involved individualised programmes that covered all aspects of development. Training techniques used for the centre-based programmes included chaining, repetition, reward, play-based learning, communication systems (such as PECS), behaviour modification techniques, speech and language and occupational therapy. The experimental group also received an additional home-based parent training intervention. Behavioural targets for the parent training intervention were jointly agreed between the family and intervention administrators and the home-based teacher worked with the child, discussed strategies (similar to those used in the centre) and helped the parents to understand the meaning of the child's challenging behaviour, demonstrated strategies to parents, and assisted parents in adapting the home environment for the needs of the child, for instance, the use of communication aids. The sample of children in RICKARDS2007 included both children with autism (66%), children with developmental delay (15%) and children with language delay (19%). For the most part the data were reported for the mixed autism and developmental/language

disabilities sample. However, for one outcome measure disaggregated (autism-only) data were available and were extracted.

Table 135: Study information table for included trials of parent training for behaviour that challenges

	Parent training versus treatment as usual	Combined parent training and antipsychotic versus antipsychotic-only	Combined parent training and early intervention centre programme versus early intervention centre programme only
No. trials (N)	2 (156)	1 (124)	1 (65)
Study IDs	(1) SOFRONOFF2004 (2) TONGE2006	AMAN2009	RICKARDS2007
Study design	(1)-(2) RCT	RCT	RCT
% female	(1) Not reported (2) 16	Not reported	20
Mean age (years)	(1) 9.3 (2) 3.9	7.4	3.7
IQ	(1) Not reported (2) 59.2 (assessed using the PEP-R – developmental quotient)	Not reported (19% mild LD; 24% moderate LD)	60.4 (test not reported)
Dose/intensity (mg/hours)	(1) Planned intensity of 1 day (6 hours) for the workshop group and 6 hours over 6 weeks (1 hour/week) for the individual sessions group (2) 25 hours (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions)	Experimental intervention: Risperidone (or aripiprazole) 0.5-3.5 mg/day (mean: 2 mg/day) and 10.8 60-90-minute sessions for parent training Control intervention: Risperidone (or aripiprazole) 0.5-3.5 mg/day (mean: 2.3 mg/day)	Planned intensity for centre-based programme of 200 hours (5 hours/week). Actual number of sessions, rather than number of hours, was reported for the additional parent training intervention but number of hours was estimated and the estimated intensity for the additional parent training component was 43.5 hours, and total hours of intervention for the experimental group was 243.5 hours
Setting	(1) University clinic (2) Not reported	Not reported	Early intervention centre and home-based
Length of treatment (weeks)	(1) 1 day for workshop group and 6 weeks for individual sessions group (2) 20	24	40 (over 12-month period)

Continuation phase (length and inclusion criteria)	(1) 19 weeks (including intervention ranging from 1 day to 6 weeks, followed by a 4-week post-intervention assessment and a 3-month follow-up) (2) 46 (including 6-month post-intervention follow-up)	54-162.5 weeks (mean: 80 weeks; including 1-year post-intervention follow-up)	108 (including post-intervention assessment at 13 months and 12-month post-intervention follow-up assessment)

Evidence for the effectiveness of parent training on behaviour that challenges and the quality of evidence for each outcome are presented in Table 136, Table 137and Table 138. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 136: Evidence summary table for effects of parent training on behaviour that challenges as a direct or indirect outcome

	Parent training versus treatment as usual		
Outcome	Frequency of problem behaviours (direct outcome)	Intensity of problem behaviours (direct outcome)	Problem behaviour (indirect outcome)
Outcome measure	ECBI: Number of problem behaviours at: (1) Post-intervention (2) 3-month follow-up	ECBI: Intensity of problem behaviours: (1) Individual sessions at post-intervention (2) Individual sessions at 3-month follow-up (3) Workshop at post-intervention (4) Workshop at 3-month follow-up	DBC: total Behaviour Problem Score
Study ID	SOFRONOFF2004		TONGE2006
Effect size (CI; p value)	(1) *Post-intervention* SMD -1.26 (-1.91, -0.61; p = 0.0002) (2) *3-month follow-up* SMD -1.23 (-1.88, -0.58; p = 0.0002)	(1) *Individual sessions at post-intervention* SMD -1.41 (-2.18, -0.63; p = 0.0004) (2) *Individual sessions at 3-month follow-up* SMD -1.35 (-2.12, -0.59; p = 0.0006) (3) *Workshop at post-intervention* SMD -0.60 (-1.30, 0.10; p = 0.09) (4) *Workshop at 3-month follow-up* SMD -0.59 (-1.30, 0.11; p = 0.10)	SMD -0.35 (-0.76, 0.06; p = 0.10)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1,2]	(1)-(2) Low[1,2] (3)-(4) Very low[1,3]	Very low[1,3]
Number of studies/participants	K = 1; N = 51	K = 1; N = 33	K = 1; N = 103

Forest plot	1.10.4; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance bias as intervention administrators were non-blind, and high risk of detection bias as outcome assessors were non-blind parents who were involved in the intervention. [2]Downgraded due to serious imprecision as N <400. [3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was evidence from a single small study (SOFRONOFF2004) for large effects of a parent training intervention (individual sessions and workshop groups combined) on the frequency of problem behaviours as measured by the ECBI at post-intervention and 3-month post-intervention follow-up (see Table 136). The two active intervention arms were combined for this outcome measure as an initial comparison between the two active intervention arms (individual sessions versus workshop) revealed no statistically significant difference for frequency of problem behaviours (post-intervention SMD 0.46 [-0.20, 1.12], test for overall effect: Z = 1.36, p = 0.17; 3-month follow-up SMD 0.62 [-0.05, 1.29], test for overall effect: Z = 1.81, p = 0.07). However, for the intensity of problem behaviours outcome, there was a statistically significant difference between individual sessions and workshop formats which favoured the former (post-intervention SMD 0.85 [0.16, 1.53], test for overall effect: Z = 2.42, p = 0.02; 3-month follow-up SMD 1.07 [0.36, 1.77], test for overall effect: Z = 2.97, p = 0.003). Therefore, the intervention arms could not be combined and were each compared with treatment as usual. This subgroup analysis revealed evidence for large and statistically significant effects of parent training delivered in individual sessions (but non-significant effects for the workshop format) on the intensity of problem behaviours as measured by the ECBI at post-intervention and 3-month follow-up (see Table 136). However, the confidence in the effect estimates for the significant treatment effects on frequency and intensity of problem behaviours was low due to risk of bias concerns (non-blind parent-rated outcome measures) and small sample size. Another larger study (TONGE2006) also failed to find significant treatment effects of parent training (PEBM and PEC groups combined) on problem behaviours as measured by the DBC (see Table 136). The two active intervention arms were combined for this outcome measure as an initial comparison between them (PEBM and PEC) revealed no statistically significant difference (SMD -0.19 [-0.67, 0.28]; test for overall effect: Z = 0.79, p = 0.43).

Table 137: Evidence summary table for effects of parent training (as an adjunct to antipsychotics) on behaviour that challenges as a direct outcome

	Combined parent training and antipsychotic versus antipsychotic-only						
Outcome	Noncompliant behaviour in everyday circumstances		Irritability	Lethargy/Social withdrawal	Stereotypic behaviour	Hyperactivity/ Non-compliance	Inappropriate speech
Outcome measure	Home Situations Questionnaire: Severity at: (1) Post-intervention (2) 1-year follow-up	Study-specific non-compliance index based on VABS Daily living skills	ABC-Irritability at: (1) Post-intervention (2) 1-year follow-up	ABC Lethargy/Social Withdrawal at: (1) Post-intervention (2) 1-year follow-up	ABC Stereotypic behaviour at: (1) Post-intervention (2) 1-year follow-up	ABC Hyperactivity/ Non-compliance at: (1) Post-intervention (2) 1-year follow-up	ABC Inappropriate speech at: (1) Post-intervention (2) 1-year follow-up
Study ID	AMAN2009						
Effect size (CI; p value)	(1) SMD -0.33 (-0.74, 0.08; p = 0.12) (2) SMD -0.17 (-0.60, 0.26; p = 0.44)	*Post-intervention* SMD -0.46 (-0.83, -0.10; p = 0.01)	(1) SMD -0.43 (-0.85, -0.02; p = 0.04) (2) SMD -0.33 (-0.75, 0.10; p = 0.14)	(1) SMD -0.36 (-0.77, 0.06; p = 0.09) (2) SMD -0.46 (-0.89, -0.03; p = 0.04)	(1) SMD -0.63 (-1.04, -0.21; p = 0.003) (2) SMD -0.35 (-0.78, 0.08; p = 0.11)	(1) SMD -0.48 (-0.89, -0.07; p = 0.02) (2) SMD -0.13 (-0.56, 0.29; p = 0.54)	(1) SMD -0.23 (-0.63, 0.18; p = 0.28) (2) SMD 0.02 (-0.41, 0.44; p = 0.94)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Very low[1,2]	Low[1,3]	(1) Low[1,3] (2) Very low[1,2]	(1) Very low[1,2] (2) Low[1,3]	(1) Low[1,3] (2) Very low[1,2]		(1) Very low[1,2] (2) Low[1,3]
Number of studies/participants	(1) K = 1; N = 95 (2) K = 1; N = 87	K = 1; N = 124	(1) K = 1; N = 95 (2) K = 1; N = 87				
Forest plot	1.10.4; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure based on interview with parents who were non-blind. Also high risk of attrition bias due to higher dropout rates in the experimental (combined risperidone and parent training) group (N = 20; 27% attrition) than the control (risperidone only) group (N = 9; 18% attrition).
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded due to serious imprecision as N <400.

There was inconsistent evidence for effects of parent training (as an adjunct to antipsychotics) on noncompliant behaviour in everyday circumstances with a small and statistically significant effect as measured by the study-specific noncompliance index (based on the VABS Daily Living Skills subscale) but a non-significant effect observed for the Home Situations Questionnaire at post-intervention and 1-year follow-up (see Table 137). There were also mixed results for behaviour that challenges as measured by the ABC with small to moderate statistically significant but transient effects (significant at post-intervention but not 1-year follow-up) observed for the Irritability, Stereotypic Behaviour and Hyperactivity subscales, a small statistically significant but delayed effect (significant at 1-year follow-up but not post-intervention) for the Lethargy subscale and non-significant effects at both post-intervention and 1-year follow-up observed for the Inappropriate Speech subscale (see Table 137). The confidence in the effect estimates for statistically significant positive treatment effects was low due to risk of bias concerns (non-blind parent-rated outcome assessment and higher attrition rate in the experimental group) and small sample size.

Table 138: Evidence summary table for effects of parent training (as an adjunct to early intervention centre programme) on behaviour that challenges as an indirect outcome

	Combined parent training and early intervention centre programme versus early intervention centre programme only	
Outcome	Parent-reported behaviour that challenges	Teacher-rated behaviour that challenges
Outcome measure	BSQ: total (1) Post-intervention (mixed autism and developmental disabilities/LD sample) (2) 12-month follow-up (mixed autism and developmental disabilities/LD sample)	Preschool Behavior Checklist: total (1) Post-intervention (mixed autism and developmental disabilities/LD sample) (2) Post-intervention (autism-only sample) (3) 12-month follow-up (mixed autism and developmental disabilities/LD sample)
Study ID	RICKARDS2007	
Effect size (CI; p value)	(1) *Post-intervention (mixed autism and developmental disabilities/LD sample)* SMD -0.02 (-0.54, 0.49; p = 0.93) (2) *12-month follow-up (mixed autism and developmental disabilities/LD sample)* SMD -0.16 (-0.71, 0.40; p = 0.58)	(1) *Post-intervention (mixed and developmental disabilities/LD sample)* SMD -0.67 (-1.23, -0.12; p = 0.02) (2) *Post-intervention (autism-only sample)* SMD -0.98 (-1.69, -0.26; p = 0.008) (3) *12-month follow-up (mixed autism and developmental disabilities/LD sample)* SMD -0.11 (-0.68, 0.47; p = 0.72)
Heterogeneity (chi²; p value; I2)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2,3]	(1) Very low[2,4,5] (2) Low[4,5] (3) Very low[2,3,4]

Number of studies/participants	(1) K = 1; N = 58 (2) K = 1; N = 50	(1) K = 1; N = 53 (2) K = 1; N = 34 (3) K = 1; N = 46
Forest plot	1.10.4; Appendix 13	
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as although there was a blinded psychologist outcome assessor this outcome measure relied on non-blind parental report. [2]Downgraded due to serious indirectness as the population was indirect (as the sample included participants with developmental delay or language delay without autism). [3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [4]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors were non-blind teachers. [5]Downgraded due to serious imprecision as N <400.		

There was evidence for non-significant effects of parent training (as an adjunct to an early intervention centre programme) on parent-reported behaviour that challenges (for the mixed autism and developmental disabilities/learning disabilities sample) as measured by the BSQ at post-intervention and 12-month post-intervention follow-up (see Table 138). Conversely, there was evidence for moderate to large effects of parent training on teacher-rated behaviour that challenges for both the mixed autism and developmental disabilities sample, and for the autism-only subgroup, at post-intervention. However, this effect was transient and was non-significant at 12-month follow-up (see Table 138). The quality of the evidence was also low to very low due to risk of bias concerns (non-blind outcome assessment) and small sample size.

Social-communication interventions for behaviour that challenges as an indirect outcome

Three of the included social-communication intervention trials examined indirect effects of social skills groups relative to treatment as usual on behaviour that challenges (FRANKEL2010, LAUGESON2009, LOPATA2010). The fourth included social-communication intervention trial compared LEGO® therapy with the SULP (OWENS2008) (see Table 139).

The specific models of social skills group intervention were variable but the content and target of interventions were comparable. See Chapter 6 for direct effects of social skills group interventions. In FRANKEL2010 the parent-assisted CFT (Frankel & Myatt, 2003) intervention taught social skills in terms of rule-based procedures using techniques including instruction, modelling, rehearsal and performance feedback. Homework assignments were also used to try and increase generalisation, including calling another member of the class, parent-supported play dates, and practicing 'making fun of the teasing' with a child who was teasing them. Children and parents were seen at the same time in separate sessions and the aim of the parent sessions was to increase generalisation through training in the organisation and implementation of play dates. LAUGESON2009 tested a very similar intervention but with specific adaptations to the manual to be appropriate for adolescents. In this modified intervention trial (Program for the Education and Enrichment of Relational

Skills social skills group), concurrent parent and teen sessions addressed: reciprocal conversational skills (and how parents could identify activities which might lead to potential friendships); appropriate use of electronic communication in developing pre-existing friendships (and parents taught the social structure of school peer groups); how to choose appropriate friends by pursuing extracurricular activities and identifying groups they might fit in with; how to join (and exit) conversations with peers; how to organise and host a get-together with friends; how to be a good sportsman during games and sports; strategies for handling teasing and bullying appropriately and for changing a bad reputation; and strategies for handling disagreements with peers. Each session involved didactic instruction, role-play by the intervention administrators of the appropriate social skill, rehearsal of the social skill by the teen with accompanying performance feedback, and a homework assignment for the next session (parents were instructed on how to overcome obstacles associated with their child completing the upcoming homework assignment). Finally, the social skills group intervention (Lopata et al., 2008) examined in LOPATA2010 also involved a parent training component and was delivered to children (grouped by age). Targeted outcomes were social skills, emotion recognition and interpretation of non-literal language and teaching techniques included direct instruction, modelling, role play, performance feedback, team-working to complete task or solve problem, a response-cost reinforcement system, and homework assignments. The weekly concurrent parent training sessions focused on increasing understanding of autism and of the intervention that their child was taking part in, and on teaching parents strategies to encourage generalisation.

In OWENS2008 the experimental intervention involved collaborative LEGO play in pairs or small groups (based on a draft manual produced by Dr LeGoff). Typical projects included building a LEGO set in groups of three with each member of the group assigned a different role (for instance, 'engineer', 'supplier' and 'builder') and 'freestyle' LEGO activities in which children designed and built a model in pairs (for instance, a space rocket). The former project type aimed to target joint attention, turn taking, sharing, joint problem solving, listening and general social communication skills. While, the 'freestyle' projects aimed to teach compromise, clear expression of ideas and taking other people's perspectives and ideas into account. During the intervention children were asked to follow 'LEGO Club Rules', which included: 'Build things together'; 'If someone else is using it, don't take it, ask first'; 'Use indoor voices-no yelling'; and 'Use polite words'. The therapists role was to highlight the presence of a problem and help children to come up with their own solutions (or remind them of strategies which they had previously used) rather than pointing out specific social problems or solutions. In this study, the control group also received an active intervention, SULP (Rinaldi, 2004). This control intervention used a direct group-based teaching approach (following the SULP manual) to target eye contact, listening, turn taking, proxemics and prosody. Instruction followed a specified framework, beginning with stories about monster characters who experienced problems with particular social or communication skills, moved on to

asking the children to evaluate adult models of good and bad skills, and finally children practiced the targeted skill through games and conversation.

Table 139: Study information table for included trials of social-communication interventions for behaviour that challenges

	Social skills group versus treatment as usual	LEGO therapy versus SULP
No. trials (N)	3 (148)	1 (31)
Study IDs	(1) FRANKEL2010 (2) LAUGESON2009 (3) LOPATA2010	OWENS2008
Study design	(1)-(3) RCT	RCT
% female	(1) 15 (2) 15 (3) 6	3
Mean age (years)	(1) 8.5 (2) 14.6 (3) 9.5	8.2
IQ	(1) Verbal IQ: 103.8 (assessed using the WISC-III) (2) Verbal IQ: 92.3 (assessed using KBIT-2) (3) 103 (assessed using the WISC-IV Short form)	110.5 (IQ test not reported)
Dose/intensity (mg/hours)	(1) 11.3 (2) Planned intensity of 18 hours (1.5 hours/week) (3) Planned intensity of 204 hours (41 hours/week, consisting of 5 1.2 hour-sessions a day every day for 5 weeks)	Planned intensity of 18 hours (1 hour/week)
Setting	(1) Outpatient (2) Outpatient (3) College campus	Educational (school)
Length of treatment (weeks)	(1) 12 (2) 12 (3) 5	18
Continuation phase (length and inclusion criteria)	(1) 24 (including 12-week post-intervention follow-up for the experimental group and 12-week intervention for the waitlist control group) (2) 24 (12-week intervention and waitlist control period followed by 12 weeks active intervention for the waitlist control) (3) 6 (post-intervention assessments completed during the 5 days following treatment)	18

Evidence for the effectiveness of parent training on behaviour that challenges and the quality of evidence for each outcome are presented in Table 140 and Table 141. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 140: Evidence summary table for effects of social-communication interventions (social skills group) on behaviour that challenges as an indirect outcome

	Social skills group versus treatment as usual		
Outcome	Conflict	Intrusive/aggressive behaviour	Social withdrawal
Outcome measure	QPQ: Conflict (1) Parent-rated (2) Self-rated	(1) Parent-rated SSRS: Externalising or Problem Behaviours subscales (2) Teacher-rated Pupil Evaluation Inventory: Aggression	(1) Parent-rated SSRS: Internalising or BASC-2-PRS: Withdrawal (2) Teacher-rated Pupil Evaluation Inventory: Withdrawal
Study ID	(1) FRANKEL2010 LAUGESON2009 (2) LAUGESON2009	(1) FRANKEL2010 LAUGESON2009 (2) FRANKEL2010	(1) FRANKEL2010 LOPATA2010 (2) FRANKEL2010
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.60 (-1.01, -0.18; p = 0.005) (2) *Self-rated* SMD -0.09 (-0.77, 0.59; p = 0.79)	(1) *Parent-rated* SMD -0.78 (-1.19, -0.37; p = 0.0002) (2) *Teacher-rated* SMD -0.24 (-0.75, 0.28; p = 0.37)	(1) *Parent-rated* SMD -0.68 (-1.08, -0.28; p = 0.0009) (2) *Teacher-rated* SMD -0.04 (-0.55, 0.47; p = 0.87)
Heterogeneity (chi²; p value; I²)	(1) Chi² = 0.81, df = 1; p = 0.37; I^2 = 0% (2) Not applicable	(1) Chi² = 1.19, df = 1; p = 0.28; I^2 = 16% (2) Not applicable	(1) Chi² = 4.81, df = 1; p = 0.03; I^2 = 79% (2) Not applicable
Quality of the evidence (GRADE)	(1) Low[1,2] (2) Very low[3,4]	(1) Low[1,2] (2) Very low[4,5]	(1) Very low[1,2,6] (2) Very low[4,5]
Number of studies/participants	(1) K = 2; N = 95 (2) K = 1; N = 33	(1) K = 2; N = 101 (2) K = 1; N = 59	(1) K = 2; N = 104 (2) K = 1; N = 59
Forest plot	1.10.5; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as parent-rated and parents were non-blind and involved in the intervention.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as self-rated.
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as teacher-rated and teachers were non-blind.
[6]Downgraded due to very serious inconsistency as I^2 value suggests considerable to substantial heterogeneity.

There was evidence for moderate and statistically significant effects of social skills groups on parent-rated conflict, intrusive/aggressive behaviour, and withdrawal as measured by the QPQ, SSRS and BASC-2-PRS. However, the effects on self-rated

conflict as measured by the QPQ and teacher-rated aggression and withdrawal as measured by the Pupil Evaluation Inventory were non-significant (see Table 140). Moreover, the confidence in the significant effect estimates was downgraded to low to very low due to risk of bias concerns (non-blind outcome assessment) and small sample size, and in the case of the very low evaluation due to considerable to substantial heterogeneity.

Table 141: Evidence summary table for effects of social-communication interventions (LEGO therapy) on behaviour that challenges as an indirect outcome

	LEGO therapy versus SULP
Outcome	Maladaptive behaviour
Outcome measure	VABS: Maladaptive behaviour index
Study ID	OWENS2008
Effect size (CI; p value)	SMD -0.51 (-1.23, 0.21; p = 0.16)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 31
Forest plot	1.10.5; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and unclear risk of detection bias as although the interviewer was a blinded research assistant, the outcome measure was based on non-blind parent report. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of LEGO therapy (relative to SULP) on maladaptive behaviour as measured by the VABS (see Table 141).

7.2.3 Clinical evidence summary – effect of psychosocial interventions on behaviour that challenges

There was low to very low quality evidence from single studies for significant effects of horseback riding, behavioural intervention, CBT and parent training on behaviour that challenges. The only meta-analysis possible was for social skills groups (two studies) and there was low to very low quality evidence for moderate effects on parent-rated behaviour that challenges.

7.3 PHARMACOLOGICAL INTERVENTIONS – BEHAVIOUR THAT CHALLENGES

7.3.1 Studies considered

Sixty-three papers from the search met the eligibility criteria for full-text retrieval. Of these, 18 RCTs provided relevant clinical evidence and were included in the review. Fifteen of these studies examined the efficacy of pharmacological interventions on behaviour that challenges as a direct outcome (target of intervention), and three provided data on behaviour that challenges as an indirect outcome. All studies were

published in peer-reviewed journals between 1993 and 2012. In addition, 45 studies were excluded from the analysis. The most common reasons for exclusion were that data could not be extracted, the drug was withdrawn from market due to significant safety concerns (in the case of fenfluramine), the sample size was too small (less than ten participants per arm), or the study was a systematic review with no useable data and any meta-analysis not appropriate to extract. Further information about both included and excluded studies can be found in Appendix 12c.

Three trials examined the effects of anticonvulsants on behaviour that challenges as a direct outcome (HELLINGS2005 [Hellings et al., 2005]; HOLLANDER2010, REZAEI2010 [Rezaei et al., 2010]).

One trial examined indirect effects of antidepressants on behaviour that challenges (KING2009[52]).

One trial examined direct effects of antihistamines (as an adjunct to antipsychotics) on behaviour that challenges (AKHONDZADEH2004).

One trial examined effects on behaviour that challenges of antioxidants as a direct outcome (HARDAN2012).

Six trials examined effects of antipsychotics on behaviour that challenges as a direct outcome (JOHNSON&JOHNSON2011, MARCUS2009, OWEN2009 [one trial reported across three papers: Owen et al., 2009; Aman et al., 2010; Varni et al., 2012], RUPPRISPERIDONE2001, SHEA2004 [one trial reported across two papers: Shea et al., 2004; Pandina et al., 2007], TROOST2005 [Troost et al., 2005]), and one trial examined effects of antipsychotics on behaviour that challenges as an indirect outcome (MIRAL2008[53]).

One study examined effects of antivirals on behaviour that challenges as a direct outcome (KING2001 [King et al., 2001]).

One study examined effects of cognitive enhancers (as an adjunct to antipsychotics) on behaviour that challenges as a direct outcome (AKHONDZADEH2008 [Akhondzadeh et al., 2008]).

One study examined effects of methylxanthines (as an adjunct to antipsychotics) on behaviour that challenges as a direct outcome (AKHONDZADEH2010 [Akhondzadeh et al., 2010]).

One trial examined effects of opioid antagonists on behaviour that challenges as a direct outcome (CAMPBELL1993 [Campbell et al., 1993]).

[52] See Chapter 6, Section 6.3.9, for direct outcomes from KING2009.
[53] See Chapter 6, Section 6.3.3, for direct outcomes from MIRAL2008.

Finally, one trial examined indirect effects of selective noradrenaline reuptake inhibitors (SNRIs) on behaviour that challenges (ELILILLY2009[54]).

7.3.2 Clinical evidence – effect of pharmacological interventions on behaviour that challenges

Anticonvulsants for behaviour that challenges as a direct outcome

Two of the included anticonvulsant trials (HELLINGS2005, HOLLANDER2010) compared divalproex with placebo in children with autism, and one (REZAEI2010) compared combined topiramate and risperidone with combined placebo and risperidone (see Table 142).

Table 142: Study information table for included trials of anticonvulsants for behaviour that challenges

	Divalproex versus placebo	Topiramate and risperidone versus placebo and risperidone
No. trials (N)	2 (63)	1 (40)
Study IDs	(1) HELLINGS2005 (2) HOLLANDER2010	REZAEI2010
Study design	(1)-(2) RCT	RCT
% female	(1) 33 (2) 16	33
Mean age (years)	(1) 11.2 (2) 9.5	8.0
IQ	(1) 54 (assessed using variable IQ tests) (2) 63.3 (assessed using the LIPS-R)	Not reported
Dose/intensity (mg/hours)	(1) Final planned dose of 20 mg/kg/day (mean valproic acid through blood levels were 77.8 mcg/mL at week 8) (2) Not reported	Final planned dose of 2-3 mg/day of risperidone (based on weight, 10-40 kg and >40 kg respectively) and 200 mg/day of topiramate
Setting	(1)-(2) Outpatient	Outpatient
Length of treatment (weeks)	(1) 8 (2) 12	8
Continuation phase (length and inclusion criteria)	(1) 8 (2) 12	8

Evidence for the effectiveness of anticonvulsants on behaviour that challenges and the quality of evidence for each outcome are presented in Table 143 and Table 144. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was only one meta-analysis possible for anticonvulsants and this meta-analysis with two studies found evidence for a statistically non-significant effect of divalproex on irritability as measured by the ABC (see Table 143). Single study data

[54] See Chapter 8, Section 8.7.5, for direct outcomes from ELILILLY2009.

also failed to find significant effects of divalproex on irritability as measured by OAS, aggression as measured by OAS total score, or global severity or global improvement as measured by the CGI (see Table 143). There was, however, moderate quality single-study evidence for a statistically significant and large effect of divalproex on a dichotomous measure of positive treatment response for global improvement ('much improved/very improved' on CGI-I) with participants who received divalproex being nearly seven times more likely to show a positive treatment response than participants receiving placebo (see Table 143).

Mixed treatment effects were also observed for topiramate (as an adjunct to risperidone) with moderate quality evidence for large and statistically significant effects on Irritability, Stereotypic Behaviour and Hyperactivity subscales of the ABC, but non-significant effects on Lethargy and Inappropriate Speech subscales (see Table 144).

There was no statistically significant evidence for harms associated with anticonvulsants (see Chapter 10, Section 10.3.2, for adverse events associated with anticonvulsants).

Table 143: Evidence summary table for effects of anticonvulsants (divalproex) on behaviour that challenges as a direct outcome

	Divalproex versus placebo				
Outcome	Irritability	Aggression	Global severity	Global improvement	
Outcome measure	(1) ABC Irritability subscale (2) OAS-M Irritability subscale	OAS: total	CGI-S	CGI-I	Positive treatment response: Number of participants who were 'much improved/very improved' on CGI-I
Study ID	(1) HELLINGS2005 HOLLANDER2010 (2) HOLLANDER2010	HELLINGS2005			HOLLANDER2010
Effect size (CI; p value)	(1) *ABC* SMD -0.43 (-1.21, 0.35; p = 0.85) (2) *OAS* SMD -0.43 (-1.21, 0.35; p = 0.28)	SMD 0.03 (-0.69, 0.75; p = 0.93)	SMD 0.00 (-0.72, 0.72; p = 1.00)	SMD -0.43 (-1.16, 0.29; p = 0.24)	RR 6.87 (1.02, 46.28; p = 0.05)
Heterogeneity (chi2; p value; I^2)	(1) $Chi^2 = 1.71$, df = 1; p = 0.19; $I^2 = 41\%$ (2) Not applicable	Not applicable			
Quality of the evidence (GRADE)	(1) Very low[1,2] (2) Low[2]	Very low[2,3]	Low[2]		Moderate[4]
Number of studies/participants	(1) K = 2; N = 57 (2) K = 1; N = 27	K = 1; N = 30			K = 1; N = 27
Forest plot	1.11.1; Appendix 13				

Note. [1]Downgraded due to serious inconsistency as I^2 value indicates moderate heterogeneity.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both the line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for strongly suspected publication bias – high risk of selective reporting bias as results for the teacher-rated OAS are not reported
[4]Downgraded due to serious imprecision as number of events <300.

Table 144: Evidence summary table for effects of anticonvulsants (as adjunct to antipsychotics) on behaviour that challenges as a direct outcome

	Topiramate and risperidone versus placebo and risperidone
Outcome	Behaviour that challenges
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/Non-compliance (5) Inappropriate Speech
Study ID	REZAEI2010
Effect size (CI; p value)	(1) *Irritability* SMD -1.88 (-2.63, -1.12; p <0.00001) (2) *Lethargy* SMD -0.25 (-0.88, 0.37; p = 0.42) (3) *Stereotypic Behaviour* SMD -2.02 (-2.80, -1.25; p <0.00001) (4) *Hyperactivity* SMD -1.87 (-2.63, -1.12; p <0.00001) (5) *Inappropriate Speech* SMD -0.16 (-0.78, 0.46; p = 0.61)
Heterogeneity (chi2; p value; I^2)	Not applicable
Quality of the evidence (GRADE)	(1) Moderate[1] (2) Low[2] (3)-(4) Moderate[1] (5) Low[2]
Number of studies/participants	K = 1; N = 40
Forest plot	1.11.1; Appendix 13
Note. [1]Downgraded due to serious imprecision as N <400. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both the line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

Antidepressants for behaviour that challenges as an indirect outcome

The one included antidepressant trial (KING2009) compared citalopram with placebo in children with autism (see Table 78).

Table 145: Study information table for included trials of antidepressants for behaviour that challenges

	Citalopram versus placebo
No. trials (N)	1 (149)
Study IDs	KING2009
Study design	RCT
% female	14
Mean age (years)	9.4
IQ	Not reported (58% IQ>70)
Dose/intensity (mg/hours)	Final dose of citalopram 16.5 mg/day; final dose of placebo 18.5 mg/day
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of citalopram on behaviour that challenges and the quality of evidence for each outcome are presented in Table 146. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 146: Evidence summary table for effects of antidepressants on behaviour that challenges as an indirect outcome

	Citalopram versus placebo
Outcome	Behaviour that challenges
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/ Non-compliance (5) Inappropriate Speech
Study ID	KING2009
Effect size (CI; p value)	(1) *Irritability* SMD -0.01 (-0.33, 0.31; p = 0.95) (2) *Lethargy* SMD -0.01 (-0.33, 0.31; p = 0.94) (3) *Stereotypic behaviour* SMD 0.05 (-0.27, 0.37; p = 0.75) (4) *Hyperactivity* SMD 0.09 (-0.23, 0.41; p = 0.58) (5) *Inappropriate Speech* SMD 0.06 (-0.26, 0.38; p = 0.73)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Moderate[1]
Number of studies/participants	K = 1; N = 149
Forest plot	1.11.2; Appendix 13
Note. [1]Downgraded due to serious imprecision as N <400.	

There was no evidence for statistically significant positive treatment effects of citalopram on behaviour that challenges as measured by the ABC subscales (see Table 146). However, there was evidence from this study for statistically significant harms associated with citalopram (including: increased energy level; disinhibited, impulsive or intrusive behaviour; decreased attention and concentration; hyperactivity; stereotypy; diarrhoea; any insomnia and initial insomnia or difficulty falling asleep; skin or subcutaneous tissue disorder; see Chapter 10, Section10.3.2, for data for adverse events associated with antidepressants).

Antihistamines for behaviour that challenges as a direct outcome

The one included antihistamine trial (AKHONDZADEH2004) compared combined cyproheptadine and haloperidol with combined placebo and haloperidol in children with autism (see Table 147).

Table 147: Study information table for included trials of antihistamines for behaviour that challenges

	Cyproheptadine and haloperidol versus placebo and haloperidol
No. trials (N)	1 (40)
Study IDs	AKHONDZADEH2004
Study design	RCT
% female	40
Mean age (years)	6.7
IQ	Not reported
Dose/intensity (mg/hours)	Planned final dose of 0.05 mg/kg/day for haloperidol, 0.2 mg/kg/day for cyproheptadine and dose of placebo not reported
Setting	Outpatient
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	8

Evidence for the effectiveness of cyproheptadine (as an adjunct to haloperidol) on behaviour that challenges and the quality of evidence for each outcome are presented in Table 148. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 148: Evidence summary table for effects of antihistamines on behaviour that challenges as a direct outcome

	Cyproheptadine and haloperidol versus placebo and haloperidol
Outcome	Behaviour that challenges
Outcome measure	ABC Total (change score)
Study ID	AKHONDZADEH2004
Effect size (CI; p value)	SMD -0.98 (-1.64, -0.32; p = 0.003)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Moderate[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.11.3; Appendix 13
Note. [1]Downgraded due to serious imprecision as N <400.	

There was single-study evidence for a large effect of cyproheptadine (as an adjunct to haloperidol) for behaviour that challenges as measured by the ABC total score (see Table 148). There was no evidence for any statistically significant adverse events associated with cyproheptadine (see Chapter 10, Section 10.3.2, for data for adverse events associated with antihistamines).

Antioxidants for behaviour that challenges as a direct outcome

The one included antioxidant trial (HARDAN2012) compared N-acetylcysteine with placebo in children with autism (see Table 149).

Table 149: Study information table for included trials of antioxidants for behaviour that challenges

	N-acetylcysteine versus placebo
No. trials (N)	1 (33)
Study IDs	HARDAN2012
Study design	RCT
% female	6
Mean age (years)	7.1
IQ	Not reported
Dose/intensity (mg/hours)	Final dose of 2,700 mg/day (three doses of 900 mg)
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of N-acetylcysteine on behaviour that challenges and the quality of evidence for each outcome are presented in Table 150. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 150: Evidence summary table for effects of antioxidants on behaviour that challenges as a direct outcome

	N-acetylcysteine versus placebo		
Outcome	Behaviour that challenges	Global severity	Global improvement
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behavior (4) Hyperactivity/ Non-compliance (5) Inappropriate Speech	CGI-S	CGI-I
Study ID	HARDAN2012		
Effect size (CI; p value)	(1) *Irritability* SMD -0.70 (-1.46, 0.05; p = 0.07) (2) *Lethargy* SMD 0.31 (-0.43, 1.04; p = 0.41) (3) *Stereotypic Behavior* SMD -0.36 (-1.10, 0.37; p = 0.33) (4) *Hyperactivity* SMD -0.73 (-1.49, 0.03; p =0.06) (5) *Inappropriate Speech* SMD -0.34 (-1.07, 0.40; p =0.37)	SMD -0.46 (-1.19, 0.28; p = 0.23)	SMD -0.29 (-1.02, 0.44; p = 0.44)

Heterogeneity (chi2; p value; I^2)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 29
Forest plot	1.11.4; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for any statistically significant treatment effects of N-acetylcysteine on behaviour that challenges as measured by the ABC, CGI-S or CGI-I (see Table 150). There was also no evidence for any statistically significant adverse events associated with N-acetylcysteine (see Chapter 10, Section 10.3.2, for date for adverse events associated with antioxidants).

Antipsychotics for behaviour that challenges as a direct or indirect outcome

Three of the antipsychotic trials (JOHNSON&JOHNSON2011, RUPPRISPERIDONE2001, SHEA2004) compared risperidone with placebo, and two studies compared aripiprazole with placebo (MARCUS2009, OWEN2009) in children with autism (see Table 151). Data from two trials also allowed for a comparison of low dose antipsychotics (0.125-0.175 mg/day risperidone [JOHNSON&JOHNSON2011]; 5 mg/day aripiprazole [MARCUS2009]) with placebo. One of the included antipsychotic trials (TROOST2005) was a discontinuation study and compared continued risperidone or switch with placebo; RUPPRISPERIDONE2001 also reported some data for relapse rate after discontinuation. Finally, one of the antipsychotic trials (MIRAL2008) compared risperidone with haloperidol (see Table 151).

Table 151: Study information table for included trials of antipsychotics for behaviour that challenges

	Antipsychotic (risperidone or aripiprazole) versus placebo	**Continued risperidone versus switch to placebo**	**Risperidone versus haloperidol**
No. trials (N)	5 (593)	1 (24)	1 (30)
Study IDs	(1) JOHNSON&JOHNSON2011 (2) MARCUS2009 (3) OWEN2009 (4) RUPPRISPERIDONE2001 (5) SHEA2004	TROOST2005	MIRAL2008
Study design	(1)-(5) RCT	RCT (discontinuation study)	RCT
% female	(1) 13 (2) 11 (3) 12 (4) 19	8	17

	(5) 23		
Mean age (years)	(1) 9.3 (2) 9.7 (3) 9.3 (4) 8.8 (5) 7.5	9.1	10.5
IQ	(1)-(5) Not reported	Not reported	Not reported
Dose/intensity (mg/hours)	(1) Low dose risperidone:0.125 mg (if <45 kg) or 0.175 mg (if ≥45 kg); High dose risperidone: 1.25 mg (if <45 kg) or 1.75 mg (if ≥45 kg) (2) Fixed doses of 5 mg/day or 10 mg/day or 15 mg/day (3 active treatment arms) (3) 2-15 mg/day (4) Final dose of 1.8 mg/day of risperidone and 2.4 mg/day of placebo (5) Final dose of 1.48 mg/day	Final dose of 1.81 mg/day	Final dose of 2.6 mg/day for risperidone and haloperidol
Setting	(1) Not reported (2) Research setting (3) Not reported (4) Study was conducted across five university sites (5) Outpatient	Not reported	Not reported
Length of treatment (weeks)	(1) 6 (2)-(5) 8	8 weeks for discontinuation phase	10
Continuation phase (length and inclusion criteria)	(1) 26 (including open-label phase; however, data cannot be extracted for follow-up as all participants received risperidone resulting in no control group for 6-month outcome measures) (2)-(3) 8 (4) 8 (in the studies included in RUPPRISPERIDONE2002, an open-label 16-week extension is reported in Aman and colleagues [2005] and 95-week open-label follow-up phase in Anderson and colleagues [2007] but efficacy or safety data are not extractable for this follow-up) (5) 8	32 weeks (including open-label treatment and discontinuation phases)	12 (including a 1-2 week screening phase)

Evidence for the effectiveness of antipsychotics on behaviour that challenges and the quality of evidence for each outcome are presented in Table 152, Table 153, Table 154, Table 155 and Table 156. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 152: Evidence summary table for effects of antipsychotics on behaviour that challenges as a direct outcome

	Antipsychotic (risperidone or aripiprazole) versus placebo					
Outcome	Positive treatment response		Maladaptive behaviour	Irritability	Lethargy/Social withdrawal	Stereotypic behaviour
Outcome measure	Number of participants who showed >25% improvement on ABC Irritability with or without 'much improved/very improved' on CGI-I with: (1) Risperidone (2) Aripiprazole	Number of participants who scored <3 'definitely improved' or better on 9-point parent-defined target symptom scale	VABS Maladaptive Behaviour index	ABC Irritability subscale with: (1) Risperidone (2) Aripiprazole	ABC Lethargy/ Social Withdrawal with: (1) Risperidone (2) Aripiprazole	ABC Stereotypic Behaviour with: (1) Risperidone (2) Aripiprazole
Study ID	(1) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001 (2) MARCUS2009 OWEN2009	RUPPRISPERIDONE2001		(1) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001 SHEA2004 (2) OWEN2009	(1) RUPPRISPERIDONE2001 SHEA2004 (2) MARCUS2009 OWEN2009	
Effect size (CI; p value)	(1)+(2) RR 2.27 (1.75, 2.94; p <0.00001) (1) *Risperidone* RR 2.72 (1.85, 3.99; p <0.00001) (2) *Aripiprazole* RR 1.95 (1.37, 2.78; p = 0.0002)	RR 3.37 (1.83, 6.21; p = 0.0001)	SMD -1.17 (-1.59, -0.75; p <0.00001)	(1)+(2) SMD -0.92 (-1.14, -0.70; p <0.00001) (1) *Risperidone* SMD -0.96 (-1.22, -0.71; p <0.00001) (2) *Aripiprazole* SMD -0.81 (-1.23, -0.39; p = 0.0001)	(1)+(2) SMD -0.28 (-0.47, -0.08; p = 0.005) (1) *Risperidone* SMD -0.45 (-0.75, -0.15; p = 0.003) (2) *Aripiprazole* SMD -0.15 (-0.40, 0.10; p = 0.23)	(1)+(2) SMD -0.48 (-0.68, -0.29; p <0.00001) (1) *Risperidone* SMD -0.34 (-0.64, -0.05; p = 0.02) (2) *Aripiprazole* SMD -0.59 (-0.84, -0.33; p <0.00001)
Heterogeneity (chi²; p value; I²)	(1)+(2) Chi² = 13.58, df = 3; p = 0.004; *I²* = 78% Test for subgroup differences: Chi² = 1.55, df = 1; p = 0.21; *I²* = 35.3% (1) *Risperidone*	Not applicable		(1)+(2) Chi² = 2.85, df = 3; p = 0.42; *I²* = 0% Test for subgroup differences: Chi² = 0.37, df = 1; p = 0.54; *I²* = 0% (1) Chi² = 2.48, df = 2;	(1)+(2) Chi² = 2.50, df = 3; p = 0.48; *I²* = 0% Test for subgroup differences: Chi² = 2.28, df = 1;	(1)+(2) Chi² = 1.78, df = 3; p = 0.62; *I²* = 0% Test for subgroup differences: Chi² = 1.47, df = 1;

	Chi^2 = 9.18, df = 1; p = 0.002; I^2 = 89% (2) *Aripiprazole* Chi^2 = 4.24, df = 1; p = 0.04; I^2 = 76%			p = 0.29; I^2 = 19% (2) Not applicable	p = 0.13, I^2 = 56.0% (1) Chi^2 = 0.08, df = 1; p = 0.77; I^2 = 0% (2) Chi^2 = 0.14, df = 1; p = 0.70; I^2 = 0%	p = 0.23, I^2 = 32.0% (1) Chi^2 = 0.04, df = 1; p = 0.84; I^2 = 0% (2) Chi^2 = 0.26, df = 1; p = 0.61; I^2 = 0%
Quality of the evidence (GRADE)	(1)+(2) Low[1] (1)-(2) Very low[1,2]	Moderate[2]		Moderate[3]	(1)+(2) Moderate[4] (1) Moderate[3] (2) Low[3,4]	
Number of studies/participants	(1)+(2) K = 4; N = 501 (1) K = 2; N = 193 (2) K = 2; N = 308	K = 1; N = 87	K = 1; N = 101	(1)+(2) K = 4; N = 363 (1) K = 3; N = 268 (2) K = 1; N = 95	(1)+(2) K = 4; N = 486 (1) K = 2; N = 178 (2) K = 2; N = 308	(1)+(2) K = 4; N = 485 (1) K = 2; N = 177 (2) K = 2; N = 308
Forest plot	1.11.5; Appendix 13					

Note. [1]Downgraded due to very serious inconsistency as the I^2 value indicates substantial to considerable heterogeneity.
[2]Downgraded due to serious imprecision as number of events <300.
[3]Downgraded due to serious imprecision as N <400.
[4]Downgraded for serious risk of bias – With the exception of RUPPRISPERIDONE2001, the blinding is unclear for the trials as the papers state 'double-blind' but give no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.

Table 153: Evidence summary table for effects of antipsychotics on behaviour that challenges as a direct outcome *(continued)*

	Antipsychotic (risperidone or aripiprazole) versus placebo					
Outcome	Hyperactivity/ Non-compliance	Inappropriate speech	Parent-defined target symptoms	Positive treatment response (global state)	Global severity	Global improvement
Outcome measure	ABC Hyperactivity/ Non-compliance subscale with: (1) Risperidone (2) Aripiprazole	ABC Inappropriate Speech subscale with: (1) Risperidone (2) Aripiprazole	Study-specific target symptom ratings or VAS for the most troublesome symptom	Number of participants who were 'much improved/very improved' on CGI-I	CGI-S with: (1) Risperidone (2) Aripiprazole	CGI-I
Study ID	(1) RUPPRISPERIDONE2001 SHEA2004 (2) MARCUS2009 OWEN2009		RUPPRISPERIDONE2001 SHEA2004	JOHNSON& JOHNSON2011 SHEA2004	(1) JOHNSON& JOHNSON2011 (2) MARCUS2009	SHEA2004
Effect size (CI; p value)	(1)+(2) SMD -0.84 (-1.04, -0.64; p <0.00001) (1) *Risperidone* SMD -1.03 (-1.34, -0.71; p <0.00001) (2) *Aripiprazole* SMD -0.72 (-0.97, -0.46; p <0.00001)	(1)+(2) SMD -0.54 (-0.74, -0.35; p <0.00001) (1) *Risperidone* SMD -0.66 (-0.96, -0.36; p <0.0001) (2) *Aripiprazole* SMD -0.46 (-0.72, -0.20; p = 0.0004)	SMD -0.96 (-1.29, -0.63; p <0.00001)	RR 2.83 (1.61, 4.95; p = 0.0003)	(1)+(2) SMD -0.32 (-0.59, -0.05; p = 0.02) (1) *Risperidone* SMD -0.28 (-0.71, 0.14; p = 0.19) (2) *Aripiprazole* SMD -0.34 (-0.69, 0.01; p = 0.06)	SMD -0.98 (-1.45, -0.51; p <0.0001)
Heterogeneity (chi²; p value; I^2)	(1)+(2) Chi² = 4.10, df = 3; p = 0.25; I^2 = 27% Test for subgroup differences: Chi² = 2.27, df = 1; p = 0.13; I^2 = 55.9% (1) Chi² = 0.00, df = 1; p = 0.97; I^2 = 0%	(1)+(2) Chi² = 5.54, df = 3; p = 0.14; I^2 = 46% Test for subgroup differences: Chi² = 0.97, df = 1; p = 0.33; I^2 = 0% (1) Chi² = 1.48, df = 1; p = 0.22; I^2 = 32%	Chi² = 5.96, df = 1; p = 0.01; I^2 = 83%	Chi² = 0.02, df = 1; p = 0.90; I^2 = 0%	(1)+(2) Chi² = 0.04, df = 1; p = 0.84; I^2 = 0% Test for subgroup differences: Chi² = 0.04, df = 1; p = 0.84, I^2 = 0% (1)-(2) Not applicable	Not applicable

	(2) Chi^2 = 1.82, df = 1; p = 0.18; I^2 = 45%	(2) Chi^2 = 3.09, df = 1; p = 0.08; I^2 = 68%				
Quality of the evidence (GRADE)	(1)+(2) Moderate[1] (1) Moderate[2] (2) Very low[1,2,3]	(1)+(2) Low[1,3] (1) Moderate[2] (2) Very low[1,2,4]	Very low[2,5,6]	Low[7,8]	(1)+(2) Low[2,9] (1) Low[10] (2) Very low[9,10]	Low[2,7]
Number of studies/participants	(1)+(2) K = 4; N = 484 (1) K = 2; N = 176 (2) K = 2; N = 308	(1)+(2) K = 4; N = 485 (1) K = 2; N = 178 (2) K = 2; N = 307	K = 2; N = 163	K = 2; N = 171	(1)+(2) K = 2; N = 273 (1) K = 1; N = 92 (2) K = 1; N = 181	K = 1; N = 77
Forest plot	1.11.5; Appendix 13					

Note. [1]Downgraded for serious risk of bias – With the exception of RUPPRISPERIDONE2001, the blinding is unclear for the trials as the papers state 'double-blind' but give no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to serious inconsistency as the I^2 value indicates moderate heterogeneity.
[4]Downgraded due to very serious inconsistency as the I^2 value indicates substantial heterogeneity.
[5]Downgraded for serious risk of bias – in RUPPRISPERIDONE2001 a study-specific outcome measure without independent reliability and validity data were used and in SHEA2004 the blinding is unclear as the paper states 'double-blind' but gives no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.
[6]Downgraded due to very serious inconsistency as the I^2 value indicates substantial to considerable heterogeneity.
[7]Downgraded for serious risk of bias – blinding is unclear in SHEA2004 as paper states 'double-blind' but gives no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.
[8]Downgraded due to serious imprecision as number of events <300.
[9]Downgraded for serious risk of bias – blinding is unclear in MARCUS2009 as paper states 'double-blind' but gives no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.
[10]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 154: Evidence summary table for effects of antipsychotics (low dose) on behaviour that challenges as a direct outcome

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo			
Outcome	Positive treatment response	Behaviour that challenges	Positive treatment response (global state)	Global severity
Outcome measure	Number of participants who showed >25% improvement on ABC Irritability with or without 'much improved/very improved' on CGI-I with: (1) Low dose risperidone (0.125-0.175 mg/day) (2) Low dose aripiprazole (5 mg/day)	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (change score) (3) Stereotypic Behaviour (change score) (4) Hyperactivity/ Non-compliance (change score) (5) Inappropriate Speech (change score)	Number of participants who were 'much improved/very improved' on CGI-I	CGI-S with: (1) Low dose risperidone (0.125-0.175 mg/day) (2) Low dose aripiprazole 5 mg/day)
Study ID	(1) JOHNSON&JOHNSON2011 (2) MARCUS2009	(1) JOHNSON&JOHNSON2011 (2)-(5) MARCUS2009	JOHNSON&JOHNSON2011	(1) JOHNSON&JOHNSON2011 (2) MARCUS2009
Effect size (CI; p value)	(1)+(2) RR 1.46 (1.03, 2.06; p = 0.03) (1) *Low dose risperidone* RR 1.26 (0.74, 2.14; p = 0.40) (2) *Low dose aripiprazole* RR 1.61 (1.02, 2.53; p = 0.04)	(1) *Irritability* SMD -0.52 (-1.02, -0.01; p = 0.04) (2) *Lethargy* SMD -0.07 (-0.46, 0.32; p = 0.73) (3) *Stereotypic Behaviour* SMD -0.55 (-0.95, -0.15; p = 0.007) (4) *Hyperactivity* SMD -0.53 (-0.93, -0.14; p = 0.008) (5) *Inappropriate Speech* SMD -0.25 (-0.65, 0.14; p = 0.21)	RR 1.13 (0.36, 3.54; p = 0.83)	(1)+(2) SMD -0.09 (-0.41, 0.24; p = 0.60) (1) *Low dose risperidone* SMD 0.10 (-0.39, 0.60; p = 0.68) (2) *Low dose aripiprazole* SMD -0.23 (-0.65, 0.20; p = 0.30)
Heterogeneity (chi²; p value; I²)	Test for subgroup differences: Chi² = 0.48, df = 1; p = 0.49; *I²* = 0%	Not applicable		Test for subgroup differences: Chi² = 0.99, df = 1; p = 0.32; *I²* = 0%
Quality of the evidence (GRADE)	(1)+(2) Low[1,2] (1) Low[3] (2) Low[1,2]	(1) Moderate[4] (2)-(4) Low[1,4] (5) Very low[1,5]	Low[3]	(1)+(2) Very low[1,5] (1) Low[5] (2) Very low[1,5]
Number of studies/participants	(1)+(2) K = 2; N = 164	(1) K = 1; N = 63	K = 1; N = 64	(1)+(2) K = 2; N = 148

	(1) K = 1; N = 63 (2) K = 1; N = 101	(2)-(4) K = 1; N = 101 (5) K = 1; N = 100		(1) K = 1; N = 63 (2) K = 1; N = 85
Forest plot	1.11.5; Appendix 13			

Note. [1]Downgraded for serious risk of bias – blinding is unclear in MARCUS2009 as paper states 'double-blind' but gives no further detail regarding who is blinded, that is, participant, parent, investigator, intervention administrator, outcome assessor.
[2]Downgraded due to serious imprecision as number of events <300.
[3]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[4]Downgraded due to serious imprecision as N <400.
[5]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 155: Evidence summary table for effects of antipsychotics (risperidone discontinuation) on behaviour that challenges as a direct outcome

	Continued risperidone versus switch to placebo		
Outcome	Relapse rate after discontinuation	Time to relapse	Behaviour that challenges
Outcome measure	Number of participants showing >25% worsening in ABC Irritability and rated as 'worse/very much worse' on CGI-I	Time to relapse (in weeks)	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/ Non-compliance (5) Inappropriate Speech
Study ID	RUPPRISPERIDONE2001 TROOST2005	TROOST2005	
Effect size (CI; p value)	RR 0.28 (0.12, 0.64; p = 0.003)	SMD 0.97 (0.11, 1.82; p = 0.03)	(1) *Irritability* SMD -0.74 (-1.58, 0.09; p = 0.08) (2) *Lethargy* SMD -0.58 (-1.40, 0.24; p = 0.16) (3) *Stereotypic Behaviour* SMD -0.02 (-0.82, 0.78; p = 0.95) (4) *Hyperactivity* SMD -0.23 (-1.03, 0.58; p = 0.58) (5) *Inappropriate Speech* SMD 0.00 (-0.80, 0.80; p = 1.00)
Heterogeneity (chi²; p value; I²)	Chi² = 0.54, df = 1; p = 0.46; *I*² = 0%	Not applicable	
Quality of the evidence (GRADE)	Moderate[1]	Moderate[2]	Low[3]
Number of studies/participants	K = 2; N = 56	K = 1; N = 24	K = 1; N = 24
Forest plot	1.11.5; Appendix 13		

Note. [1]Downgraded due to serious imprecision as number of events <300.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 156: Evidence summary table for effects of antipsychotics (risperidone versus haloperidol) on behaviour that challenges as an indirect outcome

	Risperidone versus haloperidol
Outcome	Behaviour that challenges
Outcome measure	ABC Total
Study ID	MIRAL2008
Effect size (CI; p value)	SMD -0.50 (-1.25, 0.26; p = 0.20)
Heterogeneity (chi2; p value; I^2)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 28
Forest plot	1.11.5; Appendix 13
Note. [1]Downgraded for serious risk of bias – paper states 'Double-blind' but gives no further detail regarding who is blinded; that is, participant, parent, investigator, intervention administrator, outcome assessor. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There is evidence from meta-analyses with four studies for a large and statistically significant effect of risperidone or aripiprazole (no statistically significant subgroup differences) on a dichotomous measure of positive treatment response as measured by number of participants who showed over 25% improvement on ABC Irritability and/or were rated as 'much improved/very improved' on CGI-I (see Table 152), with participants who received an antipsychotic being over two times more likely to show a positive treatment response than participants who received placebo. However, the quality of the evidence was downgraded to low due to substantial to considerable heterogeneity. There was moderate quality evidence from four-study meta-analyses for statistically significant effects of risperidone or aripiprazole (no statistically significant subgroup differences) on continuous measures of behaviour that challenges including the ABC Irritability and Hyperactivity (large effects), and Lethargy/Social Withdrawal and Stereotypic Behaviour (small effects) subscales and low quality evidence for a moderate effect on the ABC Inappropriate Speech subscale (see Table 152 and Table 153). There was also evidence from meta-analysis with two studies for large effects of risperidone on parent-defined target symptoms; however, the quality of the evidence was downgraded to very low due to risk of bias concerns (study-specific outcome measures without independent reliability or validity data and unclear blinding of outcome assessment), inconsistency (substantial to considerable heterogeneity) and small sample size (see Table 153). In addition, meta-analysis with two studies revealed a large effect of risperidone on positive treatment response for global state as measured by the CGI-I with participants who received risperidone being nearly three times more likely to score 'much improved/very improved' on the CGI-I than participants who received placebo. There was also evidence for positive treatment effects on continuous measures of global state with evidence from a two-study meta-analysis for small and statistically significant effects of risperidone or aripiprazole (no statistically significant subgroup differences) on global severity as measured by the CGI-S, and evidence from a single study for a large effect of risperidone on global improvement as measured by the CGI-I. However, the quality of the evidence for effects on global state was low due to risk of bias concerns (unclear blinding of outcome assessment)

and small sample size (see Table 153). Finally, there was moderate quality single-study evidence for a large effect of risperidone on a dichotomous measure of positive treatment response for parent-defined target symptoms (with participants who received risperidone being over three times more likely to be rated as definitely improved or better), and a large effect of risperidone on maladaptive behaviour as measured by the VABS (see Table 152).

There was also evidence for statistically significant harms associated with antipsychotics as follows: increased risk of any adverse event, increased risk of clinically relevant weight gain, continuous measure of weight gain, increased appetite, constipation, prolactin concentration, leptin change score, pulse change score, somnolence/drowsiness, fatigue, sedation, rhinitis, fever, tachycardia, drooling, and tremor (see Chapter 10, Section 10.3.2, for adverse events associated with antipsychotics).

RUPPRISPERIDONE2001, using the primary outcome measure of the ABC Irritability subscale score, also examined whether treatment effects were moderated by demographic variables. No statistically significant subgroup differences were observed for any of the demographic variables examined as follows:

- age (>8.15 years/<8.15 years; test for subgroup differences: $Chi^2 = 0.00$, df = 1, p = 1.00, $I^2 = 0\%$)
- parental education (university degree/<university degree; test for subgroup differences: $Chi^2 = 0.10$, df = 1, p = 0.75, $I^2 = 0\%$)
- ethnicity (non-white/white; test for subgroup differences: $Chi^2 = 0.31$, df = 1, p = 0.58, $I^2 = 0\%$)
- income (>$50K/<$50K; test for subgroup differences: $Chi^2 = 0.12$, df = 1, p = 0.73, $I^2 = 0\%$)
- IQ (>48/<48; test for subgroup differences: $Chi^2 = 0.57$, df = 1, p = 0.45, $I^2 = 0\%$)
- severity (CGI-S >5/CGI-S <5; test for subgroup differences: $Chi^2 = 0.01$, df = 1, p = 0.92, $I^2 = 0\%$)
- social impairment (ADI-R social impairment >27/ADI-R social impairment <27; test for subgroup differences: $Chi^2 = 0.70$, df = 1, p = 0.40, $I^2 = 0\%$)
- communication impairment (ADI-R communication impairment >17/ADI-R communication impairment <17; test for subgroup differences: $Chi^2 = 0.09$, df = 1, p = 0.77, $I^2 = 0\%$)
- stereotypy (ADI-R stereotypy >8/ADI-R stereotypy <8; test for subgroup differences: $Chi^2 = 0.06$, df = 1, p = 0.80, $I^2 = 0\%$)
- coexisting OCD symptoms (CYBOCS >16/CYBOCS <16; test for subgroup differences: $Chi^2 = 0.76$, df = 1, p = 0.38, $I^2 = 0\%$)
- coexisting ADHD inattention symptoms (Child Symptom Inventory [CSI] ADHD-Inattention >18/CSI ADHD-Inattention <18; test for subgroup differences: $Chi^2 = 4.02$, df = 1, p = 0.05, $I^2 = 75.1\%$)

- coexisting ADHD hyperactivity symptoms (CSI ADHD-Hyperactivity >17/CSI ADHD-Hyperactivity <17; test for subgroup differences: $Chi^2 = 0.97$, df = 1, p = 0.33, $I^2 = 0\%$),
- coexisting conduct disorder symptoms (CSI Conduct >3/CSI Conduct <3; test for subgroup differences: $Chi^2 = 2.75$, df = 1, p = 0.10, $I^2 = 63.7\%$)
- coexisting ODD (CSI Oppositional >10/CSI Oppositional <10; test for subgroup differences: $Chi^2 = 0.50$, df = 1, p = 0.48, $I^2 = 0\%$)
- coexisting enuresis (CSI Enuresis >1/CSI Enuresis <1; test for subgroup differences: $Chi^2 = 0.24$, df = 1, p = 0.63, $I^2 = 0\%$)
- coexisting encopresis (CSI Encopresis >0/CSI Encopresis <0; test for subgroup differences: $Chi^2 = 1.30$, df = 1, p = 0.25, $I^2 = 23.2\%$)
- coexisting anxiety symptoms (CSI Anxiety >13/CSI Anxiety <13; test for subgroup differences: $Chi^2 = 0.16$, df = 1, p = 0.69, $I^2 = 0\%$)
- coexisting anorexia symptoms (CSI Anorexia >0/CSI Anorexia <0; test for subgroup differences: $Chi^2 = 0.41$, df = 1, p = 0.52, $I^2 = 0\%$)
- coexisting bulimia symptoms (CSI Bulimia >0/CSI Bulimia <0; test for subgroup differences: $Chi^2 = 0.14$, df = 1, p = 0.71, $I^2 = 0\%$)
- coexisting depression symptoms (CSI Depression >2/CSI Depression <2; test for subgroup differences: $Chi^2 = 0.42$, df = 1, p = 0.51, $I^2 = 0\%$)
- coexisting bipolar disorder symptoms (CSI Bipolar disorder >6/CSI Bipolar disorder <6; test for subgroup differences: $Chi^2 = 0.01$, df = 1, p = 0.93, $I^2 = 0\%$).

Two of the studies included in the meta-analyses discussed above included more than one active intervention treatment arm with low, high (JOHNSON&JOHNSON2011, MARCUS2009) and moderate (MARCUS2009) dose groups. For the aforementioned meta-analyses these groups were combined; however, an additional analysis examined the effects of low dose against placebo. There was evidence from two studies for a moderate effect of low dose risperidone or aripiprazole (no statistically significant subgroup differences) on a dichotomous measure of positive treatment response as measured by number of participants who showed over 25% improvement on ABC Irritability and/or were rated as 'much improved/very improved' on CGI-I, with participants who received low dose risperidone or aripiprazole being nearly one and a half times more likely to show a positive treatment response than participants who received placebo (see Table 154). However, the quality of the evidence was downgraded to low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size. There was also single study evidence for a moderate effect of low dose risperidone on irritability as measured by the ABC subscale (moderate quality evidence), and moderate effects of low dose aripiprazole on ABC Hyperactivity and Stereotypic Behaviour subscales (low quality evidence); however, effects were non-significant for low dose aripiprazole on the Lethargy/Social Withdrawal and Inappropriate Speech subscales (see Table 154). There were also non-significant effects observed for low dose risperidone on a dichotomous measure of positive treatment response for global state and for low dose risperidone or aripiprazole (no statistically significant subgroup differences) on a continuous measure of global severity (see Table 154).

There was also evidence for statistically significant adverse events associated with low dose antipsychotics as follows: clinically relevant weight gain, continuous measure of weight gain and increased appetite (see Chapter 10, Section 10.3.2, for adverse events associated with antipsychotics).

There was moderate quality evidence from two discontinuation RCTs for a large and statistically significant effect of continued risperidone on relapse rate (number of participants showing over 25% worsening in ABC Irritability and rated as 'worse/very much worse' on CGI-I), with participants who continued to receive risperidone being 72% less likely to relapse than participants who switched to placebo (see Table 155). There was also single study moderate quality evidence for a large and statistically significant effect of continued risperidone on time to relapse (see Table 155). However, non-significant effects were observed for continued risperidone on ABC subscales (see Table 155).

Finally, one study examined indirect effects of risperidone (relative to haloperidol) on behaviour that challenges as measured by the ABC total score and found no evidence for a statistically significant treatment effect (see Table 156).

Antivirals for behaviour that challenges as a direct outcome

The one included antiviral trial (KING2001) compared amantadine hydrochloride (Symmetrel® syrup) with taste- and colour-matched placebo (see Table 157).

Table 157: Study information table for included trial of antivirals for behaviour that challenges

	Amantadine hydrochloride versus placebo
No. trials (N)	1 (39)
Study IDs	KING2001
Study design	RCT
% female	13
Mean age (years)	7.0
IQ	Not reported
Dose/intensity (mg/hours)	Planned intensity of 2.5 mg/kg (single dose) per day for first week of treatment period and 5 mg/kg (two doses) per day for remaining 3 weeks of treatment
Setting	Outpatient
Length of treatment (weeks)	4
Continuation phase (length and inclusion criteria)	5 (4-week double-blind treatment period was preceded by a 1-week single-blind placebo run-in phase [single dose of 2.5 mg/kg per day])

Evidence for the effectiveness of amantadine hydrochloride on behaviour that challenges and the quality of evidence for each outcome are presented in Table 158. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 158: Evidence summary table for effects of antivirals on behaviour that challenges as a direct outcome

	Amantadine hydrochloride versus placebo	
Outcome	Positive treatment response (parent-rated)	Positive treatment response (investigator-rated)
Outcome measure	Number of participants showing >25% improvement on ABC Irritability and/or hyperactivity	Number of participants rated as 'much improved/very improved' on CGI-I
Study ID	KING2001	
Effect size (CI; p value)	RR 1.29 (0.60, 2.74; p = 0.51)	RR 2.11 (0.88, 5.03; p = 0.09)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	Very low[1,2]
Number of studies/participants	K = 1; N = 38	K = 1; N = 39
Forest plot	1.11.6; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [2]Downgraded for serious risk of bias – blinding of outcome assessor is not clear and trial funded by pharmaceutical company.		

There was no evidence for positive treatment effects associated with amantadine hydrochloride as measured by parent-rated (>25% improvement on ABC Irritability and/or hyperactivity) or investigator-rated ('much improved/very improved' on CGI-I) positive treatment response (see Table 158). There was also no evidence for statistically significant harms associated with amantadine hydrochloride (see Chapter 10, Section 10.3.2, for adverse events associated with antivirals).

Cognitive enhancers for behaviour that challenges as a direct outcome

The one included cognitive enhancers trial (AKHONDZADEH2008) compared combined piracetam and risperidone with combined placebo and risperidone (see Table 159).

Table 159: Study information table for included trial of cognitive enhancers for behaviour that challenges

	Piracetam and risperidone versus placebo and risperidone
No. trials (N)	1 (40)
Study IDs	AKHONDZADEH2008
Study design	RCT
% female	25
Mean age (years)	6.8
IQ	Not reported
Dose/intensity (mg/hours)	Fixed final dose of risperidone 2 mg/day (for children weighing 10-40 kg) and 3 mg/day (for children weighing >40 kg) and fixed final dose of piracetam of 800 mg/day
Setting	Outpatient
Length of treatment (weeks)	10
Continuation phase (length and inclusion criteria)	10

Evidence for the effectiveness of piracetam (as an adjunct to risperidone) on behaviour that challenges and the quality of evidence for each outcome are presented in Table 160. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 160: Evidence summary table for effects of cognitive enhancers on behaviour that challenges as a direct outcome

Comparison	Piracetam and risperidone versus placebo and risperidone
Outcome	Behaviour that challenges
Outcome measure	ABC Total
Study ID	AKHONDZADEH2008
Effect size (CI; p value)	SMD -1.93 (-2.69, -1.16; p <0.00001)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Moderate[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.11.7; Appendix 13
Note. [1]Downgraded due to serious imprecision as N <400.	

There was moderate quality single study evidence for a large effect of piracetam (as an adjunct to risperidone) on behaviour that challenges as measured by the ABC total score (see Table 160). There was no evidence for statistically significant harms associated with piracetam (see Chapter 10, Section 10.3.2, for adverse events associated with cognitive enhancers).

Methylxanthines for behaviour that challenges as a direct outcome

The one included methylxanthines trial (AKHONDZADEH2010) involved a comparison between combined pentoxifylline and risperidone and combined risperidone and placebo (see Table 161).

Table 161: Study information table for included trial of methylxanthines for behaviour that challenges

	Pentoxifylline and risperidone versus placebo and risperidone
No. trials (N)	1 (40)
Study IDs	AKHONDZADEH2010
Study design	RCT
% female	28
Mean age (years)	7.7
IQ	Not reported
Dose/intensity (mg/hours)	Planned final dose of 2 mg/day (for children weighing 10-40 kg) or 3 mg/day (for children weighing >40 kg) of risperidone, and 400 mg/day (for children weighing 10-40 kg) or 600 mg/day (for children weighing >40 kg) of pentoxifylline
Setting	Outpatient
Length of treatment (weeks)	10
Continuation phase (length and inclusion criteria)	10

Evidence for the effectiveness of pentoxifylline (as an adjunct to risperidone) on behaviour that challenges and the quality of evidence for each outcome are presented in Table 162. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 162: Evidence summary table for effects of methylxanthines on behaviour that challenges as a direct outcome

	Pentoxifylline and risperidone versus placebo and risperidone
Outcome	Behaviour that challenges
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/Non-compliance (5) Inappropriate Speech
Study ID	AKHONDZADEH2010
Effect size (CI; p value)	(1) *Irritability* SMD -1.71 (-2.44, -0.97; p <0.00001) (2) *Lethargy* SMD -1.69 (-2.42, -0.96; p <0.00001) (3) *Stereotypic Behaviour* SMD -1.55 (-2.27, -0.83; p <0.0001) (4) *Hyperactivity* SMD -1.14 (-1.81, -0.47; p = 0.0009) (5) *Inappropriate Speech* SMD -2.10 (-2.89, -1.31; p <0.00001)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Moderate[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.11.8; Appendix 13
Note. [1]Downgraded due to serious imprecision as N <400.	

There was moderate quality single study evidence for a large effect of pentoxifylline (as an adjunct to risperidone) on behaviour that challenges as measured by the ABC subscales (see Table 162). There was no evidence for statistically significant harms associated with pentoxifylline (see Section 10.3.2 for adverse events associated with methylxanthines).

Opioid antagonists for behaviour that challenges as a direct outcome

The one included trial of opioid antagonists (CAMPBELL1993) compared naltrexone with placebo (see Table 163).

Table 163: Study information table for included trial of opioid antagonists for behaviour that challenges

	Naltrexone versus placebo
No. trials (N)	1 (45)
Study IDs	CAMPBELL1993
Study design	RCT
% female	17
Mean age (years)	4.9
IQ	Full-scale IQ not reported. For N = 37: 22% severe LD; 24% moderate LD; 38% mild LD; 13% borderline; 3% normal IQ. For

	N = 38 adaptive and language DQs (as measured by Gesell Developmental Schedules) were reported as 51.5 for adaptive behaviour and 28.7 for language
Dose/intensity (mg/hours)	Optimal dose of 1 mg/kg/day
Setting	Inpatient
Length of treatment (weeks)	3
Continuation phase (length and inclusion criteria)	6 (including 2-week placebo washout period at beginning of trial and 1-week post-treatment placebo period)

Evidence for the effectiveness of naltrexone on behaviour that challenges and the quality of evidence for each outcome are presented in Table 164. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 164: Evidence summary table for effects of opioid antagonists on behaviour that challenges as a direct outcome

	Naltrexone versus placebo
Outcome	Positive treatment response
Outcome measure	Number of participants rated as 'much improved/very improved' on CGI-I
Study ID	CAMPBELL1993
Effect size (CI; p value)	RR 1.45 (0.74, 2.87; p = 0.28)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 41
Forest plot	1.11.9; Appendix 13
Note. [1]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).	

There was no evidence for positive treatment effects associated with naltrexone as measured by dichotomous measure of positive treatment response, 'much improved/very improved' on CGI-I (see Table 164). There was also no evidence for statistically significant harms associated with naltrexone (see Chapter 10, Section 10.3.2, for adverse events associated with opioid antagonists).

Selective noradrenaline reuptake inhibitors (SNRIs) for behaviour that challenges as an indirect outcome

The one included SNRI trial (ELILILLY2009) compared atomoxetine with placebo and examined indirect effects on behaviour that challenges (see Table 165).

Table 165: Study information table for included trial of SNRIs for behaviour that challenges

	Atomoxetine versus placebo
No. trials (N)	1 (97)
Study Ids	ELILILLY2009
Study design	RCT
% female	14
Mean age (years)	9.9

IQ	92.9 (assessed using the WISC-III)
Dose/intensity (mg/hours)	Planned final dose of 1.2 mg/kg/day
Setting	Not reported
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	28 weeks (8-week double-blind phase followed by 20-week open-label continuation phase; however, data only extracted for the double-blind phase as no control group data were available for open-label continuation)

Evidence for the effectiveness of atomoxetine on behaviour that challenges and the quality of evidence for each outcome are presented in Table 166. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 166: Evidence summary table for effects of SNRIs on behaviour that challenges as an indirect outcome

	Atomoxetine versus placebo
Outcome	Behaviour that challenges
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/Non-compliance (5) Inappropriate Speech
Study ID	ELILILLY2009
Effect size (CI; p value)	(1) *Irritability* SMD -0.09 (-0.51, 0.32; p = 0.66) (2) *Lethargy* SMD -0.05 (-0.46, 0.37; p = 0.83) (3) *Stereotypic Behaviour* SMD 0.00 (-0.42, 0.42; p = 1.00) (4) *Hyperactivity* SMD -0.19 (-0.61, 0.22; p = 0.36) (5) *Inappropriate Speech* SMD -0.22 (-0.64, 0.19; p = 0.29)
Heterogeneity (chi2; p value; I2)	Not applicable
Quality of the evidence (GRADE)	(1) Low[1] (2)-(3) Moderate[2] (4)-(5) Low[1]
Number of studies/participants	(1)-(3) K = 1; N = 89 (4) K = 1; N = 88 (5) K = 1; N = 89
Forest plot	1.11.10; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to serious imprecision as N <400.	

There was no evidence for indirect positive treatment effects on behaviour that challenges associated with atomoxetine as measured by the ABC subscales (see Table 166). There was, however, evidence from this study for statistically significant harms associated with atomoxetine with increased risk of nausea and decreased appetite during the trial (see Chapter 10, Section 10.3.2, for adverse events associated with SNRIs).

7.3.3 Clinical evidence summary – effect of pharmacological interventions on behaviour that challenges

There is evidence for positive treatment effects of antipsychotic drugs on behaviour that challenges. The majority of the evidence on the use of antipsychotics for behaviour that challenges in children and young people with autism compared risperidone or aripiprazole with placebo, and there is moderate to low quality evidence for treatment effects on irritability, lethargy, stereotypic behaviour, hyperactivity, inappropriate speech and parent-defined target behaviours that challenge. However, there are also robust data suggestive of adverse events associated with risperidone or aripiprazole, in particular, weight gain, prolactin concentration and tachycardia. It is also important to note that these trials were run over short time periods and very little is known about the long-term effects of antipsychotic drugs in children and young people with autism.

There was insufficient or inconclusive evidence regarding the effects of anticonvulsants, antioxidants, antivirals, or opioid antagonists. There was evidence that antidepressants (citalopram) are associated with harms, but no benefit. There was evidence that antihistamines (cyproheptadine), cognitive enhancers (piracetam), and methylxanthines (pentoxifylline) used as an adjunct to an antipsychotic drug, may improve behaviour that challenges. However, this was based on only one small trial for each drug.

7.4 BIOMEDICAL INTERVENTIONS – BEHAVIOUR THAT CHALLENGES

7.4.1 Studies considered

Thirty-five papers from the search met the eligibility criteria for full-text retrieval. Of these, 15 RCTs provided relevant clinical evidence and were included in the review. Six of these studies examined the efficacy of biomedical interventions on behaviour that challenges as a direct outcome (target of intervention), and nine provided data on behaviour that challenges as an indirect outcome. All studies were published in peer-reviewed journals between 1996 and 2012. In addition, 20 studies were excluded from the analysis. The most common reasons for exclusion were that data could not be extracted, group assignment was non-randomised, sample size was too small (less than ten participants per arm), or the study was a systematic review with no useable data and any meta-analysis not appropriate to extract. Further information about both included and excluded studies can be found in Appendix 12c.

One trial (PIRAVEJ2009 [Piravej et al., 2009]) examined effects of a complementary therapy on behaviour that challenges as a direct outcome, and two trials

(WONG2008, WONG2010B[55]) examined indirect effects of complementary therapies on behaviour that challenges.

Two trials (OWLEY1999, UNIS2002[56]) examined indirect effects of hormones on behaviour that challenges.

One trial (ROSSIGNOL2009) examined effects of a medical procedure on behaviour that challenges as a direct outcome, and two trials (ADAMS2009A, GRANPEESHEH2010[57]) examined effects of medical procedures on behaviour that challenges as an indirect outcome.

Four trials (BENT2011, HASANZADEH2012 [Hasanzadeh et al., 2012], JOHNSON2010, KERN2001 [Kern et al., 2001]) examined effects of nutritional interventions on behaviour that challenges as a direct outcome, and two trials (ADAMS2011, HANDEN2009[58] [Handen et al., 2009]) examined indirect effects of nutritional interventions on behaviour that challenges.

Finally, one trial (BETTISON1996[59]) examined indirect effects of a sensory intervention on behaviour that challenges.

7.4.2 Clinical evidence – effect of biomedical interventions on behaviour that challenges

Complementary interventions for behaviour that challenges as a direct or indirect outcome

One of the included complementary therapies trials (PIRAVEJ2009) involved a comparison between combined Thai massage and sensory integration therapy and sensory integration therapy only. One of the included trials compared electro-acupuncture with sham electro-acupuncture (WONG2010B). Finally, the remaining included complementary intervention trial (WONG2008) compared electro-acupuncture and a conventional educational programme with a conventional educational programme only (see Table 167). In PIRAVEJ2009, a standardised Thai massage was delivered to children in the intervention group by the same masseuse. The masseuse built a rapport with the child before starting the massage to reduce any anxieties, and massage was then applied to the whole body (feet, legs, arms, hands, fingers, back, neck, shoulders and ears) using moderate pressure. In addition, children in both the experimental and control groups received sensory integration therapy delivered by an occupational therapist, and creative and playful activities that included use of all the senses (including vestibular, tactile and proprioception)

[55] See Section 6.4.3 for direct outcomes from WONG2008 and Section 8.4.7 for direct outcomes from WONG2010B.
[56] See Section 6.4.5 for direct outcomes from OWLEY1999 and UNIS2002.
[57] See Section 6.4.3 for direct outcomes from ADAMS2009A and Section 6.4.5 for direct outcomes from GRANPEESHEH2010.
[58] See Section 6.4.3 for direct outcomes from ADAMS2011 and Section 8.8.5 for direct outcomes from HANDEN2009.
[59] See Section 8.5.6 for direct outcomes from BETTISON1996.

were used to encourage the children to develop new skills and abilities. In WONG2010B electro-acupuncture was delivered via eight acupoints using an electro-acupuncture machine that provided electrical spacing-density stimulation for 30 minutes, and sham acupuncture was delivered in the same way but with needles only inserted to a superficial level. In WONG2008 five acupoints were stimulated for 30 minutes per session. However, participants in experimental and control groups were also receiving a conventional educational programme and no detail is reported about this adjunctive intervention.

Table 167: Study information table for included trials of complementary therapies for behaviour that challenges

	Thai massage and sensory integration therapy versus sensory integration therapy only	**Electro-acupuncture versus sham electro-acupuncture**	**Electro-acupuncture and conventional educational programme versus conventional educational programme only**
No. trials (N)	1 (60)	1 (59)	1 (36)
Study IDs	PIRAVEJ2009	WONG2010B	WONG2008
Study design	RCT	RCT	RCT (crossover)
% female	18	15	6
Mean age (years)	4.7	9.3	7.5
IQ	Not reported	Not reported	Not reported
Dose/intensity (mg/hours)	Sensory integration therapy: 16 hours/16 sessions (2 hours/week). Thai massage: No details on intensity reported, but the exclusion criteria states that children had to attend a minimum of 13 sessions in order to be included in the study	Not reported	12 hours/24 sessions (1.5 hours/week; three sessions/week)
Setting	Not reported	Hospital	Not reported
Length of treatment (weeks)	8	4	8
Continuation phase (length and inclusion criteria)	8	4	8

Evidence for the effectiveness of complementary therapies on behaviour that challenges and the quality of the evidence is presented in Table 168 and Table 169. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 168: Evidence summary table for effects of complementary therapies (Thai massage) on behaviour that challenges as a direct outcome

	Thai massage and sensory integration therapy versus sensory integration therapy only		
Outcome	Teacher-rated behaviour that challenges	Parent-rated behaviour that challenges	Parent-rated sleep-related problems
Outcome measure	CTRS subscales: (1) Conduct Problem (2) Hyperactivity (3) Inattention-passivity (4) Hyperactivity index	Conners' Parent Rating Scale subscales: (1) Conduct Problem (2) Learning Problem (3) Psychosomatic (4) Impulsivity-hyperactivity (5) Anxiety (6) Hyperactivity	Sleep Diary: Sleep behaviour
Study ID	PIRAVEJ2009		
Effect size (CI; p value)	(1) *Conduct problem* SMD -0.22 (-0.73, 0.28; p = 0.39) (2) *Hyperactivity* SMD -0.56 (-1.08, -0.04; p = 0.03) (3) *Inattention-passivity* SMD -0.36 (-0.87, 0.15; p = 0.17) (4) *Hyperactivity index* SMD -0.40 (-0.91, 0.11; p = 0.13)	(1) *Conduct problem* SMD -0.10 (-0.61, 0.41; p = 0.70) (2) *Learning problem* SMD -0.21 (-0.72, 0.29; p = 0.41) (3) *Psychosomatic* SMD 0.07 (-0.44, 0.57; p = 0.79) (4) *Impulsivity-hyperactivity* SMD -0.50 (-1.02, 0.01; p = 0.06) (5) *Anxiety* SMD -0.20 (-0.71, 0.30; p = 0.43) (6) *Hyperactivity* SMD -0.24 (-0.75, 0.27; p = 0.36)	SMD -0.53 (-1.04, -0.01; p = 0.04)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	(1) Low[1] (2) Moderate[2] (3)-(4) Low[1]	Very low[1,3]	Low[2,3]
Number of studies/participants	K = 1; N = 60		
Forest plot	1.12.1; Appendix 13		

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure parent-rated and parents were non-blind.

There was single-study moderate quality evidence for a moderate effect of Thai massage (as an adjunct to sensory integration therapy) on teacher-rated hyperactivity; however, all other subscales of the CTRS were non-significant as were all Conners' Parent Rating Scale subscales (see Table 168). There was also evidence for a moderate effect of Thai massage on sleep problems as measured by parent-completed sleep diary (see Table 168). However, the quality of the evidence was downgraded to low due to risk of bias concerns (non-blind outcome assessment) and small sample size.

Table 169: Evidence summary table for effects of complementary therapies (acupuncture) on behaviour that challenges as an indirect outcome

	Electro-acupuncture versus sham electro-acupuncture	**Electro-acupuncture and conventional educational programme versus conventional educational programme only**
Outcome	Behaviour that challenges	
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/ Non-compliance (5) Inappropriate Speech	ABC (change scores): (1) Total score (2) Irritability (3) Lethargy/Social Withdrawal (4) Stereotypic Behaviour (5) Hyperactivity/ Non-compliance (6) Inappropriate Speech
Study ID	WONG2010B	WONG2008
Effect size (CI; p value)	(1) *Irritability* SMD 0.18 (-0.36, 0.71; p = 0.52) (2) *Lethargy* SMD -0.02 (-0.56, 0.51; p = 0.93) (3) *Stereotypic Behaviour* SMD 0.05 (-0.48, 0.58; p = 0.86) (4) *Hyperactivity* SMD -0.01 (-0.54, 0.52; p = 0.96) (5) *Inappropriate Speech* SMD -0.14 (-0.68, 0.39; p = 0.59)	(1) *Total score* SMD 0.30 (-0.36, 0.95; p = 0.38) (2) *Irritability* SMD 0.42 (-0.24, 1.08; p = 0.21) (3) *Lethargy* SMD 0.23 (-0.42, 0.89; p = 0.48) (4) *Stereotypic Behaviour* SMD 0.29 (-0.37, 0.94; p = 0.39) (5) *Hyperactivity* SMD -0.06 (-0.72, 0.59; p = 0.85) (6) *Inappropriate Speech* SMD 0.58 (-0.09, 1.25; p = 0.09)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	Very low[1,3]
Number of studies/participants	K = 1; N = 55	K = 1; N = 36
Forest plot	1.12.1; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported. [3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and potential for care confounds as the conventional education programme differed for each participant which may introduce bias. There was also an		

unclear risk of detection bias as although all outcomes were measured by blinded assessors, some outcomes involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data were extracted does not report which outcome measures relied on non-blind parental report.

There was no evidence for statistically significant indirect effects of electro-acupuncture, relative to sham electro-acupuncture or as an adjunct to a conventional educational programme, on behaviour that challenges as measured by ABC subscales (see Table 169).

Hormones for behaviour that challenges as an indirect outcome

Both of the included hormone trials (OWLEY1999, UNIS2002) compared secretin with placebo (see Table 170). OWLEY1999 compared porcine secretin with placebo and UNIS2002 was a three-armed trial comparing porcine secretin, synthetic porcine secretin and placebo. For data analysis with UNIS2002, initial comparisons tested for significant differences between the two active intervention arms (porcine secretin and synthetic porcine secretin), where there were significant differences the two active intervention arms were entered into meta-analysis as subgroups (with the subtotal function disabled) and where there were no significant differences between these two groups data were combined.

Table 170: Study information table for included trials of hormones for behaviour that challenges

	Secretin versus placebo
No. trials (N)	2 (146)
Study IDs	(1) OWLEY1999 (2) UNIS2002
Study design	(1) RCT (crossover) (2) RCT
% female	(1) 14 (2) Not reported
Mean age (years)	(1) 6.7 (2) 6.5
IQ	(1) Non-verbal IQ 56.4 (assessed using DAS or MSEL) (2) Not reported
Dose/intensity (mg/hours)	(1) 2 CU/kg (2) 2 CU/kg of porcine secretin or 0.4 µg/kg of synthetic porcine secretin
Setting	(1) Not reported (2) Academic
Length of treatment (weeks)	(1)-(2) Single dose
Continuation phase (length and inclusion criteria)	(1) 8 (including crossover period but data were extracted only for 4 week period corresponding to the end of the first phase) (2) 4

Evidence for the effectiveness of secretin on behaviour that challenges and the quality of the evidence is presented in Table 171. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Initial analysis of the data from UNIS2002 revealed only one statistically significant difference between the porcine secretin and synthetic porcine secretin active intervention arms, this difference was observed on the teacher-rated ABC Lethargy subscale in favour of the synthetic porcine secretin group, for all other outcome measures data from the two active intervention arms were combined.

Meta-analysis with two studies revealed evidence for a small and statistically significant effect of secretin on the parent-rated Inappropriate Speech subscale of the ABC (see Table 171). However, non-significant effects were observed on all other parent-rated ABC subscales. Moreover, single study data for teacher-rated ABC subscales found inconsistent effects with evidence for moderate placebo effects with secretin on the teacher-rated ABC total score, the teacher-rated ABC Lethargy subscale (for the porcine secretin subgroup only), and the teacher-rated ABC Hyperactivity subscale (see Table 171). Narrative review of these placebo effects revealed improvement in both groups but greater improvement in the placebo group.

Table 171: Evidence summary table for effects of hormones on behaviour that challenges as an indirect outcome

	Secretin versus placebo					
Outcome	Behaviour that challenges	Irritability	Lethargy/Social withdrawal	Stereotypic behaviour	Hyperactivity	Inappropriate speech
Outcome measure	ABC Total (change score) (1) Parent-rated (2) Teacher-rated	ABC Irritability subscale (endpoint and change scores) (1) Parent-rated (2) Teacher-rated	ABC Lethargy/ Social Withdrawal subscale (endpoint and change scores) (1) Parent-rated (2) Teacher-rated (porcine secretin) (3) Teacher-rated (synthetic porcine secretin)	ABC Stereotypic Behaviour subscale (endpoint and change scores) (1) Parent-rated (2) Teacher-rated	ABC Hyperactivity/ Non-compliance subscale (endpoint and change scores) (1) Parent-rated (2) Teacher-rated	ABC Inappropriate Speech subscale (endpoint and change scores) (1) Parent-rated (2) Teacher-rated
Study ID	UNIS2002	(1) OWLEY1999 UNIS2002 (2) UNIS2002	(1) OWLEY1999 UNIS2002 (2) UNIS2002 (3) UNIS2002	(1) OWLEY1999 UNIS2002 (2) UNIS2002		
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.13 (-0.59, 0.33; p = 0.58) (2) *Teacher-rated* SMD 0.51 (0.00, 1.01; p = 0.05)	(1) *Parent-rated* SMD -0.11 (-0.45, 0.24; p = 0.54) (2) *Teacher-rated* SMD 0.20 (-0.30, 0.69; p = 0.44)	(1) *Parent-rated* SMD 0.11 (-0.24, 0.46; p = 0.54) (2) *Teacher-rated (porcine secretin)* SMD 0.74 (0.15, 1.33; p = 0.01) (3) *Teacher-rated (synthetic porcine secretin)* SMD 0.05 (-0.56, 0.67; p = 0.86)	(1) *Parent-rated* SMD 0.10 (-0.25, 0.45; p = 0.57) (2) *Teacher-rated* SMD 0.33 (-0.17, 0.82; p = 0.20)	(1) *Parent-rated* SMD -0.01 (-0.36, 0.34; p = 0.95) (2) *Teacher-rated* SMD 0.53 (0.03, 1.04; p = 0.04)	(1) *Parent-rated* SMD -0.39 (-0.75, -0.04; p = 0.03) (2) *Teacher-rated* SMD 0.28 (-0.22, 0.78; p = 0.28)
Heterogeneity (chi²; p value; I^2)	Not applicable	(1) Chi² = 0.01, df = 1; p = 0.91; I^2 = 0% (2) Not applicable	(1) Chi² = 1.55, df = 1; p = 0.21; I^2 = 35% (2)-(3) Not	(1) Chi² = 0.47, df = 1; p = 0.49; I^2 = 0% (2) Not applicable	(1) Chi² = 0.00, df = 1; p = 1.00; I^2 = 0% (2) Not applicable	(1) Chi² = 0.36, df = 1; p = 0.55; I^2 = 0% (2) Not applicable

			applicable			
Quality of the evidence (GRADE)	(1) Low[1] (2) Moderate[2]	(1) Moderate[2] (2) Low[1]	(1)-(2) Moderate[2] (3) Low[1]	(1) Moderate[2] (2) Low[1]	Moderate[2]	(1) Moderate[2] (2) Low[1]
Number of studies/participants	(1) K = 1; N = 77 (2) K = 1; N = 65	(1) K = 2; N = 133 (2) K = 1; N = 65	(1) K = 2; N = 133 (2) K = 1; N = 48 (3) K = 1; N = 43	(1) K = 2; N = 133 (2) K = 1; N = 65		(1) K = 2; N = 131 (2) K = 1; N = 65
Forest plot	1.12.2; Appendix 13					

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded due to serious imprecision as N <400.

Medical procedures for behaviour that challenges as a direct or indirect outcome

Two of the included medical procedure RCTs (GRANPEESHEH2010, ROSSIGNOL2009) compared HBOT with attention-placebo control condition. The other included medical procedure trial (ADAMS2009A) compared long-term chelation (seven rounds of DMSA therapy) and short-term chelation (one-round of DMSA therapy and six-rounds of placebo) (see Table 92). In GRANPEESHEH2010 and ROSSIGNOL2009, experimental group participants were delivered 1.3 atm and 24% oxygen in a HBOT chamber, while control participants in GRANPEESHEH2010 were provided with free airflow through the HBOT chamber at ambient pressure and control participants in ROSSIGNOL2009 were provided with slightly pressurised room air (1.03 atm and 21% oxygen). In ADAMS2009Aparticipants received one screening round of DMSA (a round consisted of three doses per day for 3 days, followed by 11 days off) and children who met criteria for phase two (in particular those excreting significant heavy metals) were randomised to receive continued DMSA (six subsequent rounds) or placebo (six subsequent rounds of methyl cellulose). DMSA was compounded individually for each child from pharmaceutical grade DMSA (over 99% pure) supplied by Spectrum Chemical. To control for the strong smell of DMSA the bottles of placebo included a small slotted container that contained DMSA so that the medication smell was present.

Table 172: Study information table for included trials of medical procedures for behaviour that challenges

	HBOT versus attention-placebo	**Long-term chelation (seven-rounds of DMSA therapy) versus short-term chelation (one-round of DMSA therapy and six-rounds of placebo)**
No. trials (N)	2 (108)	1 (49)
Study IDs	(1) GRANPEESHEH2010 (2) ROSSIGNOL2009	ADAMS2009A
Study design	(1)-(2) RCT	RCT
% female	(1) Not reported (2) 16	7
Mean age (years)	(1) 6.2 (2) 4.9	6.6
IQ	(1)-(2) Not reported	Not reported
Dose/intensity (mg/hours)	(1) Planned intensity of 80 hours (6-10 hours/week) (2) Planned intensity of 40 hours (10 hours/week)	Planned intensity for the experimental group of 180 mg/day (l-glutathione) and seven rounds of DMSA (each round consists of 3 days of DMSA [10 mg/kg-dose, nine doses over 3 days], followed by 11 days off [no treatment], and then repeating). For the control group one round of DMSA and six rounds of placebo planned
Setting	(1) Outpatient	Outpatient

	(2) Not reported	
Length of treatment (weeks)	(1) 10-15 (2) 4	17
Continuation phase (length and inclusion criteria)	(1) 34 (ClinicalTrials.gov reports 1-month and 3-month follow-ups but paper does not report follow-up data) (2) 4	17

Evidence for the effectiveness of medical procedures on behaviour that challenges and the quality of the evidence is presented in Table 173 and Table 174. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was no evidence for a statistically significant effect of HBOT on behaviour that challenges (as a direct or indirect outcome) as measured by the ABC subscales or behavioural observation (see Table 173). There was, however, evidence from another study (SAMPANTHAVIVAT2012) for statistically significant adverse events associated with HBOT with participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotraumas than participants who received sham HBOT (see Chapter 10, Section 10.4.2, for adverse events associated with HBOT).

There was also no evidence for a statistically significant effect of chelation on behaviour that challenges as measured by the PDDBI Maladaptive Behaviours composite, Arousal Regulation Problems subscale or Aggressiveness subscale (see Table 174). Data could not be extracted from this study for adverse events associated with chelation.

Table 173: Evidence summary table for effects of medical procedures (HBOT) on behaviour that challenges as a direct or indirect outcome

	HBOT versus attention-placebo					
Outcome	Behaviour that challenges	Irritability	Lethargy/Social withdrawal	Stereotypic behaviour	Hyperactivity	Inappropriate speech
Outcome measure	(1) Direct outcome – ABC Total (2) Indirect outcome – Behavioural observation: Challenging behaviour (change score)	ABC Irritability subscale (direct outcome)	ABC Lethargy/ Social Withdrawal subscale (direct outcome)	ABC Stereotypic Behaviour subscale (direct outcome)	(1) Direct outcome – ABC Hyperactivity/ Non-compliance subscale (2) Indirect outcome – Behavioural observation: Hyperactivity (change score)	ABC Inappropriate Speech subscale (direct outcome)
Study ID	(1) ROSSIGNOL2009 (2) GRANPEESHEH2010	ROSSIGNOL2009			(1) ROSSIGNOL2009 (2) GRANPEESHEH2010	ROSSIGNOL2009
Effect size (CI; p value)	(1)+(2) SMD -0.17 (-0.59, 0.24; p = 0.41) (1) *Direct outcome – ABC Total* SMD 0.04 (-0.48, 0.57; p = 0.88) (2) *Indirect outcome – Behavioural observation: Challenging behaviour* SMD -0.54 (-1.23, 0.15; p = 0.12)	SMD -0.11 (-0.64, 0.41; p = 0.67)	SMD 0.06 (-0.46, 0.59; p = 0.81)	SMD 0.17 (-0.36, 0.70; p = 0.53)	(1)+(2) SMD 0.06 (-0.36, 0.47; p = 0.79) (1) *Direct outcome – ABC Hyperactivity subscale* SMD 0.12 (-0.41, 0.64; p = 0.67) (2) *Indirect outcome – Behavioural observation: Hyperactivity* SMD -0.04 (-0.72, 0.63; p = 0.90)	SMD -0.24 (-0.77, 0.28; p = 0.37)
Heterogeneity (chi²; p value; I²)	Chi² = 1.74, df = 1; p = 0.19; *I²* = 42.6%	Not applicable			Chi² = 0.13, df = 1; p = 0.72; *I²* = 0%	Not applicable
Quality of the evidence (GRADE)	Very low[1,2,3]	Low[2]			Low[3,4]	Low[2]
Number of	K = 2; N = 90	K = 1; N = 56			K = 2; N = 90	K = 1; N = 56

studies/participants				
Forest plot	1.12.3; Appendix 13			
Note. [1]Downgraded due to serious inconsistency – I^2 value indicates moderate heterogeneity. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias for GRANPEESHEH2010 as data cannot be extracted for the ABC. [4]Downgraded due to serious imprecision as N <400.				

Table 174: Evidence summary table for effects of medical procedures (chelation) on behaviour that challenges as an indirect outcome

	Long-term chelation (seven-rounds of DMSA therapy) versus short-term chelation (one-round of DMSA therapy and six-rounds of placebo)		
Outcome	Maladaptive behaviours	Arousal regulation problems	Aggressiveness
Outcome measure	PDDBI: Maladaptive behaviours composite	PDDBI: Arousal regulation problems	PDDBI: Aggressiveness
Study ID	ADAMS2009A		
Effect size (CI; p value)	SMD 0.17 (-0.47, 0.81; p = 0.61)	SMD 0.20 (-0.44, 0.85; p = 0.53)	SMD 0.20 (-0.44, 0.84; p = 0.54)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]		
Number of studies/participants	K = 1; N = 40		
Forest plot	1.12.3; Appendix 13		
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).			

Nutritional interventions for behaviour that challenges as a direct or indirect outcome

Two of the included nutritional intervention trials examined effects of omega-3 fatty acids; however, in one trial the comparator was placebo (BENT2011), while in the other trial a healthy-diet control comparator was used (JOHNSON2010). One of the nutritional intervention trials (HASANZADEH2012) compared combined ginkgo biloba and risperidone with combined placebo and risperidone. One of the trials (KERN2001) compared a dimethylglycine supplement with placebo. One of the nutritional intervention studies (ADAMS2011) compared a multivitamin and mineral supplement with placebo. Finally, one of the trials (HANDEN2009) compared oral human immunoglobulin with placebo (see Table 175). HANDEN2009 was a four-armed trial and included three active intervention arms (low dose [140 mg/day], moderate dose [420 mg/day] or high dose [840 mg/day]). Initial analysis compared high dose with low dose groups; however, as no statistically significant differences were found on behaviour that challenges outcomes the groups were combined (across dosages) and compared with placebo.

Evidence for the effectiveness of nutritional interventions on behaviour that challenges and the quality of the evidence is presented in Table 176, Table 177, Table 178, Table 179 and Table 180. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was no evidence for statistically significant positive treatment effects of omega-3 fatty acids (compared with placebo or a healthy diet control) on behaviour that challenges as measured by the ABC, BASC or CBCL/1.5-5 (see Table 176). There was also no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

There was no evidence for statistically significant positive treatment effects of ginkgo biloba (as an adjunct to risperidone) on behaviour that challenges as measured by the ABC subscales (see Table 177). There was also no statistically significant evidence for harms associated with ginkgo biloba (see Chapter 10, Section 10.4.2, for adverse events associated with ginkgo biloba).

Table 175: Study information table for included trials of nutritional interventions for behaviour that challenges

	Omega-3 fatty acids versus placebo	Omega-3 fatty acids versus healthy diet control	Ginkgo biloba and risperidone versus placebo and risperidone	Dimethylglycine supplement versus placebo	Multivitamin/mineral supplement versus placebo	Immunoglobulin versus placebo
No. trials (N)	1 (27)	1 (23)	1 (47)	1 (39)	1 (141)	1 (125)
Study IDs	BENT2011	JOHNSON2010	HASANZADEH2012	KERN2001	ADAMS2011	HANDEN2009
Study design	RCT					
% female	11	Not reported	17	Not reported	11	14
Mean age (years)	5.8	3.4	6.4	Not reported	10.8	7.3
IQ	77.5 (assessed using the Stanford-Binet Intelligence Scales)	Not reported				
Dose/intensity (mg/hours)	1.3 g of omega-3 fatty acids per day (with 1.1 g of EPA and DHA) administered as two daily doses (with 650 mg of omega-3 fatty acids, 350 mg of EPA and 230 mg of DHA per dose)	Planned intensity of 400 mg/day (in two daily doses)	Planned final dose of 2 or 3 mg/day of risperidone (for children weighing 10-30 kg and >30 kg respectively) and 80 or 120 mg/day of ginkgo biloba (for children weighing <30 kg and >30 kg respectively)	Planned intensity of 125-625 mg/day dependent on weight (125 mg/day for children weighing <40 lbs; 250 mg/day for children weighing 41-70 lbs; 375 mg/day for children weighing 71-100 lbs; 500 mg/day for children weighing 101-130 lbs; and 625 mg/day for children weighing >131 lbs)	One dose a day at lunchtime (formulation of vitamin/mineral supplement based on 60 lb which was adjusted up or down according to body weight up to a maximum of 100 lb: 1000 IU vitamin A; 600 mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70 mg mixed tocopherols; 20 mg B1, 20 mg B2, 15 mg niacin and 10 mg niacinamide B3; 15 mg B5; 40 mg B6; 500 mcg	Planned intensity of 140 mg/day, 420 mg/day or 840 mg/day for low, moderate and high dose arms respectively

					B12; 100 mcg folic acid; 550 mcg folinic acid; 150 mcg biotin; 250 mcg choline; 100 mcg inositol; 3.6 mg mixed carotenoids; 50 mg coenzyme Q10; 50 mg N-acetylcysteine; 100 mg calcium; 70 mcg chromium; 100 mcg iodine; 500 mcg lithium; 100 mg magnesium; 3 mg manganese; 150 mcg molybdenum; 50 mg potassium; 22 mcg selenium; 500 mg sulphur; 12 mg zinc)	
Setting	Outpatient			Not reported	Outpatient	Not reported
Length of treatment (weeks)	12	13	10	4	13	12
Continuation phase (length and inclusion criteria)	12	13	10	4	13	12

Table 176: Evidence summary table for effects of nutritional interventions (omega-3) on behaviour that challenges as a direct outcome

	Omega-3 fatty acids versus placebo		**Omega-3 fatty acids versus healthy diet control**
Outcome	Behaviour that challenges		
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/ Non-compliance (5) Inappropriate Speech	BASC: (1) Externalizing (2) Behavioural symptoms (3) Hyperactivity	CBCL/1.5-5: (1) Total problem score (2) Externalizing (3) Emotional regulation (4) Withdrawn (5) Attention problems (6) Aggressive behaviours (7) ODD symptoms
Study ID	BENT2011		JOHNSON2010
Effect size (CI; p value)	(1) SMD -0.09 (-0.89, 0.71; p = 0.83) (2) SMD -0.28 (-1.09, 0.52; p = 0.49) (3) SMD -0.81 (-1.65, 0.03; p = 0.06) (4) SMD -0.42 (-1.23, 0.39; p = 0.31) (5) SMD -0.68 (-1.51, 0.14; p = 0.11)	(1) SMD -0.44 (-1.25, 0.37; p = 0.29) (2) SMD -0.24 (-1.06, 0.58; p = 0.56) (3) SMD -0.19 (-0.99, 0.61; p = 0.64)	(1) SMD -0.17 (-0.99, 0.66; p = 0.69) (2) SMD -0.10 (-0.92, 0.73; p = 0.82) (3) SMD -0.09 (-0.92, 0.73; p = 0.82) (4) SMD -0.81 (-1.67, 0.05; p = 0.07) (5) SMD -0.53 (-1.37, 0.31; p = 0.22) (6) SMD -0.00 (-0.83, 0.82; p = 1.00) (7) SMD -0.04 (-0.87, 0.78; p = 0.92)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]		Very low[1,2]
Number of studies/ participants	K = 1; N = 24	(1) K = 1; N = 24 (2) K = 1; N = 23 (3) K = 1; N = 24	K = 1; N = 23
Forest plot	1.12.4; Appendix 13		

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded.

Table 177: Evidence summary table for effects of nutritional interventions (ginkgo biloba) on behaviour that challenges as a direct outcome

	Ginkgo biloba and risperidone versus placebo and risperidone
Outcome	Behaviour that challenges
Outcome measure	ABC subscales: (1) Irritability (2) Lethargy/Social Withdrawal (3) Stereotypic Behaviour (4) Hyperactivity/ Noncompliance (5) Inappropriate Speech
Study ID	HASANZADEH2012
Effect size (CI; p value)	(1) SMD 0.10 (-0.47, 0.67; p = 0.74) (2) SMD -0.08 (-0.65, 0.49; p = 0.78) (3) SMD -0.02 (-0.59, 0.55; p = 0.95) (4) SMD 0.22 (-0.35, 0.80; p = 0.44) (5) SMD -0.21 (-0.79, 0.36; p = 0.46)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 47
Forest plot	1.12.4; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

Table 178: Evidence summary table for effects of nutritional interventions (dimethylglycine) on behaviour that challenges as a direct outcome

	Dimethylglycine supplement versus placebo
Outcome	Positive treatment response
Outcome measure	Parental report of positive response (study-specific)
Study ID	KERN2001
Effect size (CI; p value)	RR 1.10 (0.62, 1.95; p = 0.74)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 38
Forest plot	1.12.4; Appendix 13
Note. [1]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [2]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as data could not be extracted for the ABC (Irritability, Lethargy/Social Withdrawal, Stereotypic Behaviour, Hyperactivity and Inappropriate Speech subscales) or the Maladaptive Behavior Domain of the VABS and potential conflict of interest as trial funded by manufacturer of supplement.	

There was no evidence for a statistically significant positive treatment response of a dimethylglycine supplement on behaviour that challenges as measured by study-specific parental report (see Table 178). Data could not be extracted from this paper for adverse events associated with dimethylglycine.

Table 179: Evidence summary table for effects of nutritional interventions (multivitamin) on behaviour that challenges as an indirect outcome

	Multivitamin/mineral supplement versus placebo	
Outcome	Hyperactivity improvement	Tantrumming improvement
Outcome measure	PGI-R: Hyperactivity improvement	PGI-R: Tantrumming improvement
Study ID	ADAMS2011	
Effect size (CI; p value)	SMD 0.60 (0.20, 0.99; p = 0.003)	SMD 0.52 (0.13, 0.91; p = 0.009)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Moderate[1]	
Number of studies/participants	K = 1; N = 104	
Forest plot	1.12.4; Appendix 13	
Note. [1]Downgraded due to serious imprecision as N <400.		

There was moderate quality single study evidence for a moderate and statistically significant effect of a multivitamin and mineral supplement on hyperactivity and tantrumming improvement as measured by a study-specific PGI-R scale (see Table 179). There was no statistically significant evidence for harms associated with the multivitamin/mineral supplement (see Chapter 10, Section 10.4.2, for adverse events associated with the multivitamin/mineral supplement).

Table 180: Evidence summary table for effects of nutritional interventions (immunoglobulin) on behaviour that challenges as an indirect outcome

	Immunoglobulin versus placebo
Outcome	Positive treatment response
Outcome measure	Number of participants who were 'much improved/very improved' on CGI-I: (1) Clinician-rated (2) Parent-rated
Study ID	HANDEN2009
Effect size (CI; p value)	(1) *Clinician-rated* RR 0.52 (0.28, 0.97; p = 0.04) (2) *Parent-rated* RR 0.55 (0.34, 0.87; p = 0.01)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	(1) K = 1; N = 111 (2) K = 1; N = 112
Forest plot	1.12.4; Appendix 13
Note. [1]Downgraded due to serious imprecision as number of events <300. [2]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as continuous data could not be extracted for the CGI-I or PGI-Improvement (PGI-I) scale.	

There was single study evidence for placebo effects with immunoglobulin (dosages combined) on behaviour that challenges as measured by parent-rated or clinician-rated positive treatment response defined as 'much improved/very improved' on CGI-I, with participants who received placebo being around one and a half times more likely to show a positive treatment response than participants who received immunoglobulin (see Table 180). Narrative review of this placebo effect showed that participants in both experimental and control conditions showed improvement; however, there were a greater number of participants who were rated as responders

in the placebo group. There was no statistically significant evidence for harms associated with immunoglobulin (see Chapter 10, Section 10.4.2, for adverse events associated with immunoglobulin).

Sensory interventions for behaviour that challenges as an indirect outcome

The one included sensory intervention study (BETTISON1996) compared auditory integration training with an attention-placebo condition and examined effects on behaviour that challenges as an indirect outcome (see Table 181). The auditory integration training was based on the method of Berard (1993). Experimental group participants listened to filtered and modulated music that was specially modified for each participant based on their pre-test audiogram. While participants in the control group listened to the same music for the same number of sessions as the experimental group; however, for the control group the music was unmodified (structured listening condition).

Table 181: Study information table for included trial of sensory interventions for behaviour that challenges

	Auditory integration training versus attention-placebo (structured listening)
No. trials (N)	1 (80)
Study IDs	BETTISON1996
Study design	RCT
% female	18
Mean age (years)	Not reported
IQ	PIQ 76 (as assessed using the LIPS)
Dose/intensity (mg/hours)	10 hours (7 hours/week)
Setting	Educational
Length of treatment (weeks)	1.4
Continuation phase (length and inclusion criteria)	52 (follow-up assessments at 1 month, 3 months, 6 months and 1 year)

Evidence for the effectiveness of auditory integration training on behaviour that challenges and the quality of the evidence is presented in Table 182. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 182: Evidence summary table for effects of sensory interventions on behaviour that challenges as an indirect outcome

	Auditory integration training versus attention-placebo (structured listening)	
Outcome	Behaviour that challenges	
Outcome measure	Parent-rated DBC: total at: (1) 1-month post-intervention follow-up (2) 3-month post-intervention follow-up (3) 6-month post-intervention	Teacher-rated DBC: total at: (1) 1-month post-intervention follow-up (2) 3-month post-intervention follow-up (3) 6-month post-intervention

	follow-up (4) 12-month post-intervention follow-up	follow-up (4) 12-month post-intervention follow-up
Study ID	BETTISON1996	
Effect size (CI; p value)	(1) *1-month follow-up* SMD 0.06 (-0.38, 0.50; p = 0.79) (2) *3-month follow-up* SMD 0.20 (-0.24, 0.64; p = 0.37) (3) *6-month follow-up* SMD 0.26 (-0.18, 0.70; p = 0.25) (4) *12-month follow-up* SMD 0.24 (-0.20, 0.68; p = 0.28)	(1) *1-month follow-up* SMD -0.16 (-0.60, 0.28; p = 0.47) (2) *3-month follow-up* SMD -0.15 (-0.59, 0.29; p = 0.51) (3) *6-month follow-up* SMD -0.04 (-0.48, 0.39; p = 0.84) (4) *12-month follow-up* SMD 0.09 (-0.35, 0.53; p = 0.68)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	(1)-(2) Low[1] (3) Moderate[2] (4) Low[1]
Number of studies/participants	K = 1; N = 80	
Forest plot	1.12.5; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to serious imprecision as N <400.		

There was no evidence for statistically significant indirect effects of auditory integration training on behaviour that challenges as measured by the DBC total score (see Table 182).

7.4.3 Clinical evidence summary – effect of biomedical interventions on behaviour that challenges

There was single study data for positive treatment effects of massage or a multivitamin and mineral supplement on behaviour that challenges. However, the evidence was very limited and further randomised placebo-controlled studies are required to corroborate the existing evidence for massage and dietary supplements in children and young people with autism.

There was insufficient evidence to reach a conclusion about the effect of electro-acupuncture, hormone treatment (secretin), medical procedures (HBOT and DMSA), nutritional or sensory interventions on behaviour that challenges.

7.5 HEALTH ECONOMIC EVIDENCE – BEHAVIOUR THAT CHALLENGES

Systematic literature review

No studies assessing the cost effectiveness of interventions aimed at behaviour that challenges were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

Economic modelling

Introduction – objective of economic modelling

Assessment of the findings of the guideline systematic review of clinical evidence indicated that antipsychotic medication is effective in the management of behaviour that challenges in children and young people with autism. Therefore, an economic analysis was undertaken to assess the cost effectiveness of antipsychotic drugs for the management of behaviour that challenges in children and young people with autism.

Economic modelling methods

Interventions assessed

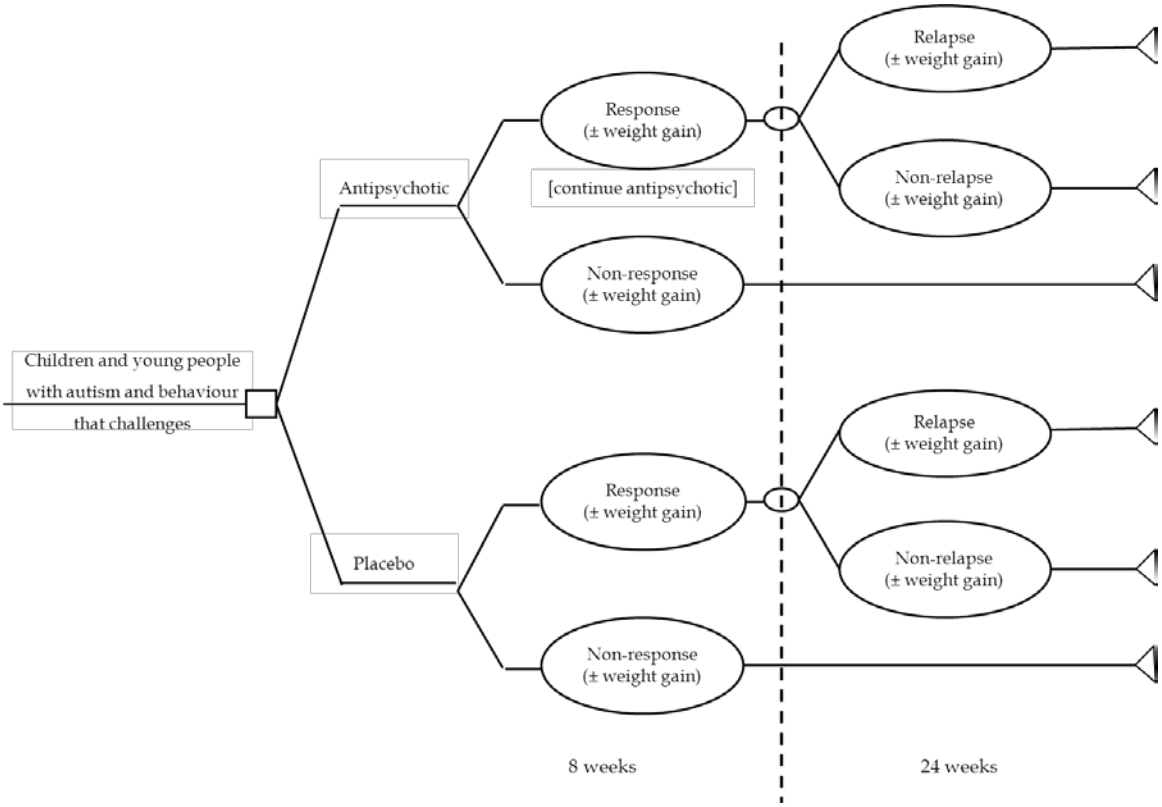
The trials on antipsychotics aimed at behaviour that challenges that were included in the guideline systematic review assessed various doses of either risperidone or aripiprazole versus placebo; consequently, the guideline economic analysis assessed the relative cost effectiveness of risperidone, aripiprazole and placebo. Risperidone is available in tablets and orodispersible tablets, as well as in oral solution formulation, all of which were considered in the analysis as they entail different acquisition costs. Aripiprazole is available only in tablet formulation which was assessed in the analysis.

Model structure

A simple decision-tree was constructed to estimate the cost effectiveness of antipsychotics versus placebo for the management of behaviour that challenges in children and young people with autism. According to the model structure, hypothetical cohorts of children and young people with autism and behaviour that challenges received either an antipsychotic or placebo for 8 weeks. At the end of the 8 weeks children and young people either responded to treatment and showed improvement in their behaviour, or they did not respond. All cohorts were further followed for 24 weeks. Children and young people that had responded to the 8-week antipsychotic treatment continued medication over the follow-up 24-week period. At the end of 24 weeks children and young people that had responded to treatment (antipsychotics or placebo) either relapsed or remained improved. Children and young people that did not respond to treatment at the end of the first 8 weeks (that is, at completion of treatment) were assumed to retain the same levels of behaviour that challenges over the next 24 weeks. Children and young people in both arms of the model could experience weight gain as an adverse event of treatment. Weight gain is one of the most common adverse events of antipsychotic medication; the guideline systematic review and meta-analysis demonstrated a statistically significant increase in weight following antipsychotic medication. Therefore, given also the availability of relevant utility data, weight gain was selected out of a range of adverse events associated with antipsychotics, for incorporation into the model structure. Other common side effects that have been associated with antipsychotic medication, such as prolactine elevation, neurological symptoms, gastrointestinal and metabolic side effects were not considered in the model due to lack of

appropriate clinical and/or utility data, or lack of statistical significance in the guideline meta-analysis. The time horizon of the model was 32 weeks (8 weeks of treatment and 24 weeks of follow-up). The duration of treatment and follow-up periods was determined by respective time periods in the trials that provided clinical data in the economic analysis. Response to treatment was defined as an improvement of at least 25% on the ABC-irritability scale. A schematic diagram of the decision-tree is presented in Figure 3.

Figure 3. Schematic diagram of the structure of the economic model evaluating antipsychotic drugs versus placebo for the management of behaviour that challenges in children and young people with autism



Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and personal social services, as recommended by NICE (*The Guidelines Manual* [NICE 2012]). Costs consisted of intervention costs only, as no data on costs incurred by children and young people with autism due to the presence of behaviour that challenges were identified in the relevant literature. The measure of outcome was the QALY.

Clinical input parameters

Clinical input parameters included the probability of response to placebo at 8 weeks, the risk ratio of response for antipsychotics versus placebo, the 24-week probability

of relapse after response to treatment, the risk of weight gain associated with placebo and the risk ratio of weight gain for antipsychotics versus placebo.

Four RCTs included in the guideline systematic review assessed antipsychotics versus placebo aimed at behaviour that challenges and reported response rates defined as at least 25% improvement on the ABC-irritability scale post-treatment (JOHNSON&JOHNSON2011, MARCUS2009, OWEN2009, RUPPRISPERIDONE2001). Two of the trials assessed risperidone (JOHNSON&JOHNSON2011 and RUPPRISPERIDONE2001), while the other two assessed aripiprazole (MARCUS2009, OWEN2009). Pooled weighted data from the placebo arms of the four trials were used to estimate the probability of response for placebo at 8 weeks that was utilised in the model. Meta-analysis of the trials provided the risk ratio of response for antipsychotics versus placebo.

Two trials assessed relapse to behaviour that challenges in children and young people that had responded to antipsychotic treatment over an open-label phase and were subsequently either continued on or discontinued from antipsychotic medication (RUPPRISPERIDONE2001, TROOST2005). Pooled weighted relapse data from the antipsychotic continuation arms were used to estimate the 24-week probability of relapse in both arms of the economic model (that is, antipsychotics and placebo). It should be noted that the relapse data reported for the discontinuation arms of the RCTs (that is, arms that discontinued the antipsychotic and received placebo following response to treatment) were not deemed to be relevant to the placebo arm of the economic model, as in discontinuation arms of the trials participants had already received an antipsychotic and discontinued it, whereas in the placebo arm of the economic model children and young people had never been initiated on an antipsychotic.

Data on weight gain (defined as an increase in weight of at least 7%) were derived from two trials included in the guideline systematic review that compared aripiprazole versus placebo (MARCUS2009, OWEN2009). The risk of weight gain associated with placebo was based on pooled weighted data from the placebo arms of these two trials, while the risk ratio of weight gain for antipsychotics versus placebo was derived from meta-analysis of the two trials.

Utility data and estimation of quality adjusted life years

In order to express outcomes in the form of QALYs, the health states of the economic model need to be linked to appropriate utility scores. Utility scores represent the health related quality of life (HRQoL) associated with specific health states on a scale from 0 (death) to 1 (perfect health); they are estimated using preference-based measures that capture people's preferences on the HRQoL experienced in the health states under consideration. Preference-based measures are instruments consisting of a health state classification system, that is, an instrument that allows determination of the health state of the respondent, and an algorithm that links every health state described by the instrument with a utility score. Utility scores (which express preferences) can be elicited from various population groups (for example, service

users, their parents and carers, healthcare professionals or members of the general population). The main methods of valuation are the VAS, the time trade-off and the standard gamble (Brazier et al., 2007).

The systematic search of the literature identified three studies that reported utility scores for children and young people with autism (Petrou et al., 2010; Petrou & Kupek, 2009; Tilford et al., 2012).

Petrou and Kupek (2009) reported utility scores relating to a large number of childhood conditions using data on 2,236 children aged 6 years, the principal carers of which had participated in a survey on childhood disabilities conducted in the UK in 2000. Diagnosis of children's disorders, including autism, was confirmed by each child's GP, using ICD-9 codes. Carers rated children's HRQoL using the Health Utility Index (HUI). HUI is a family of preference-based multi-attribute utility measures (Torrance et al., 1995). The third version of the HUI health state classification system (HUI3) is the most widely used among the measures of the HUI family, and has been recommended by its developers for the estimation of QALYs in cost-utility analysis. HUI3 covers eight attributes: cognition, vision, hearing, speech, ambulation, dexterity, emotion and pain; each attribute has five or six levels of response. Responses to HUI3 can be converted into utility scores using a published algorithm that was developed based on the principles of multi-attribute utility theory, following a valuation survey of members of the general population in Canada; respondents' preferences were elicited using VAS and standard gamble (Feeny et al., 2002). The HUI version completed by carers in the survey on childhood disabilities contained the items of the HUI3 health state classification system, and therefore allowed Petrou and Kupek to estimate utility scores corresponding to specific childhood disabilities. The autism-related utility data were estimated from the responses of 105 principal carers of children with autism.

Petrou and colleagues (2010) reported utility scores relating to different psychiatric conditions as well as different levels of cognitive impairment in children, estimated from parent-reported data on 331 children, aged 11 years, 190 of which were born extremely preterm and 141 were term-born, all of which had participated in a whole-population longitudinal study of extremely preterm children and term-born controls conducted in the UK and Ireland in 1995. Diagnosis of any psychiatric disorder in the study sample was made using the Development and Well Being Assessment interview and the Kaufman–Assessment Battery for Children. This information was used to assign DSM-IV text revision (DSM–IV–TR) diagnoses. Utility scores were estimated using parents' ratings of their children's HRQoL using the second version of HUI (HUI2) and HUI3. HUI2 is a health state classification system that belongs in the HUI family and has been specifically designed for children. HUI2 has seven attributes: sensation, mobility, emotion, cognition, self-care, pain and fertility, each having between three and five levels of response (Torrance et al., 1996). The HUI2 version used in the study by Petrou and colleagues covered six attributes (all of the above except fertility). HUI2 profiles can be converted into utility scores using an algorithm constructed following a valuation survey of members of the UK general

population that employed standard gamble techniques (McCabe et al., 2005). Among other data, Petrou and colleagues reported utility scores for 11 children with any autistic disorder and 128 term-born children with no diagnosis of psychiatric disorder (controls).

Tilford and colleagues (2012) reported utility data corresponding to various health states and symptoms associated with autism in children and young people. The study recruited 150 children aged 4 to 17 years from two different sites in the US. All children had a clinical diagnosis of autism meeting DSM-IV-TR criteria (that is, autistic disorder, PDD-NOS or Asperger's syndrome) and confirmed by scores meeting or exceeding cut-offs for classification with autism on the ADOS. Autism-related symptoms (such as sensory issues, social interactions) as well as other behavioural symptoms (such as aggression and hyperactivity) were assessed using the Autism Treatment Network battery. Utility scores were estimated using parents' ratings of their children's HRQoL on HUI3 and the Quality of Well Being Self-Administered scale (QWB-SA). The latter is an instrument that includes three scales of functioning (mobility, physical activity and social activity) and a measure of 58 symptom and problem complexes; two of the symptoms (sexuality and hangovers) were not applicable to younger children with autism and were therefore excluded from the questionnaires. QWB-SA has been valued by 866 community members in the US using VAS (Kaplan & Anderson, 1988).

Table 183 summarises the methods used to derive and value health states associated with autism in children and young people and the resulting utility scores, as reported in the three studies identified in the systematic literature search conducted for this guideline. Two of the studies included in the guideline systematic review (Petrou et al., 2010; Petrou & Kupek, 2009) report overall utility scores for children with autism, and not utility scores corresponding to autism-related health states and symptoms. In addition, Petrou and Kupek (2009) report reductions in utility of children with autism relative to childhood norms, whereas Petrou and colleagues (2010) report utility scores for children without psychiatric diagnosis that can be used as a comparison, in order to estimate the disutility caused by autism. It can be seen that the reported mean utility scores relating to autism vary widely: in Petrou and Kupek (2009) the mean reported utility score, which was derived from analysis of HUI3 data, is as low as 0.433, while in the study by Petrou and colleagues (2010) the mean reported utility score is 0.721, if derived from HUI2, and 0.609, if derived from HUI3. For comparison, the overall mean utility score for children with autism reported by Tilford and colleagues (2012) is 0.64 when estimated using the HUI3, and 0.58 when estimated using the QWB-SA. These discrepancies in the mean utility score of children with autism across studies (range 0.433-0.721) may be partly explained by differences in the study samples regarding the definition of autism, the inclusion or exclusion of various types of autism (such as Asperger's syndrome), and the use of different preference-based measures.

The study by Tilford and colleagues (2012) was the only study that reported utility scores for a wide range of health states and symptoms associated with autism in

children. Table 183 includes utility data only for a selection of health states and symptoms of those considered in the study. Health states and symptoms presented in this table are those reflecting or relating closer to states and symptoms considered in economic modelling undertaken for this guideline. The table also includes the level of adjusted statistical significance (p) in the utility scores characterising different severity levels of a symptom. It can be seen that, with the exception of utility scores derived from HUI3 for different severity levels of 'aggression', utility scores based on either HUI3 or QWB-SA can distinguish across different severity levels of all other symptoms included in this table. The authors reported that HUI3 was more sensitive to clinical measures used to characterise children with autism compared with the QWB-SA score and proposed the use of HUI3 for the estimation of QALYs in cost-utility analyses of interventions for children with autism.

Table 183: Summary of studies reporting utility scores for children and young people with autism

Study	Definition of health states	Valuation method	Population valuing	Health states and corresponding utility scores		
Petrou & Kupek, 2009	HUI3 profiles of 105 children with autism, aged 6 years, based on principal carers' responses; data derived from a UK survey on childhood disabilities in 2000. Autism definition confirmed by child's GP, using ICD-9 codes.	Standard gamble	504 members of the Canadian general population	Autism (n = 105) Adjusted change from childhood norms	0.433 (25th/75th percentiles: 0.239/0.695) -0.494 (95%CI: -0.372 to -0.624)	
Petrou et al., 2010	HUI2 and HUI3 profiles of 11 children with autism and 130 term-born children without psychiatric disorder, aged 11 years, that had participated in a study of extremely preterm children and term-born controls in the UK and Ireland in 1995; profiles based on parents' responses. DSM–IV–TR diagnosis assigned using the Development and Well Being Assessment interview and the Kaufman–Assessment Battery for Children.	HUI2 – standard gamble HUI3 – standard gamble	198 members of the UK general population 504 members of the Canadian general population		HUI2	HUI3
				Any autistic disorder (n = 11)	0.721 (SD 0.152)	0.609 (SD 0.257)
				No psychiatric disorder (n = 130)	0.948 (SD 0.077)	0.967 (SD 0.070)
Tilford et al., 2012	HUI3 and QWB-SA profiles of 150 children and young people with autism aged 4 to 17 years, in the US; profiles constructed for different health states and symptoms associated with autism, based on parents' responses.	HUI3 – standard gamble QWB-SA –	504 members of the Canadian general population 866	Full sample Autistic disorder PDD-NOS Asperger's disorder <u>Compulsive behaviours</u> No problem Minor problem	HUI3 (n=136) 0.66 (SD 0.23) 0.64 (SD 0.23) 0.70 (SD 0.24) 0.79 (SD 0.16) (p=0.04) 0.72 (SD 0.19)	QWB-SA (n=140) 0.59 (SD 0.16) 0.58 (SD 0.16 0.62 (SD 0.18) 0.62 (SD 0.15) (p=0.02) 0.63 (SD 0.16)

	Diagnosis of autism based on DSM-IV criteria	VAS	community members in the US	Moderate problem Severe problem <u>Aggression</u> No problem Minor problem Moderate problem Severe problem <u>Hyperactivity</u> No problem Mild problem Moderate problem Severe problem <u>Attention span</u> No problem Mild problem Moderate problem Severe problem <u>Anxiety</u> No problem Mild problem Moderate problem Severe problem	0.69 (SD 0.23) 0.64 (SD 0.24) 0.61 (SD 0.23) (p = 0.12) 0.69 (SD 0.21) 0.69 (SD 0.22) 0.50 (SD 0.29) 0.66 (SD 0.22) (p <0.01) 0.73 (SD 0.26) 0.72 (SD 0.20) 0.66 (SD 0.21) 0.59 (SD 0.23) (p <0.01) 0.82 (SD 0.14) 0.72 (SD 0.19) 0.69 (SD 0.24) 0.60 (SD 0.22) (p = 0.01) 0.72 (SD 0.23) 0.69 (SD 0.21) 0.65 (SD 0.24) 0.63 (SD 0.19)	0.58 (SD 0.13) 0.58 (SD 0.15) 0.53 (SD 0.19) (p = 0.03) 0.61 (SD 0.17) 0.57 (SD 0.14) 0.49 (SD 0.14) 0.55 (SD 0.14) (p = 0.03) 0.59 (SD 0.21) 0.61 (SD 0.15) 0.61 (SD 0.14) 0.52 (SD 0.15) (p <0.01) 0.72 (SD 0.18) 0.64 (SD 0.16) 0.57 (SD 0.16) 0.55 (SD 0.14) (p = 0.01) 0.66 (SD 0.15) 0.55 (SD 0.16) 0.58 (SD 0.15) 0.56 (SD 0.17)

According to NICE guidance on the selection of utility values for use in cost-utility analysis, the measurement of changes in HRQoL should be reported directly from people with the condition examined, and the valuation of health states should be based on public preferences elicited using a choice-based method, such as the time trade-off or standard gamble, in a representative sample of the UK population. When changes in HRQoL cannot be obtained directly by the people with the condition examined, then data should be obtained from their carers. NICE recommends European Quality of Life - 5 Dimensions (Brooks, 1996; Dolan, 1997) for use in cost-utility analyses of interventions for adults; for economic evaluation of interventions for children, the Institute recommends use of standardised and validated preference-based measures of HRQoL, such as HUI2, that have been designed specifically for use in children (NICE, 2008 guide to the methods of technology appraisal).

The studies by Petrou and colleagues (2010) and Petrou and Kupek (2009) do not provide utility scores for different autism-related health states and therefore they are not useful in populating economic models that incorporate different health states and symptoms associated with autism in their structure. The study by Tilford and colleagues (2012) is the only study identified that reported utility data for different health states of autism and consequently can be used in economic modelling of interventions for autism in children. The study provides utility scores based on HUI3 and QWB-SA, but the authors reported that HUI3 appeared to be more sensitive than QWB-SA to clinical measures used to characterise children with autism. Valuation of HUI3 was undertaken using standard gamble, which is a method recommended by NICE, while QWB-SA has been valued using VAS. For these reasons the economic models developed for this guideline were populated with HUI3-derived utility scores reported in Tilford and colleagues (2012). However, it should be noted that HUI3 has not been designed specifically for use in children. The GDG felt that HUI3 is not appropriate for use in children and young people with autism as its items are not directly relevant to the symptoms of autism. Moreover, HUI3 scores are not directly applicable to the UK context, since valuation was based on the preferences of members of the Canadian population. Nevertheless, given the lack of other appropriate utility data, the utility scores derived from HUI3 that were reported in Tilford and colleagues (2012) were used in the economic modelling performed to assist guideline development.

The guideline economic analysis utilised data on response to treatment defined by an at least 25% improvement on the ABC-irritability scale. Irritability levels were not connected to utility scores in the study by Tilford and colleagues (2012). However, the study reported utility scores corresponding to different levels of aggression, hyperactivity, compulsive behaviour and attention, all of which are related to behaviour that challenges. The changes in utility scores corresponding to different aggression levels were found to be non-significant. It was therefore decided to use utility scores

for different levels of hyperactivity as a proxy for changes in irritability following treatment with antipsychotics or placebo. The economic analysis conservatively assumed that at initiation of treatment the HRQoL of children and young people with autism corresponded to moderate levels of hyperactivity/irritability that improved to mild symptoms following response to treatment. Children that relapsed were assumed to return to the utility score corresponding to moderate symptom levels of hyperactivity/irritability. It was assumed that all improvements and decrements in utility occurred linearly between initiation and completion of the 8-week treatment, and between that point and the end of the 24-week follow-up, respectively.

Adverse events from medication are expected to result in a reduction in utility scores of children with autism. The economic analysis considered the disutility caused by weight gain, which is one of the most common side effects of antipsychotics. Disutility data associated with the presence of weight gain in children with autism were reported in Tilford and colleagues (2012), but these were generated using QWB-SA and therefore did not meet NICE requirements. Moreover, the study showed discrepancies between utility scores generated using HUI3 and those generated using QWB-SA, and therefore utility scores derived from these 2 measures could not be combined in the economic model. Instead, the analysis utilised relevant data from Lenert and colleagues (2004), who reported the disutility caused by weight gain in adults with schizophrenia; HRQoL in this population was measured using the Positive and Negative Syndrome Scale, a schizophrenia-specific measure, and utility values were elicited from members of the US public using standard gamble. Consequently these data are not directly applicable to children and young people with autism; moreover, they do not express preferences of the UK population. However, given the lack of any other relevant disutility data, these data were utilised in the guideline economic analysis.

Table 184 presents the values of clinical input parameters as well as utility data that were used to populate the economic model.

Table 184: Clinical input parameters and utility data used to populate the economic model of antipsychotics versus placebo for the management of behaviour that challenges in children and young people with autism

Input parameter	*Deterministic value*	*Probabilistic distribution*	*Source of data – comments*
Clinical input parameters			
Probability of response at 8 weeks – placebo	0.239	**Beta distribution** A = 44, β = 140	Pooled weighed rate for placebo, guideline meta-analysis
Risk ratio of response, antipsychotics versus placebo	2.27	**Log-normal distribution** 95% CI: 1.75 to 2.94	Guideline meta-analysis
Probability of relapse at 24 weeks' follow-up	0.179	**Beta distribution** α= 5, β= 23	Pooled weighted rate for antipsychotic continuation arm in relapse prevention trials, guideline meta-analysis
Risk of weight gain – placebo	0.069	**Beta distribution** α= 7, β= 94	Pooled weighed rate for placebo, guideline meta-analysis
Risk ratio of weight gain, antipsychotics versus placebo	3.80	**Log-normal distribution** 95% CI: 1.79 to 8.05	Guideline meta-analysis
Utility scores		**Beta distribution**	Tilford et al., 2012; based on method of moments. Utility score for 'mild hyperactivity' not allowed to fall below that for 'moderate hyperactivity'
Mild hyperactivity	0.72	α = 26, β = 10	
Moderate hyperactivity	0.66	α = 30, β = 16	
Weight gain – multiplicative function	0.959	α = 61, β = 3	Lenert et al., 2004; based on method of moments. Value needs to be multiplied by base condition utility score to give the overall utility in the presence of weight gain

Cost data

The intervention cost of antipsychotics consists of the drug acquisition cost and the cost of clinical management (healthcare professional time). The intervention cost of placebo comprises the cost of clinical management only. Healthcare professional time was estimated to be the same in both arms of the model, and was therefore excluded from further consideration. Consequently, in the economic analysis the intervention cost of antipsychotics included exclusively drug acquisition costs, while the intervention cost of placebo was zero.

As described earlier, the model considered all 3 available formulations of risperidone (tablets, orodispersible tablets and oral solution) and the only available formulation of aripiprazole (tablets). The daily dosage of drugs was determined by the daily dosage administered in the trials that provided clinical data used in the economic model. The acquisition costs of the various formulations of risperidone and of aripiprazole tablets were taken from the Electronic Drug Tariff for England and Wales, January 2013 (NHS, Business Services Authority 2013). Daily dosage and drug acquisition costs are presented in Table 185.

Costs incurred by behaviour that challenges were not included in the analysis due to unavailability of relevant data, but it is recognised that behaviour that challenges incurs significant extra costs to health and social care services. Costs of treating side effects were also not included in the analysis; it is likely that the cost of managing weight gain, which is the only adverse event considered in the model structure, is not substantial. However, there are other adverse events, such as extrapyramidal symptoms, that require more intensive clinical management and consequently may incur considerable healthcare costs. Omission of costs associated with the presence of behaviour that challenges and with side effects from antipsychotic medication is acknowledged as a limitation of the analysis.

As the time horizon of the analysis was 32 weeks, no discounting of costs and outcomes was necessary.

Table 185: Drug acquisition costs considered in the economic analysis of antipsychotics aimed at behaviour that challenges in children and young people with autism

Drug	*Dosage*	*Daily cost per child or young person*	*Notes on estimation of cost (NHS Drug Tariff, January 2013)*
Risperidone – tablets	1.5 mg or 2 mg (mean 1.75 mg)	£0.06	Risperidone (non-proprietary) 0.5 mg 20 tablets – £0.91; 1 mg 20 tablets – £0.83; 2 mg 60 tablets – £1.61
Risperidone – oral solution	1.75 mg	£0.97	Risperidone (non-proprietary) oral solution 1 mg/ml – 100 ml – £55.32
Risperidone – orodispersible tablets	1.5 mg or 2 mg (mean 1.75 mg)	£1.38	Risperidone (non-proprietary) 0.5 mg 28 orodispersible tablets – £21.79; 1 mg 28 orodispersible tablets – £19.45; 2 mg 28 orodispersible tablets – £35.77
Aripiprazole – tablets	5 mg or 10 mg or 15 mg	£3.43	Abilify© 5 mg or 10 mg or 15 mg – 28 tablets – £96.04

Handling uncertainty

Model input parameters were synthesised in a *probabilistic* analysis. This means that model input parameters were assigned probability distributions (rather than being expressed as point estimates), to reflect the uncertainty characterising the available data. Subsequently, 1000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Results (mean costs and QALYs for each intervention) were averaged across the 1000 iterations. This exercise provides more accurate estimates than those derived from a *deterministic* analysis (which utilises the mean value of each input parameter ignoring any uncertainty around the mean), by capturing the non-linearity characterising the economic model structure (Briggs et al., 2006).

The probability of responding to placebo at 8 weeks, the 6-month probability of relapse following response, and the risk of weight gain with placebo were assigned a beta distribution. Beta distributions were also assigned to utility values, using the method of moments. Risk ratios were assigned a log-normal distribution. Drug costs were not assigned a distribution as there is no uncertainty around their cost. The estimation of distribution ranges was based on the guideline meta-analysis and available data in the published sources of evidence.

Table 184 provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

Results are presented in the form of the Incremental Cost Effectiveness Ratio (ICER) of each antipsychotic versus placebo, expressing the additional cost per QALY gained associated with provision of the antipsychotic in children and young people with autism and behaviour that challenges. In addition, the probability of each antipsychotic being cost-effective at the NICE cost effectiveness threshold of £20,000-£30,000/QALY (NICE 2008, social value judgments) is reported.

Validation of the economic model

The economic model (including the conceptual model and the excel spreadsheet) was developed by the guideline health economist and checked by a second modeller not working on the guideline. The model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The results were discussed with the GDG for their plausibility.

Results

Over the 32 weeks of the analysis, antipsychotics resulted in 0.84 additional QALYs per 100 children and young people with autism and behaviour that challenges compared with placebo. Risperidone in tablet formulation dominated all other options, as it has the lowest acquisition cost. However, ICERs of all assessed drug/formulation options versus placebo were calculated because different drugs/formulations of a drug may be indicated for different subgroups of children

and young people with autism and challenging behaviour, and therefore their cost effectiveness relative to placebo is relevant in such cases.

The ICERs of the three formulations of risperidone, that is, tablet, oral solution and orodispersible tablet were £1,004/QALY, £17,083/QALY, and £24,267/QALY, respectively. The first two ICERs are below the NICE lower cost effectiveness threshold of £20,000/QALY; the ICER of risperidone orodispersible tablet versus placebo is below the NICE upper cost effectiveness threshold of £30,000/QALY. The ICER of aripiprazole versus placebo is well beyond the NICE cost effectiveness threshold, at £60,527/QALY. Full results are presented in Table 186.

Table 186: Results of probabilistic economic analysis of antipsychotics versus placebo for the management of behaviour that challenges in children and young people with autism – mean costs and QALYs for 100 children and young people with autism receiving treatment

Antipsychotic drug	*Mean total cost*	*Mean total QALYs*	*ICER versus placebo*
Risperidone – tablets	£846	42.20	£1,003/QALY
Risperidone – oral solution	£14,385	42.20	£17,065/QALY
Risperidone – orodispersible tablets	£20,433	42.20	£24,240/QALY
Aripiprazole – tablets	£50,965	42.20	£60,461/QALY
Placebo	£0	41.36	NA

The probability of the three formulations of risperidone (tablet, oral solution, and orodispersible tablets) being cost-effective at the NICE lower threshold (£20,000/QALY) were 0.63, 0.47 and 0.40, respectively. The probabilities of their being cost-effective at the NICE upper threshold (£30,000/QALY) were 0.64, 0.53 and 0.48, respectively. The probability of aripiprazole being cost-effective at the NICE lower (£20,000/QALY) and upper (£30,000/QALY) cost effectiveness threshold was 0.10 and 0.23, respectively.

Discussion of findings – limitations of the analysis

The results of the economic model indicate that risperidone (and potentially other antipsychotics with similar acquisition costs, for example those available as generics) is likely to be a cost-effective intervention for the management of behaviour that challenges in children and young people with autism. The ICER of risperidone in tables or oral solution formulation was found to be below the lower NICE cost effectiveness threshold of £20,000/QALY. The ICER of risperidone in orodispersible tablet formulation was between £20,000 and £30,000/QALY, whereas the ICER of aripiprazole was well above the upper NICE cost effectiveness threshold of £30,000/QALY.

The analysis considered risperidone and aripiprazole because these were the only antipsychotics for which clinical evidence was available. The evidence base was

limited and not adequate to reveal potential differences in the effectiveness across different antipsychotics. Thus the economic analysis used pooled efficacy data from the two antipsychotics. Regarding adverse events, the economic model considered the risk for weight gain and the resulting decrements in utility. Weight gain data were available for aripiprazole only, but were applied to risperidone arms as well, due to lack of risperidone-specific weight gain data. Consequently, any differences in the relative cost effectiveness of the two drugs resulted exclusively from differences in their acquisition costs. For this reason the results cannot lead to safe conclusions regarding the relative cost effectiveness between different antipsychotics.

Nevertheless, the analysis demonstrated that drug acquisition cost is an important driver of cost effectiveness, as more expensive drugs or formulations of the same drug are significantly less cost-effective than options with lower acquisition cost. Of the drugs and drug formulations assessed, risperidone in tablet formulation was the least costly and thus the most cost-effective option. However, there may be instances where other formulations of risperidone or other antipsychotics may be more appropriate for some children and young people with autism, depending on the drug's side effect profile, contra-indications and other individual circumstances.

Weight gain was selected for incorporation in the model structure as it is one of the most common adverse events associated with antipsychotic medication, and relevant clinical and utility data were available to populate the model. However, antipsychotic medication is linked to a number of other adverse events, such as extrapyramidal symptoms or elevation in prolactin levels, all of which have a negative impact on the HRQoL of children and young people with autism and most likely incur extra healthcare costs for their management. These parameters (disutility due to adverse events other than weight gain and costs of management of adverse events) were not taken into account in the model due to lack of relevant data. It should be noted that different antipsychotics have different side effect profiles, and this may potentially affect their relative cost effectiveness.

Estimation of QALYs was based on utility data derived from HUI3 responses of parents of children with autism in the US. However, HUI3 has not been specifically designed for children. Most importantly, the GDG judged that HUI3 is not appropriate for use in children and young people with autism as its items are not directly relevant to autism symptoms. Moreover, utility scores for HUI3 have been elicited from members of the Canadian general population and therefore they are not directly applicable to the UK context. Ideally an alternative utility measure should have been used for the estimation of QALYs, but at the moment no such measure designed specifically for children and young people with autism is available.

The model was populated with HUI3-based utility scores corresponding to different levels of hyperactivity, although response to treatment in the model was measured on the ABC Irritability subscale, due to lack of utility data specific to irritability. It

must be noted that utility data specific to different aggression levels are available, but changes in utility following changes in the severity of aggression were found to be non-significant in the published literature. The model also utilised disutility data associated with weight gain. These data were based on analysis of Positive and Negative Syndrome Scale scores of adults with schizophrenia and subsequent elicitation of preferences for schizophrenia-related health states from members of the US public. Consequently, these data are not directly relevant to children and young people with autism, but they were nevertheless utilised in the economic model due to lack of any other relevant data.

Costs incurred by behaviour that challenges were not included in the analysis due to unavailability of relevant data. However, behaviour that challenges requires extra healthcare resources for its management and is a common reason for admission to CAMHS inpatient services, long-term care settings or boarding schools. It is also likely that the presence of challenging behaviour in this population incurs extra intangible as well as informal care costs to the family, which have not been taken into account in the economic analysis. The analysis had a time horizon of 32 weeks. Longer term benefits and cost-savings resulting from a reduction in behaviour that challenges were not considered in the model, due to lack of relevant data. This means that the cost effectiveness of antipsychotics for the management of behaviour that challenges in children and young people with autism is probably higher than that estimated by the guideline analysis.

Overall conclusions from economic modelling

Taking into account the results and limitations of the analysis, it appears that risperidone (and potentially other antipsychotics with similar acquisition costs, for example those available as generics) is likely to be a cost-effective intervention for the management of behaviour that challenges in children and young people with autism. Drug acquisition cost is an important driver of cost effectiveness and should be taken into account at the selection of the antipsychotic drug and the formulation administered.

7.6 FROM EVIDENCE TO RECOMMENDATIONS

Based on their expert knowledge and experience, the GDG judged that, in order to minimise the risk of behaviour that challenges, it is crucial that regular assessments are carried out to determine the presence of factors that are known to influence such behaviours, such as communication problems and pain. In addition, the GDG took the view that children and young people with autism and their families and carers should be involved in the development of a care plan to outline how the relevant risk factors should be treated and/or managed. When behaviour that challenges occurs, the GDG recommended that the first response should be a reassessment of the possible factors that could be causing the behaviour, followed by relevant environmental changes or treatment of any identified coexisting physical, mental health or behavioural disorders.

If the behaviour persists, the GDG judged that health and social care professionals should consult senior colleagues for advice, while also arranging a review to discuss the behaviour. Based on their expertise and knowledge, the GDG recommended that the review should involve all members of the multidisciplinary team who are involved in the child or young person's care, with the aim of identifying possible interventions for the behaviour. Discussion within the GDG highlighted the need for a range of factors to be considered when trying to identify a suitable intervention, including the nature, severity and impact of the behaviour and the support and training that families and carers may need to help deliver the intervention.

There was no conclusive evidence for the use of psychosocial interventions for behaviour that challenges in children and young people with autism. However, the GDG judged that this was an important issue for children and young people with autism and that these interventions may be beneficial. Thus, based on their expert knowledge and judgement, the GDG decided that psychosocial interventions should be used for managing behaviour that challenges in the context of a comprehensive behaviour management and treatment approach. The GDG considered the need for an assessment of behaviour that challenges itself and of any underlying communication impairments or unrecognised physical or mental disorders in order to inform the care plan for behaviour that challenges. The GDG proposed that a functional analysis of the behaviour should be the basis for the development of any psychosocial intervention.

The nature and intensity of psychosocial interventions and care pathways aimed at behaviour that challenges are expected to vary widely, depending on the cause, nature, severity and chronicity of the behaviour, its persistence or responsiveness to minimal treatment, and the individual circumstances of the child or young person and the family or carers. This means that a wide variety of health and social care resources are required to provide such interventions, and therefore a wide variation in intervention costs. However, the economic impact of behaviour that challenges in children and young people with autism, although considerable, is not reported in the published literature. Due to lack of evidence on the use of psychosocial interventions for behaviour that challenges in children and young people with autism, the diversity of care pathways, the huge variation in required resource use and associated costs, and the lack of cost data specific to behaviour that challenges in children and young people with autism, it was decided that formal economic modelling of the interventions in this area would not be useful in decision-making. Nevertheless, the GDG judged that provision of such interventions is essential and that the costs of providing such interventions are justified by the expected clinical benefits and improvements in the quality of life of children and young people with autism as well as their families and carers. The GDG estimated that it is likely that the costs of providing such interventions will be offset, at least partially, by cost-savings in health, social and education services resulting from improvements in behaviour. For example, behaviour that challenges is the usual reason for admission to CAMHS inpatient services, long-term care or boarding schools.

There was evidence for positive treatment effects of antipsychotic medication on behaviour that challenges. However, there was also evidence for significant harms associated with risperidone or aripiprazole. The mechanisms by which these drugs exerted any beneficial effect was unclear from the data reviewed and it was also unclear whether the effects were mediated by a change in any psychotic symptoms, reduced levels of anxiety or more general sedation. Therefore, the GDG's judgement was that antipsychotics may be considered for the treatment and management of behaviour that challenges, including irritability, lethargy and social withdrawal, stereotypic behaviour, hyperactivity and noncompliance, and inappropriate speech, in children and young people with autism. The GDG recognised that antipsychotics were often used for the management of behaviour that challenges without review of the underlying causes of that behaviour and agreed that a functional analysis of behaviour should be a core component of treatment. This analysis, along with a consideration of any coexisting mental or physical disorders and the wider social and physical environment, should help determine whether an antipsychotic should be used.

The results of the guideline economic analysis suggested that risperidone, and potentially other antipsychotic drugs with acquisition costs comparable with risperidone's (for example, antipsychotics available as generics), are likely to be cost effective for the management of behaviour that challenges in children and young people with autism. Risperidone appeared to be cost effective according to the results of the analysis, especially in tablet and oral solution formulation, but aripiprazole was not. The analysis considered risperidone and aripiprazole because these were the only antipsychotics for which clinical evidence was available. As there was no evidence for any significant differences in effectiveness or side effect profile between the two drugs, the economic analysis used pooled clinical data from the two antipsychotics; consequently, any differences in the relative cost effectiveness of the two drugs resulted exclusively from differences in their acquisition costs. For this reason the results cannot lead to safe conclusions regarding the relative cost effectiveness of different antipsychotics.

The economic analysis was characterised by a number of limitations, including the lack of consideration of side effects other than weight gain due to unavailability of relevant utility and cost data and the use of utility data based on HUI3, as these were the only utility data available for children with autism. The GDG judged that HUI3 was not appropriate for use in this population as it is not directly relevant to symptoms of autism; moreover, utility scores for the HUI3 have been elicited from the Canadian population, and it is difficult to judge whether these values express preferences of the UK population. Another important limitation of the analysis was that it was not possible to consider potential short and long-term cost savings resulting from a reduction in behaviour that challenges, as well as other associated long-term benefits, due to lack of relevant data. Therefore, the economic analysis is likely to have underestimated the cost effectiveness of antipsychotics.

The GDG considered the use of antipsychotics in other NICE guidelines, such as schizophrenia in adults, psychosis and schizophrenia in children and young people, and bipolar disorder. In these other contexts, where numerous antipsychotics have been evaluated for a range of different uses, including behaviour that challenges and rapid tranquillisation, through nearly two hundred RCTs, there was little difference, if any, in the clinical efficacy or effectiveness of any of the antipsychotics. The major difference between one antipsychotic and another lay in the range of side effects with which each individual drug was most commonly associated. By comparison, there was very little evidence about the efficacy or effectiveness of antipsychotics in children and young people with autism, except some for behaviour that challenges, and then only in regard to two drugs (risperidone and aripiprazole) and one (haloperidol) for comparison. Therefore, the GDG did not conclude that it was appropriate to recommend any specific antipsychotic but considered that the choice of antipsychotic medication should be influenced by a consideration of the side-effect profile, the service user's personal preferences, any past experience of taking the drug, and, importantly, their acquisition costs.

The GDG felt that an integrated approach to treating behaviour that challenges in children and young people with autism was important and consequently judged that antipsychotics should normally be used in conjunction with psychosocial interventions except where the behaviour is very severe. In addition, due to the concerns regarding side effects associated with antipsychotic use, and the lack of data about long-term effects, the GDG concluded that where antipsychotics are used for the treatment of behaviour that challenges in children and young people with autism the clinician should consider starting with a low dose and there should be regular review of the benefits of the drug, any side effects, with particular emphasis on monitoring weight gain and the minimum effective dose should be chosen to maintain improvement in the target behaviour. The GDG was of the view that treatment should not be continued after 6 weeks in the absence of clear evidence of important clinical benefit.

The GDG was aware that after prescribing care of the child or young person may be transferred to primary or community care, and felt that it was important that where this was the case the specialist who initiated the prescription should give clear guidance to the practitioner responsible for continued prescribing about the selection of target behaviours, monitoring of benefits and harms, the potential for minimally effective dosing, the proposed duration of treatment, and plans for discontinuation.

There was either no or very little evidence to answer the subquestions about particular subgroups (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

7.7 RECOMMENDATIONS

7.7.1 Clinical practice recommendations

Anticipating and preventing behaviour that challenges

7.7.1.1 Assess factors that may increase the risk of behaviour that challenges in routine assessment and care planning in children and young people with autism, including:

- impairments in communication that may result in difficulty understanding situations or in expressing needs and wishes
- coexisting physical disorders, such as pain or gastrointestinal disorders
- coexisting mental health problems such as anxiety or depression and other neurodevelopmental conditions such as ADHD
- the physical environment, such as lighting and noise levels
- the social environment, including home, school and leisure activities
- changes to routines or personal circumstances
- developmental change, including puberty
- exploitation or abuse by others
- inadvertent reinforcement of behaviour that challenges
- the absence of predictability and structure.

7.7.1.2 Develop a care plan with the child or young person and their families or carers that outlines the steps needed to address the factors that may provoke behaviour that challenges, including:

- treatment, for example, for coexisting physical, mental health and behavioural problems
- support, for example, for families or carers
- necessary adjustments, for example, by increasing structure and minimising unpredictability.

Assessment and initial intervention for behaviour that challenges

7.7.1.3 If a child or young person's behaviour becomes challenging, reassess factors identified in the care plan and assess for any new factors that could provoke the behaviour.

7.7.1.4 Offer the following to address factors that may trigger or maintain behaviour that challenges:

- treatment for physical disorders, or coexisting mental health and behavioural problems
- interventions aimed at changing the environment, such as:
  - providing advice to families and carers
  - making adjustments or adaptations to the physical surroundings (see recommendation 5.5.1.9).

7.7.1.5 If behaviour remains challenging despite attempts to address the underlying possible causes, consult senior colleagues and undertake a multidisciplinary review.

7.7.1.6 At the multidisciplinary review, take into account the following when choosing an intervention for behaviour that challenges:

- the nature, severity and impact of the behaviour
- the child or young person's physical and communication needs and capabilities
- the environment
- the support and training that families, carers or staff may need to implement the intervention effectively
- the preferences of the child or young person and the family or carers
- the child or young person's experience of, and response to, previous interventions.

Psychosocial interventions for behaviour that challenges

7.7.1.7 If no coexisting mental health or behavioural problem, physical disorder or environmental problem has been identified as triggering or maintaining the behaviour that challenges, offer the child or young person a psychosocial intervention (informed by a functional assessment of behaviour) as a first-line treatment.

7.7.1.8 The functional assessment should identify:

- factors that appear to trigger the behaviour
- patterns of behaviour
- the needs that the child or young person is attempting to meet by performing the behaviour
- the consequences of the behaviour (that is, the reinforcement received as a result of the behaviour).

7.7.1.9 Psychosocial interventions for behaviour that challenges should include:

- clearly identified target behaviour
- a focus on outcomes that are linked to quality of life
- assessment and modification of environmental factors that may contribute to initiating or maintaining the behaviour
- a clearly defined intervention strategy that takes into account the developmental level and coexisting problems of the child or young person
- a specified timescale to meet intervention goals (to promote modification of intervention strategies that do not lead to change within a specified time)
- a systematic measure of the target behaviour taken before and after the intervention to ascertain whether the agreed outcomes are being met

- consistent application in all areas of the child or young person's environment (for example, at home and at school)
- agreement among parents, carers and professionals in all settings about how to implement the intervention.

Pharmacological interventions for behaviour that challenges

7.7.1.10 Consider antipsychotic medication[60] for managing behaviour that challenges in children and young people with autism when psychosocial or other interventions are insufficient or could not be delivered because of the severity of the behaviour. Antipsychotic medication should be initially prescribed and monitored by a paediatrician or psychiatrist who should:

- identify the target behaviour
- decide on an appropriate measure to monitor effectiveness, including frequency and severity of the behaviour and a measure of global impact
- review the effectiveness and any side effects of the medication after 3–4 weeks
- stop treatment if there is no indication of a clinically important response at 6 weeks.

7.7.1.11 If antipsychotic medication is prescribed:

- start with a low dose
- use the minimum effective dose needed
- regularly review the benefits of the antipsychotic medication and any adverse events.

7.7.1.12 When choosing antipsychotic medication, take into account side effects, acquisition costs, the child or young person's preference (or that of their parent or carer where appropriate) and response to previous treatment with an antipsychotic.

7.7.1.13 When prescribing is transferred to primary or community care, the specialist should give clear guidance to the practitioner who will be responsible for continued prescribing about:

- the selection of target behaviours
- monitoring of beneficial and side effects
- the potential for minimally effective dosing
- the proposed duration of treatment
- plans for stopping treatment.

[60] At the time of publication (August 2013), no antipsychotic medication had a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

7.7.2 Research recommendations

7.7.2.1 Is a group-based parent training intervention for parents or carers of children and young people with autism clinically and cost effective in reducing early and emerging behaviour that challenges in the short- and medium-term compared with treatment as usual?

8 INTERVENTIONS AIMED AT ASSOCIATED FEATURES OF AUTISM AND COEXISTING CONDITIONS

8.1 INTRODUCTION

Autism is strongly associated with a number of coexisting conditions that are not part of the diagnostic criteria but nevertheless have a significant, and often negative impact on the well being of the child or young person and family. Common coexisting conditions include other neurodevelopmental disorders (speech and language problems, intellectual disability, academic and learning problems, motor coordination difficulties, ADHD, tics); functional disorders (for example, sleeping, eating and elimination problems) and poor adaptive behaviour skills; mental health problems (for example, anxiety, depression, oppositional disorder); medical and genetic conditions (for example, epilepsy, neurofibromatosis, Down syndrome and Fragile X. Behaviours that challenge (aggression to objects or people, destructiveness and self injury) are also more common in autism than in other conditions with similar levels of intellectual impairment (see Chapter 7)

It is often these coexisting conditions, rather than the core autism impairments themselves, that have the greatest impact on the young person's ability to participate in society as he or she grows older. Hence, the *Autism Diagnosis in Children and Young People* guideline (NICE, 2011) recommends a systematic search for coexisting conditions as part of the diagnostic assessment. Successful management of coexisting conditions is an extremely important part of the care plan for treatment, intervention and support. In most instances, treatment for any coexisting conditions should follow the guidelines for that condition, but care and management may be made more difficult by the presence of autism.

This chapter describes some common coexisting conditions and modifications to usual treatments because of the presence of autism. Chapter 4 describes the importance of access to good medical care and the modifications that may have to be made to ensure access for those with autism and their families.

8.1.1 Review protocol – interventions aimed at associated features and coexisting problems or disorders

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 187 (further information about the search strategy can be found in Appendix 7).

Table 187: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s)	**RQ 6.1**: For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for coexisting problems or disorders (including adaptive behaviour, speech and language problems, IQ and academic skills, sensory sensitivities, motor skills, common coexisting mental health problems and common functional problems)* when compared with alternative management strategies? *Subgroup analyses will examine and compare treatment effects on coexisting problems or disorders when the interventions are specifically aimed at these features (direct outcomes) and when the primary target of the intervention was another outcome but effects on coexisting problems or disorders are examined (indirect outcomes)
Sub-question(s)	**RQ 6.1.1:** For children and young people with autism, and their families and carers, is the engagement with or effectiveness of interventions aimed at coexisting problems or disorders different for: • looked-after children? • immigrant groups? • children with regression in skills? **RQ 6.1.2**: For children and young people with autism is the effectiveness of interventions aimed at coexisting problems or disorders moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)? **RQ 6.1.3**: For children and young people with autism is the effectiveness of interventions aimed at coexisting problems or disorders mediated by: • the intensity of the intervention? • the duration of the intervention? • the length of follow-up? • programme components?
Objectives	To evaluate the clinical and cost effectiveness of interventions aimed at coexisting problems or disorders for children and young people with autism.
Criteria for considering studies for the review	
Population	Children and young people (from birth until their 19th birthday) with autism, (across the full range of intellectual ability) and their families and carers. If some, but not all, of a study's participants are eligible for our review, we will ask the study authors for disaggregated data. If we are unable to

	obtain the appropriate disaggregated data, then we will include a study if the majority (at least 51%) of its participants are eligible for our review. If we are unable to determine the exact percent of a study's participants who are eligible, then we will include the study if its participants are eligible on average (for example, the mean participant age is less than 19 years). Consideration will be given to the particular management and support needs of: • looked-after children • immigrant groups • children with regression in skills Excluded groups include: • adults (19 years and older).
Intervention	Psychosocial, biomedical or pharmacological interventions which are aimed at coexisting problems or disorders as a direct or indirect outcome
Comparison	No treatment or treatment as usual (includes placebo and waitlist control up until receiving intervention), other active interventions
Critical outcomes	• **Adaptive behaviour** (as measured by behaviour checklists including VABS) • **Speech and language** (receptive and expressive language as measured by rating scales including the Reynell Developmental Language Scales [RDLS], the Preschool Language Scales, 3rd edition [PLS-3], the MSEL; the MacArthur Communication Developmental Inventories [CDIs]) • **IQ** (as measured by the MSEL early learning composite score) • **Academic skills** • **Sensory sensitivities** • **Fine and gross motor skills** (as measured by the motor subscales of the VABS and the MSEL) • **Anxiety** • **Hyperactivity/ADHD symptoms** • **Sleep problems** • **Gastrointestinal or eating problems**
Time points	Some studies may measure outcomes at multiple time points. We will run the following analyses: • Post-intervention (end of treatment) • Longest follow-up
Study design	• RCTs • Systematic reviews Non-English language papers will be excluded, as will books, dissertation abstracts, trade magazines, policy and guidance, and non-empirical research.
Include unpublished data?	Yes but only where: • the evidence was accompanied by a trial report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	No limit

Minimum sample size	• N ≥10 per arm (ITT) Exclude studies with >50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
Study setting	• Primary, secondary and tertiary health and social care. This guideline will also be relevant to other health and social care settings (including forensic services and youth justice settings) although they are not explicitly covered. • The guideline will also address interventions relevant to early years services and educational settings.
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, HTA, IBSS, MEDLINE, PreMEDLINE, PsycEXTRA, PsycINFO, Social Policy and Practice, Sociological Abstracts, SSA, SSCI
Date searched	Systematic reviews: 1995 up to January 2013 RCTs: inception of database up to January 2013
Searching other resources	Hand-reference searching and citation searches of included studies, hand-searching of the 'Research Autism' website, and searching the ISRCTN and ClinicalTrials.gov website using the term 'autism'
The review strategy	• The initial aim is to conduct a meta-analysis evaluating the clinical effectiveness of the interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. Consider subgroup meta-analyses that takes into account the effectiveness of interventions as moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)?

8.1.2 Outcomes – associated features of autism and coexisting problems or disorders

A large number of outcome measures for associated features of autism and coexisting problems or disorders were reported, those that reported sufficient data to be extractable and were not excluded (see Appendix 12d) are in Table 21.

Table 188: Outcome measures for coexisting problems or disorders extracted from studies of interventions aimed at coexisting problems or disorders

Category	Sub-category	Scale
Adaptive behaviour	Adaptive behaviour	• BASC – Adaptive Skills • Bayley Scales of Infant Development – Behavior Rating Scale (Bayley, 1993) • Behavioural observation during ADOS coded based on study-specific behavioural coding scheme (Johnson et al., 2010) – Attending to task/activity • DBC – total score • Early Intervention Developmental Profile (EIDP)/Preschool Developmental Profile (PSDP) (Schafer & Moersch, 1981) – Self-care subscale • Functional Emotional Assessment Scale (Greenspan et al., 2001) – total score (child behaviours) • Functional Emotional Developmental Questionnaire (Greenspan & Greenspan, 2002) – total score • Functional Independence Measure for Children (WeeFIM; Uniform Data System for Medical Rehabilitation, 2000; Wong et al., 2002) – total score, and Self-care, Mobility, Cognition, Comprehension, Expression, Social Interaction, Problem Solving and Memory subscales • PDDBI – Adaptive Behaviours Composite • Pediatric Evaluation Disability Inventory (Haley et al., 1992) – Self-care (functional skill and independence), Mobility (functional skill and independence) and Social Function (functional skill and independence) subscales • Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales (Limbers et al., 2009) – total score, and Emotional Functioning, Social Functioning and Cognitive Functioning subscales • Positive treatment response ('much improved/very improved' on CGI/PGI-I for overall functioning) • SSRS – Self-control subscale • VABS – adaptive behaviour composite score, and Daily Living Skills, Socialisation, and Communication subscales
Speech and language	Verbal/non-verbal communication/PECS use	• Behavioural observation (study-specific; Howlin et al., 2007) – Frequency of Child Communicative Initiations; Frequency of Use of PECS Symbols; Frequency of Speech (including non-word vocalisations) • Behavioural observation (semistructured free-play with examiner; study-specific, Yoder & Stone [2006]) – Frequency of non-imitative spoken communication acts and the number of different non-imitative words spoken

		• CARS adapted for Brazil (CARS-BR; Pereira et al., 2008) – Verbal Communication and Non-verbal Communication subscales • Comprehensive Assessment of Spoken Language (Carrow-Woolfolk, 1999) – Idiomatic language subscale • ESCS-Abridged (Mundy et al. 1996) • MacArthur CDIs (Fenson et al., 1993) – total gestures produced • Pragmatics Profile of Everyday Communication (Dewart & Summers, 1995) – total Q range
	Receptive language	• Brigance Inventory of Early Development – Receptive Language subscale • BPVS (Dunn et al., 1997a) • CDIs – Vocabulary Comprehension and Phrases Understood subscales • MSEL – Receptive language • PPVT (Dunn & Dunn, 1981b) – total score • PPVT, 3rd edition (PPVT-III; Dunn & Dunn, 1997b) – total score • PGI-R – Receptive Language Improvement • PLS-3 (Zimmerman et al., 1992) – Auditory Comprehension subscale • Receptive One Word Picture Vocabulary Test (Gardiner, 1985) – total score • RDLS (Reynell, 1990) – Comprehension subscale
	Expressive language	• Behavioural observation (study-specific; Molloy et al. 2002) – mean length of utterance and Type/Token Ratio • Brigance Inventory of Early Development – Expressive Language subscale • CDIs – Vocabulary Production subscale • Dichotomous measure of overall language rating (based on ADI-R) – Number of participants who were non-verbal (<5 words), Number of participants with single words, Number of participants with phrase speech • Expressive One-Word Picture Vocabulary Test (EOWPVT; Academic Therapy Publications, 2000) – Total score • EOWPVT -Revised (EOWPVT-R; Gardener, 1990) – Total score • Expressive Vocabulary Test (Williams, 1997) – Total score • MSEL – Expressive language subscale • PLS-3 – Expressive communication subscale • PGI-R – Expressive language improvement • Positive treatment response: Frequency of improvement in basic developmental assessment (test used in Zhou & Zhang, 2008 not reported in Cheuk et al., 2011) – Vocalisation, Babbling, and Speech • RDLS – Expressive language subscale • Verbal Production Evaluation Scale (study-

		specific; Lim, 2010) – Production of target words
	Receptive and expressive language	• Arabic Language Test (Kotby et al, 1995) – Receptive semantics, Expressive semantics, and Attention level subscales • CCC-2 – Speech production, Syntax, Semantics, and Coherence subscales • PLS-3 – Total score • Positive treatment response: Frequency of improvement on China Rehabilitation Research Council (CRRC) sign-significance relations scale (cited in Cheuk et al., 2011, but no reference reported) – Speech comprehension, Speech expression, Speech imitation, Vocabulary comprehension, Vocabulary expression, Phrase comprehension, Phrase expression, Communication attitude • Positive treatment response: Number of participants showing ≥4 points improvement on PLS-3 total score • EIDP/PSDP – Language subscale • PDDBI – Semantic pragmatic problems, Expressive language, and Learning, memory and receptive language subscales • PLS, 4th edition (PLS-4; Zimmerman et al., 2001) • RDLS – Total score
IQ and academic skills	IQ	• Bayley Scales of Infant Development: – Mental Development Index • Griffiths Mental Development Scale – General quotient and Mental age, and Locomotor, Personal-Social, Hearing and Speech, Eye and Hand Coordination, Performance, and Practical Reasoning subscales • Griffiths Scale of Mental Development – D and E scales (non-verbal IQ Non-Verbal Mental Age/age) • LIPS – Total score • LIPS-R – full-scale IQ and Attention and memory subscale • Merrill-Palmer Scale (used in Molloy et al., 2002, but no reference cited) • MSEL – early-learning composite score or developmental quotient • PGI-R: Cognition improvement • PEP-R – developmental quotient • WPPSI-R (Wechsler, 1989)
	Academic skills	• Classroom Analogue Task (Handen et al., 1990) – Total number of maths problems correctly calculated • Wechsler Individualized Achievement Test (Wechsler, 1992) – Total score
Sensory sensitivities	Sensory sensitivities	• Brigance Inventory of Child Development – Auditory processing • PDDBI – Sensory score • Sense and Self-Regulation Checklist (Silva & Schalock, 2012a) – Sense score

		• Sensory Evaluation Form for Children with Autism (study-specific; Fazlioğlu & Baran, 2008) – Total score • Sensory Problems checklist (Edelson, 1992) – Total score • Sensory Profile – Total score, and Sensory seeking, and Sensory sensitivity subscales • Sound Sensitivity Questionnaire (modified version used in Bettison [1996] of Rimland [1991] Hearing Sensitivity Questionnaire) – Total score and Sound distress subscale
Motor skills	Total score	• Movement Assessment Battery for Children (Henderson & Sugden, 1992): Test of Motor Impairment • VABS – Motor skills subscale
	Fine motor skills	• Developmental Test of Visual Perception, 2nd edition (DTVP-2; Hammill et al., 1993) – Fine motor subscale • EIDP/PSDP – Perceptual/Fine motor skills subscale • MSEL – Fine motor subscale • Sensory Profile – Fine motor/perception subscale
	Gross motor skills	• EIDP/PSDP – Gross motor skills subscale
Common coexisting mental health problems	Anxiety	• Anxiety Disorders Interview Schedule for DSM-IV–Child and Parent Versions (ADIS-C/P; Silverman & Albano, 1996) – Clinical Severity Rating, and Social, Separation, Generalized, and Specific phobia subscales • BASC – Internalizing subscale • CBCL/1.5-5 – Internalizing, Anxious/Depressed, Affective, and Anxiety subscales • Children's Automatic Thoughts Scale (CATS; Schniering & Rapee, 2002) – Internalizing and Hostile intent subscales • Multidimensional Anxiety Scale for Children (MASC; March, 1998): Child or Parent version – Total score • PDDBI – Specific fears subscale • Positive treatment response: Number of participants who no longer met DSM-IV criteria for a current primary anxiety disorder • Positive treatment response: Number of participants who were 'much improved/very improved' on CGI-I • Revised Children's Manifest Anxiety Scale (Reynolds & Richmond, 1978) – Chronic anxiety (trait) • Spence Children's Anxiety Scale (SCAS; Spence, 1998 [child version]; SCAS-P [Parent Version]) – Total score, and Social phobia, Separation Anxiety Disorder, Generalized Anxiety Disorder, Panic, Personal injury, and OCD subscales • SDQ – Internalizing subscale
	ADHD	• ABC – Hyperactivity and Non-compliance

		subscale • ADHD-Rating Scale based on DSM-IV (ADHD-RS; DuPaul et al., 1998) – Total score • CBCL/1.5-5 – ADHD subscale • CGI-ADHD-I – Improvement in ADHD symptoms • —Revised: Short Form (CTRS-R:S; Conners et al., 1998) – Hyperactivity, ADHD, Cognitive/Attention, and Oppositional subscales
Common functional problems	Sleep problems	• Actigraph (averaged over 7 nights): Sleep onset latency (time from parents' note of lights out to actigraphically measured first sleep onset); Total duration of sleep (actual sleep time, excluding sleep latency and wakening after sleep onset); Number of night wakings (>5 minutes in duration per episode); Wake after sleep onset; and Sleep efficiency (ratio of total sleep time to total time in bed x 100) • CBCL/1.5-5 – Sleep problems subscale • Children's Sleep Habits Questionnaire (CSHQ; Owens et al., 2000) – Total score, and Bedtime resistance, Sleep onset delay, Sleep duration, Sleep anxiety, Night-wakings, Parasomnias, Sleep-disordered breathing, and Daytime sleepiness subscales • PGI-R: Sleep improvement subscale • Positive treatment response: Sleep onset latency (sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on actigraph data); Sleep efficiency (≥85% for sleep efficiency based on actigraph data) • Sleep diary (study-specific; Gringras et al., 2012) – Sleep onset latency (averaged over 7 nights) and Total sleep time (averaged over 7 nights) • Sleep Measure Scale (study-specific; Eli Lilly & Company, 2009) – Time to fall asleep, Total hours of sleep, Difficulty falling asleep, Quality of sleep, and Functional outcome during the day subscales
	Gastrointestinal or eating problems	• Gastrointestinal symptoms questionnaire (study-specific; Dunn-Geier et al., 2000) – Total score • PGI-R: gastrointestinal improvement subscale • Positive treatment response: Number of participants who scored 'moderately or substantially improved' on at least two of last four assessments or 'somewhat improved' for all of last four assessments of the Modified Global Improvement Scale (Gordon et al., 2003) for gastrointestinal symptoms

8.2 IMPAIRMENTS IN ADAPTIVE BEHAVIOUR

8.2.1 Introduction

As noted in Section 8.3 below, many children with autism have an IQ in the intellectually impaired range. However, it is also well established that everyday adaptive behaviours – communication, socialisation and daily living/self-care skills – are frequently markedly lower than general cognitive abilities (Charman et al., 2011; Klin et al., 2007). This reflects the fact that the core symptoms of autism disrupt and challenge the development of life and independence skills whatever the individual's level of ability and potential. It is particularly important to recognise that children/ young people with autism of average or above average intellectual ability (sometimes described as having 'high functioning autism'), who may perform well in a structured clinical assessment, frequently function much less adequately in other aspects of their lives. Thus, an average or above average IQ score may not translate into social competence, independence and autonomy in everyday settings at home, at school and in the community.

Current practice

Many interventions that target the core symptoms of autism (see Chapter 6), behaviours that challenge (see Chapter 7) and co-occurring mental health difficulties (see Section 8.7), and language and communication difficulties (see Section 8.3), may also have a positive impact on adaptive behaviours. However, few interventions and few services have been developed specifically to promote or improved adaptive behaviour and independence skills. Although, within education (particularly in special education settings) there is considerable focus on promoting life and independence skills, generalising skills is a particular problem and such support services for the child/young person and their family are not routinely available in many health service settings.

8.2.2 Studies considered – effect of psychosocial interventions on adaptive behaviour

Fifty papers from the search met the eligibility criteria for full-text retrieval. Of these, 15RCTs provided relevant clinical evidence and were included in the review. Five of these studies examined the efficacy of psychosocial interventions on adaptive behaviour as a direct outcome (target of intervention), and ten provided data on adaptive behaviour as an indirect outcome. All studies were published in peer-reviewed journals between 1998 and 2013. In addition, 35studies were excluded from the analysis. The most common reasons for exclusion were that the study was a systematic review with no new useable data and any meta-analysis results were not appropriate to extract or group allocation was non-randomised. Further information about both included and excluded studies can be found in Appendix 12d.

Three behavioural intervention trials (DAWSON2010, ROBERTS2011 [Roberts et al., 2011], SMITH2000) examined effects on adaptive behaviour as a direct outcome, and

one behavioural intervention trial (ROGERS2012[61]) examined indirect effects on adaptive behaviour.

One cognitive-behavioural intervention trial (DRAHOTA2011[62] [one trial reported across two papers: Drahota et al., 2011; Wood et al., 2009]) examined effects of CBT on adaptive behaviour as an indirect outcome.

Two parent training studies (PAJAREYA2011, RICKARDS2007) examined effects on adaptive behaviour as a direct outcome, and three parent training trials (AMAN2009, JOCELYN1998, TONGE2006[63]) examined indirect effects of parent training on adaptive behaviour.

Finally, five social-communication intervention trials (ALDRED2001, CARTER2011, GREEN2010, OWENS2008, SCHERTZ2013[64]) examined effects on adaptive behaviour as an indirect outcome.

8.2.3 Clinical evidence – effect of psychosocial interventions on adaptive behaviour

Behavioural interventions for adaptive behaviour as a direct or indirect outcome

One of the included behavioural intervention trials (DAWSON2010) involved a comparison between EIBI (Early Start Denver Model [ESDM]) and treatment as usual and another behavioural intervention trial (ROGERS2012) involved a comparison between EBI (Parent-mediated Early Start Denver Model [P-ESDM]) and treatment as usual. One of the behavioural intervention studies (SMITH2000) compared EIBI with parent training. Finally, the remaining included behavioural intervention trial (ROBERTS2011) involved a comparison between a home-based EBI programme and a centre-based EBI programme (see Table 189).

In DAWSON2010 the ESDM was based on developmental and applied behavioural analytic principles and teaching strategies were consistent with the principles of ABA, such as the use of operant conditioning, shaping, and chaining and each child's plan was individualised. In ROGERS2012 the P-ESDM was a briefer, less intensive, parent-mediated version of the ESDM intervention examined in DAWSON2010.

In SMITH2000 children in the experimental group received EIBI based on Lovaas et al.'s (1981) manual and the principles of ABA. The intervention began with one-to-one treatment delivered by a student therapist in the child's home and involved parental input. Treatment progressed gradually from relatively simple tasks (for

[61] See Section 8.4.3 for direct outcomes from ROGERS2012.
[62] See Section 8.3.3 for direct outcomes from DRAHOTA2011.
[63] See Section 7.2.2 for direct outcomes from AMAN2009, Section 6.2.3 for direct outcomes from JOCEYLN1998 and Section 9.2.2 for direct outcomes from TONGE2006.
[64] See Section 6.2.5 for direct outcomes from ALDRED2001, CARTER2011, GREEN2010, OWENS2008, SCHERTZ2013.

example, responding to basic requests made by an adult) to more complex tasks (such as conversing). Once the child had achieved certain behavioural criteria (speaking in short phrases; cooperating with verbal requests from others; playing appropriately with toys; and had acquired self-care skills such as dressing and toileting) the intervention was implemented away from the home and in group settings such as classrooms. This shift usually occurred approximately one year after onset of intervention but there was large variation across children. The control group in SMITH2000 also received an active intervention, parent training. Parent training was also based on Lovaas and colleagues' (1981) manual and parents were trained in the basic principles of discrimination learning, discrete trial formats and functional analyses of maladaptive behaviours and applied these techniques to help their children acquire parent-identified skills.

Finally, in ROBERTS2011, the 'Building Blocks' programme was delivered in a home-based EBI condition (Autism Association of NSW, 2004a) or a centre-based EBI condition (Autism Association of NSW, 2004b). For the experimental group (home-based EBI) the EBI intervention was individualised and delivered in the home to both the child and their parent/s. Intervention targets included behaviour management, functional communication skills, social development, attending and play skills, sensory processing issues, self-care skills, motor skills and academic skills and the intervention administrator trained parents to work effectively with their child using techniques including direct modelling of skills and constructive feedback to parents. In the control group (centre-based EBI) the EBI intervention involved group-based playgroup sessions for the children and concurrent group-based parent support and training groups. The playgroup programme was run according to a condensed preschool programme manual which aimed to prepare children for integration into regular preschool settings by focusing on the development of social play skills, functional communication skills and participation in small group activities. The parent training and support groups were also run according to a manual and intended to provide parents with an opportunity to meet with other parents and professionals and to discuss a range of set topics (prioritised according to interest and need) including positive behaviour support, communication, self-care issues, school options, specialist services and sensory issues.

Table 189: Study information table for included trials of behavioural interventions for adaptive behaviour

	EIBI or EBI (ESDM or P-ESDM) versus treatment as usual	**EIBI versus parent training**	**Home-based EBI versus centre-based EBI**
No. trials (N)	2 (146)	1 (28)	1 (67)
Study IDs	(1) DAWSON2010 (2) ROGERS2012	SMITH2000	ROBERTS2011
Study design	(1)-(2) RCT	RCT	RCT
% female	(1) 29 (2) 31	18	Not reported
Mean age (years)	(1) 2.0 (2) 1.7	3.0	3.5
IQ	(1) 60.2 (assessed using the MSEL: early-learning composite score; Mullen, 1995) (2) Not reported (inclusion criteria developmental quotient >35 as measured by MSEL)	51 (assessed using the Stanford-Binet Intelligence scale or Bayley Scales of Infant Development)	61.8 (assessed using the GMDS)
Dose/intensity (mg/hours)	(1) 1581 with a trained therapist (20 hours/week) Parents reported spending 1,695 hours using ESDM strategies. (2) Planned intensity of 12 hours (1 hour/week) and weekly mean intensity of all intervention was 1.48 hours	**Experimental group**: 2137 (intensive treatment was defined as 30 hours/week but the actual intervention intensity was 15 hours/week) **Control group**: No mean reported (range 65-195). Children's families received two sessions per week of parent training, totalling 5 hours per week.	Planned intensity of 40 hours (2 hours/fortnightly) for the home-based intervention and 80 hours (2 hours/weekly) for the centre-based intervention
Setting	(1) Academic research (university) and home (2) Three university clinics	Home-based (and educational for the experimental group)	Home-based versus centre-based
Length of treatment (weeks)	(1) 104 (2) 12	**Experimental group**: 145 **Control group**: 39	40
Continuation phase (length and inclusion criteria)	(1) 104 (2) 12	Up to 260 (follow-up evaluations occurred when children were aged 7-8 years)	40

Evidence for the effectiveness of behavioural interventions on adaptive behaviour and the quality of the evidence is presented in Table 190 and Table 191. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 190: Evidence summary table for effects of behavioural interventions (EIBI or EBI) on adaptive behaviour as a direct or indirect outcome

	EIBI or EBI (ESDM or P-ESDM) versus treatment as usual	**EIBI versus parent training**
Outcome	Adaptive behaviour	
Outcome measure	VABS: (1) Composite score (2) Daily living skills (3) Socialisation (4) Communication	
Study ID	DAWSON2010 ROGERS2012	SMITH2000
Effect size (CI; p value)	(1) *Composite score* SMD 0.03 (-0.31, 0.36; p = 0.88) (2) *Daily living skills* SMD 0.10 (-0.23, 0.43; p = 0.56) (3) *Socialisation* SMD 0.08 (-0.25, 0.41; p = 0.64) (4) *Communication* SMD 0.11 (-0.23, 0.44; p = 0.53)	(1) *Composite score* SMD 0.11 (-0.64, 0.85; p = 0.78) (2) *Daily living skills* SMD -0.03 (-0.77, 0.71; p = 0.94) (3) *Socialisation* SMD -0.12 (-0.86, 0.63; p = 0.76) (4) *Communication* SMD 0.28 (-0.47, 1.02; p = 0.47)
Heterogeneity (chi²; p value; I^2)	(1) Chi² = 7.23, df = 1; p = 0.007; I^2 = 86% (2) Chi² = 4.17, df = 1; p = 0.04; I^2 = 76% (3) Chi² = 3.65, df = 1; p = 0.06; I^2 = 73% (4) Chi² = 4.47, df = 1; p = 0.03; I^2 = 78%	Not applicable
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,3]
Number of studies/participants	K = 2; N = 143	K = 1; N = 28
Forest plot	1.13.1; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and high risk of detection bias as the outcome measure was based on interview with (non-blind) parent rather than direct observation
[2]Downgraded for very serious inconsistency as the I^2 value indicates substantial to considerable heterogeneity.
[3]Downgraded due to serious imprecision as N <400.

There was no evidence from a meta-analysis with two studies for statistically significant effects of EIBI/EBI (ESDM/P-ESDM) on adaptive behaviour (see Table 190). However, the I^2 values indicate substantial to considerable heterogeneity and imply differences between the two interventions combined in meta-analysis. Review of the single study data provides evidence for moderate and statistically significant effects of EIBI (ESDM) relative to treatment as usual on adaptive behaviour as measured by the VABS total score, and daily living skills and communication

subscales (and a trend for a statistically significant effect on the socialisation subscale [p = 0.06]). However, the quality of this evidence was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size. Conversely, review of the single study evidence for EBI (P-ESDM) revealed no evidence for statistically significant treatment effects on adaptive behaviour. Effects also failed to reach significance when EIBI was compared with parent training (see Table 190).

Table 191: Evidence summary table for effects of behavioural interventions (home-based versus centre-based EBI) on adaptive behaviour as a direct outcome

	Home-based EBI versus centre-based EBI	
Outcome	Adaptive behaviour	Adaptive functioning and psychopathology
Outcome measure	VABS: (1) Socialisation (2) Communication	DBC: total
Study ID	ROBERTS2011	
Effect size (CI; p value)	(1) *Socialisation* SMD -0.63 (-1.17, -0.09; p = 0.02) (2) *Communication* SMD -0.46 (-1.00, 0.07; p = 0.09)	SMD -0.11 (-0.70, 0.48; p = 0.71)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	(1) Low[1,2] (2) Very low[1,3]	Very low[1,3]
Number of studies/participants	(1) K = 1; N = 56 (2) K = 1; N = 55	K = 1; N = 44
Forest plot	1.13.1; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as, despite blinding outcome assessors, the outcome measure relies on interview with parent and parents were non-blind to group assignment and other potentially confounding factors and were also part of the intervention so problems with self-assessment.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

There was inconsistent evidence for positive treatment effects associated with a home-based EBI programme relative to a centre-based EBI programme on adaptive behaviour with evidence for a moderate and statistically significant effect on the socialisation subscale of the VABS, but non-significant effects on the communication subscale of the VABS and adaptive functioning and psychopathology as measured by the DBC total score (see Table 191). In addition, the confidence in the effect estimate for the statistically significant positive treatment response was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size.

Cognitive-behavioural interventions for adaptive behaviour as an indirect outcome

The one included cognitive-behavioural intervention trial (DRAHOTA2011) examined indirect effects of CBT that was targeted at anxiety on adaptive behaviour (see Table 192). The CBT was manualised and based on the 'Building Confidence' CBT programme (Wood & McLeod, 2008) modified for use with children with autism (Wood et al., 2007). The intervention included coping skills training (for instance, affect recognition, cognitive restructuring, and the principle of exposure) followed by in vivo practice of the skills. The intervention also included a parent training component where parents were taught to support in vivo exposures and use positive reinforcement and communication skills to encourage their children's independence and autonomy. Autism-specific adaptations included the addition of some new modules aimed at social skills training for children with autism. For instance, additional intervention components included social coaching provided at school, home or in public immediately before the child attempted to join a social activity, reinforcement for positive social skills and a mentoring system at school. Other adaptations included an additional module which focused on building independence in self-care skills. In addition to adding new modules autism-specific adaptations were also made to general teaching approaches, for example, children's special interests were used as examples and rewards in teaching.

Table 192: Study information table for included trial of cognitive-behavioural interventions for adaptive behaviour

	CBT versus waitlist
No. trials (N)	1 (40)
Study IDs	DRAHOTA2011
Study design	RCT
% female	33
Mean age (years)	9.2
IQ	Not reported
Dose/intensity (mg/hours)	24 (1.5 hours/week) (individual sessions with therapist)
Setting	Research setting (no further details reported)
Length of treatment (weeks)	16
Continuation phase (length and inclusion criteria)	29 (6-week intervention followed by 3-month follow-up; however, outcome data is for post-treatment only as there is no follow-up data for the control group)

Evidence for the effectiveness of CBT on adaptive behaviour and the quality of the evidence is presented in Table 193. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 193: Evidence summary table for effects of cognitive-behavioural interventions on adaptive behaviour as an indirect outcome

	CBT versus waitlist
Outcome	Adaptive behaviour (self-care)
Outcome measure	VABS: Daily living skills
Study ID	DRAHOTA2011
Effect size (CI; p value)	SMD 0.63 (-0.01, 1.26; p = 0.05)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 40
Forest plot	1.13.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as outcome measure based on interview with non-blind parent rather than direct behavioural observation. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for statistically significant indirect effects of CBT on adaptive behaviour as measured by the VABS daily living skills subscale (see Table 193).

Parent training for adaptive behaviour as a direct or indirect outcome

Two of the parent training intervention trials involved a comparison between parent training and treatment as usual, with one of these studies examining effects on adaptive behaviour as a direct outcome (PAJAREYA2011), and the other examining indirect effects on adaptive behaviour (TONGE2006). One of the parent training studies (RICKARDS2007) compared combined parent training and an early intervention centre programme and an early intervention centre programme only. One of the parent training studies (JOCELYN1998) compared parent and day-care staff training with standard day care. Finally, the last included parent training intervention trial (AMAN2009) compared parent training combined with an antipsychotic with antipsychotic medication only (see Table 194).

PAJAREYA2011 examined effects of the Developmental Individual-difference, Relationship-based/Floortime™ intervention (Greenspan & Lewis, 2005) relative to treatment as usual. This programme involved parent training (with no contact with the child) and parents receiving didactic instruction about the principles of the intervention and psychoeducation about autism and one-on-one interactive home visits. During the home visits parents were trained to observe their child's cues and follow the child's lead and were taught to implement the Floortime techniques appropriate to their child's current level of functional development.

TONGE2006 examined effects of the 'Preschoolers with Autism' programme (Brereton & Tonge, 2005) relative to treatment as usual on adaptive behaviour as an indirect outcome. This study included two active intervention arms, the PEBM training intervention and the PEC intervention. In both cases, intervention consisted of small group parent training sessions and individual family sessions. Group sessions (for both PEBM and PEC) included: education about autism; features of

communication, social, play, and behavioural impairments; principles of managing behaviour and change; teaching new skills; improving social interaction and communication; services available; managing parental stress, grief and mental health problems; and sibling, family and community responses to autism. The key 'active' ingredient which differed between PEBM and PEC intervention arms was that in the PEBM individual family sessions the parents were provided with workbooks, modelling, videos, rehearsal (with child when present), homework tasks and feedback, while for the PEC intervention although the educational material in the manual was the same no skills training or homework tasks were set for the individual sessions and the emphasis was on non-directive interactive discussion and counselling. Initially the two active intervention arms (PEBM and PEC) were compared and as there were significant differences between them the subgroups were entered into the analysis (with the subtotal function disabled).

In RICKARDS2007 both experimental and control group children participated in an early intervention centre programme that involved individualised programmes that covered all aspects of development. Training techniques used for the centre-based programmes included chaining, repetition, reward, play-based learning, communication systems (such as PECS), behaviour modification techniques, speech and language and occupational therapy. The experimental group also received an additional home-based parent training intervention. Behavioural targets for the parent training intervention were jointly agreed between the family and intervention administrators and the home-based teacher worked with the child, discussed strategies (similar to those used in the centre) and helped the parents to understand the meaning of the child's challenging behaviour, demonstrated strategies to parents, and assisted parents in adapting the home environment for the needs of the child, for instance, the use of communication aids. The sample of children in RICKARDS2007 included children with autism (66%), children with developmental delay (15%) and children with language delay (19%).

In JOCELYN1998 the intervention was delivered through hospital-based educational seminars (covering an introduction to autism, behaviour analysis techniques, interventions aimed at communication, techniques to improve social interaction and engage the child in play, and problem solving); on-site consultations to day care centres (conducted in parallel with seminars to facilitate practical application of techniques); and psychoeducational and supportive work with the family (including review meetings at the day care centre with the parents, and home visits to parents where written information about autism was provided, parents were given the opportunity to discuss concerns and questions, expectations and goals for the child were discussed, and videotapes of the child at day care were reviewed to share intervention strategies and techniques).

Finally, in AMAN2009 both experimental and control groups received risperidone (or aripiprazole if risperidone was ineffective). In addition, the experimental group received a parent training intervention delivered by a behaviour therapist. Parent training was based on the RUPP manual (Scahill et al., 2009) and involved seven to

nine weekly 60-90-minute sessions where parents were taught to use preventative approaches (for example, visual schedules), and were instructed in the effective use of positive reinforcement, and in strategies for teaching compliance, functional communication skills and specific adaptive skills. Parent training teaching techniques included direct instruction, use of video vignettes, practice activities, behaviour rehearsal with feedback, role-playing, and individualised homework assignments.

Evidence for the effectiveness of parent training on adaptive behaviour and the quality of the evidence is presented in Table 195 and Table 196. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 194: Study information table for included trials of parent training interventions for adaptive behaviour

	Parent training versus treatment as usual	Combined parent training and early intervention centre programme versus early intervention centre programme only	Parent and day-care staff training versus standard day-care	Combined parent training and antipsychotic versus antipsychotic-only
No. trials (N)	2 (137)	1 (65)	1 (36)	1 (124)
Study IDs	(1) TONGE2006 (2) PAJAREYA2011	RICKARDS2007	JOCELYN1998	AMAN2009
Study design	(1)-(2) RCT	RCT	RCT	RCT
% female	(1) 16 (2) 13	20	3	Not reported
Mean age (years)	(1) 3.9 (2) 4.5	3.7	3.6	7.4
IQ	(1) 59.2 (assessed using the PEP-R – developmental quotient; Schopler et al., 1990) (2) Not reported	60.4 (test not reported)	PIQ 63.1 (assessed using LIPS; Leiter, 1948)	Not reported (19% mild LD; 24% moderate LD)
Dose/intensity (mg/hours)	(1) 25 (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions) (2) 197.6 (15.2 hours/week)	Planned intensity for centre-based programme of 200 hours (5 hours/week). Actual number of sessions, rather than number of hours, was reported for the additional parent training intervention but number of hours was estimated and the estimated intensity for the additional parent training component was 43.5 hours, and total hours of	50 hours (3 hours/week of educational seminars for 5 weeks and 3 hours/week of on-site day-care staff consultation for 10 weeks, and three parent-staff review meetings at day care centre [estimated at 3 hours] and 2 in-home visits [estimated at 2 hours]; equating to 4 hours/week)	Experimental intervention: Risperidone (or aripiprazole) 0.5-3.5 mg/day (mean: 2 mg/day) and 10.8 60-90 minutes sessions for parent training Control intervention: Risperidone (or aripiprazole) 0.5-3.5 mg/day (mean: 2.3 mg/day)

		intervention for the experimental group was 243.5 hours		
Setting	(1) Not reported (2) Home	Early intervention centre and home-based	Outpatient, educational (day care centre) and home-based	Not reported
Length of treatment (weeks)	(1) 20 (2) 13	40 (over 12-month period)	12	24
Continuation phase (length and inclusion criteria)	(1) 46 (including 6-month post-intervention follow-up) (2) 13	108 (including post-intervention assessment at 13 months and 12-month post-intervention follow-up assessment)	12	54-162.5 weeks (mean: 80 weeks; including 1-year post-intervention follow-up)

Table 195: Evidence summary table for effects of parent training on adaptive behaviour as a direct or indirect outcome

	Parent training versus treatment as usual			
Outcome	Functional emotional development (direct outcome)	Adaptive behaviour (indirect outcome)		
Outcome measure	(1) Clinician-rated (Functional Emotional Assessment Scale) (2) Parent-rated (Functional Emotional Developmental Questionnaire)	VABS: Daily living skills (1) PEBM (2) PEC	VABS: Socialisation (1) PEBM (2) PEC	VABS: Communication (1) PEBM (2) PEC
Study ID	PAJAREYA2011	TONGE2006		
Effect size (CI; p value)	(1) *Clinician-rated (Functional Emotional Assessment Scale)* SMD -0.25 (-0.95, 0.45; p = 0.48) (2) *Parent-rated (Functional*	(1) *PEBM* SMD 0.46 (-0.01, 0.94; p = 0.06) (2) *PEC* SMD -0.14 (-0.61, 0.34; p = 0.57)	(1) *PEBM* SMD 0.35 (-0.12, 0.83; p = 0.14) (2) *PEC* SMD -0.26 (-0.74, 0.21; p = 0.28)	(1) *PEBM* SMD 0.10 (-0.37, 0.57; p = 0.68) (2) *PEC* SMD -0.56 (-1.04, -0.07; p = 0.02)

	Emotional Developmental Questionnaire) SMD -0.20 (-0.90, 0.49; p = 0.57)			
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	(1) Low[1] (2) Very low[1,2]	Very low[1,3]		(1) Very low[1,3] (2) Low[1,4]
Number of studies/participants	K = 1; N = 32	(1) K = 1; N = 70 (2) K = 1; N = 68		
Forest plot	1.13.3; Appendix 13			

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and high risk of detection bias as parent-rated and parents were non-blind and involved in the intervention so problems with self-assessment. There was also no independent reliability and validity data for the Thai-version of this outcome measure which was used in the study.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as although the outcome assessor was a blinded clinician the measure is based on parental interview and simultaneous child observation and parents non-blind and involved in intervention.
[4]Downgraded due to serious imprecision as N <400.

Table 196: Evidence summary table for effects of parent training on adaptive behaviour as a direct or indirect outcome *(continued)*

	Combined parent training and early intervention centre programme versus early intervention centre programme only		**Parent and day-care staff training versus standard day-care**	Combined parent training and antipsychotic versus antipsychotic-only
Outcome	Parent-reported adaptive behaviour (direct outcome)	Clinician-rated adaptive behaviour (direct outcome)	Self-care (indirect outcome)	Adaptive behaviour (indirect outcome)
Outcome measure	VABS: total at: (1) Post-intervention (2) 12-month post-intervention follow-up	Bayley Scales of Infant Development: Behavior Rating Scale at: (1) Post-intervention (2) 12-month post-	EIDP/PSDP developmental age: Self-care	VABS: (1) Composite score (2) Daily living skills (3) Socialisation (4) Communication

		intervention follow-up		
Study ID	RICKARDS2007		JOCELYN1998	AMAN2009
Effect size (CI; p value)	(1) *Post-intervention* SMD 0.25 (-0.27, 0.77; p = 0.34) (2) *12-month follow-up* SMD 0.31 (-0.24, 0.87; p = 0.27)	(1) *Post-intervention* SMD 0.40 (-0.12, 0.93; p = 0.13) (2) *12-month follow-up* SMD 0.62 (0.04, 1.21; p = 0.04)	SMD -0.04 (-0.70, 0.63; p = 0.92)	(1) *Composite score* SMD 0.56 (0.19, 0.93; p = 0.003) (2) *Daily living skills* SMD 0.48 (0.12, 0.85; p = 0.01) (3) *Socialisation* SMD 0.60 (0.23, 0.96; p = 0.001) (4) *Communication* SMD 0.47 (0.11, 0.84; p = 0.01)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Very low[1,2,3]	(1) Very low[2,3] (2) Low[2,4]	Low[3]	Low[4,5]
Number of studies/participants	(1) K = 1; N = 58 (2) K = 1; N = 51	(1) K = 1; N = 57 (2) K = 1; N = 47	K = 1; N = 35	K = 1; N = 124
Forest plot	1.13.3; Appendix 13			

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrator and participants were non-blind, and risk of detection bias was unclear/unknown as, although the interviewer was a blinded research assistant, the outcome measure was based on non-blind parent report and parents were involved in the intervention.
[2]Downgraded due to serious indirectness – population was indirect (as the sample included participants with developmental delay or language delay without autism).
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded due to serious imprecision as N <400.
[5]Downgraded for serious risk of bias – high risk of selection bias as significant group differences at baseline on this outcome measure. High risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome measure based on interview with parents who were non-blind. Also high risk of attrition bias due to higher dropout rates in the experimental (combined risperidone and parent training) group (N = 20; 27% attrition) than the control (risperidone only) group (N = 9; 18% attrition).

Results for the effects of parent training relative to treatment as usual on adaptive behaviour were inconsistent. There were no statistically significant effects of parent training on clinician-rated or parent-rated functional emotional development as measured by the Functional Emotional Assessment Scale or Functional Emotional Developmental Questionnaire (see Table 195). As mentioned previously, there were two active intervention arms in TONGE2006. These active intervention arms were initially compared and there were significant differences between the two in favour of the PEBM group as measured by the VABS Communication Subscale (SMD 0.75 [0.26, 1.25]; test for overall effect: Z = 2.99, p = 0.003), daily living skills subscale (SMD 0.67 [0.19, 1.16]; test for overall effect: Z = 2.70, p = 0.007), and socialisation subscale (SMD 0.63 [0.14, 1.12]; Test for overall effect: Z = 2.54, p = 0.01). As these active intervention arms could not be combined, subgroups were retained for the comparison with treatment as usual and non-significant effects were observed for both PEBM and PEC (relative to treatment as usual) as measured by the VABS Daily Living Skills and Socialization Subscales, and for the PEBM group for the Communication Subscale. However, for the PEC group a statistically significant effect was found on the VABS communication subscale; however, this effect was in favour of the treatment as usual group (see Table 195). Narrative review of this effect showed improvement across both groups but greater improvement in the control group.

There was evidence for a moderate and statistically significant delayed effect of parent training (as an adjunct to an early intervention centre programme) on clinician-rated adaptive behaviour as measured by the Bayley Behavior Rating Scale at 12-month post-intervention follow-up (see Table 196). However, the quality of the evidence was low due to indirectness (as the sample included participants with developmental delay or language delay without autism) and small sample size. There were also inconsistent results with non-significant effects observed for parent-rated adaptive behaviour as measured by the VABS at both post-intervention and 12-month post-intervention follow-up (see Table 196).

There was no evidence for statistically significant effects of parent and day-care staff training (relative to standard day-care) on self-care as measured by the EIDP/PSDP (see Table 196).

Finally, there was evidence for small to moderate and statistically significant effects of parent training (as an adjunct to antipsychotics) on adaptive behaviour as measured by the VABS composite score and subscales (see Table 196). However, confidence in these effect estimates was due to risk of bias concerns (non-blind outcome assessment and higher dropout in the experimental group) and small sample size.

Social-communication interventions for adaptive behaviour as an indirect outcome

Four of the included social-communication intervention trials (ALDRED2001, CARTER2011, GREEN2010, SCHERTZ2013) involved a comparison between caregiver-mediated social-communication interventions and treatment as usual. One of the social-communication intervention trials (FRANKEL2010) compared a social skills group with treatment as usual. Finally, the last included social-communication intervention trial (OWENS2008) compared LEGO® therapy with the SULP (see Table 197).

In one of the studies included in ALDRED2001 (Aldred et al., 2001) the Child's Talk intervention aimed to increase the quality of parental adaptation and communication with their autistic children. Techniques included initial psychoeducation (teaching parents about the developmental stages of early social communication) followed by parent–child sessions in which parents were encouraged to establish shared attention between themselves and their child, decrease intrusive demands they made on their child, model language output based on child capabilities and consolidate and expand their child's social communication by establishing predictable routines and repetition in rehearsed interactive play and adding variations and expansions to the child's play and language, for instance, leaving openings for child to fill with a social and verbal response. CARTER2011 used Hanen's 'More than Words' programme. This intervention is delivered by speech and language therapists and involves group-based parent training and individualised in-home parent–child sessions focused on improving the child's social communication through teaching parents to use techniques including using joint action routines, using visual supports, supporting peer interactions, responding to the child's communicative attempts and following their lead, and using books and play to elicit and to reward communication. In GREEN2010, the PACT programme was also delivered by speech and language therapists and consisted of one-to-one clinic sessions between therapist and parent (with the child present) and used techniques such as video feedback to increase parental sensitivity and responsiveness to child communication. Strategies such as joint action routines, familiar repetitive language and pauses were also encouraged in order to develop the child's communication. SCHERTZ2013 examined effects of a Joint Attention Mediated Learning intervention. This intervention was delivered via parent-mediation and targets progressed through three phases: the Focusing on Faces phase where the child was helped to look freely and often to the parent's face; the Turn-Taking phase where the child and parent engage in reciprocal and repetitive play that acknowledges the other's shared interest by accommodating the parent's turn; and the joint attention phase where triadic engagement is encouraged using toys. Parent–child interactions were recorded and discussed and parents were required to spend 30 minutes a day with the child, integrating what had been learnt into other daily activities. The

intervention was 'complete' when children showed three examples of initiating joint attention in multiple sessions.

In FRANKEL2010 the Parent-assisted CFT (Frankel & Myatt, 2003) intervention was examined**.** This group-based social skills intervention involved individuals with autism being integrated into a mixed clinical group (18.6% Adjustment Disorder, 46% ADHD, 2.7% ADHD and ODD, 0.5% ODD alone, 0.7% fetal alcohol spectrum disorder, 4.9% anxiety disorder, 1.3% mood disorder, 1.3% learning disabilities and 25.2% no diagnosis) and children were taught social skills in terms of rule-based procedures using techniques including instruction, modelling, rehearsal and performance feedback. Homework assignments were also used to try and increase generalisation, including calling another member of the class, parent-supported play dates, and practicing 'making fun of the teasing' with a child who was teasing them. Children and parents were seen at the same time in separate sessions and the aim of the parent sessions was to increase generalisation through training in the organisation and implementation of play dates.

Finally, in OWENS2008 the experimental intervention involved collaborative LEGO play in pairs or small groups (based on a draft manual produced by Dr LeGoff). Typical projects included building a LEGO set in groups of three with each member of the group assigned a different role (for instance, 'engineer', 'supplier' and 'builder') and 'freestyle' LEGO activities in which children designed and built a model in pairs (for instance, a space rocket). The former project type aimed to target joint attention, turn taking, sharing, joint problem solving, listening and general social communication skills. While, the 'freestyle' projects aimed to teach compromise, clear expression of ideas and taking other people's perspectives and ideas into account. During the intervention children were asked to follow 'LEGO Club Rules', which included: 'Build things together'; 'If someone else is using it, don't take it, ask first'; 'Use indoor voices-no yelling'; and 'Use polite words'. The therapists role was to highlight the presence of a problem and help children to come up with their own solutions (or remind them of strategies which they had previously used) rather than pointing out specific social problems or solutions. In this study, the control group also received an active intervention, SULP (Rinaldi, 2004). This control intervention used a direct group-based teaching approach (following the SULP manual) to target eye contact, listening, turn taking, proxemics and prosody. Instruction followed a specified framework, beginning with stories about monster characters who experienced problems with particular social or communication skills, moved on to asking the children to evaluate adult models of good and bad skills, and finally children practiced the targeted skill through games and conversation.

Table 197: Study information table for included trials of social-communication interventions for adaptive behaviour

	Caregiver-mediated social-communication intervention versus treatment as usual	Social skills group versus treatment as usual	LEGO® therapy versus SULP
No. trials (N)	4 (265)	1 (76)	1 (31)
Study IDs	(1) ALDRED2001 (2) CARTER2011 (3) GREEN2010 (4) SCHERTZ2013	FRANKEL2010	OWENS2008
Study design	(1)-(4) RCT	RCT	RCT
% female	(1) 11 (2) Not reported (3) 9 (4) Not reported	15	3
Mean age (years)	(1) Median 4-4.3 (2) 1.8 (3) 3.8 (4) 2.2	8.5	8.2
IQ	(1)-(2) Not reported (3) Non-verbal IQ age equivalent: 26.2 months (assessed using the MSEL) (4) Not reported	Verbal IQ: 103.8 (assessed using the WISC-III)	110.5 (IQ test not reported)
Dose/intensity (mg/hours)	(1) Not reported (parents and children attended monthly intervention sessions for 6 months, followed by a further 6 months of less frequent maintenance sessions) (2) Hours of intervention not reported (intervention consisted of eight group parent-training sessions and three individualised parent–child sessions) (3) 28 (4) Not reported	11.3	Planned intensity of 18 hours (1 hour/week)
Setting	(1) Not reported (2) Clinic and home (3) Outpatient (4) Home	Outpatient	Educational (school)
Length of treatment	(1) 52	12	18

(weeks)	(2) 15 (3) 56 (4) 17-52 (mean: 30)		
Continuation phase (length and inclusion criteria)	(1) 52 (2) 39 (with post-intervention assessments at 22 weeks and follow-up assessments at 39 weeks) (3) 56 (4) 60 (including 4-8-week post-intervention follow-up assessments)	24 (including 12-week post-intervention follow-up for the experimental group and 12-week intervention for the waitlist control group)	18

Evidence for the effectiveness of social-communication interventions on adaptive behaviour and the quality of the evidence is presented in Table 198. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 198: Evidence summary table for effects of social-communication interventions on adaptive behaviour as an indirect outcome

	Caregiver-mediated social-communication intervention versus treatment as usual	**Social skills group versus treatment as usual**	**LEGO® therapy versus SULP**
Outcome	Adaptive behaviour	Self-control	Adaptive behaviour
Outcome measure	VABS: (1) Composite score (2) Daily living skills (3) Socialisation (4) Communication	SSRS: Self-control	VABS: (1) Socialisation (2) Communication
Study ID	(1) GREEN2010 (2) CARTER2011 (3) CARTER2011 (4) ALDRED2001 CARTER2011 GREEN2010 SCHERTZ2013	FRANKEL2010	OWENS2008
Effect size (CI; p value)	(1) *Composite score* SMD -0.17 (-0.48, 0.15; p = 0.31) (2) *Daily living skills* SMD 0.55 (-0.09, 1.19; p = 0.09) (3) *Socialisation* SMD 0.10 (-0.53, 0.73; p = 0.75) (4) *Communication* SMD -0.04 (-0.29, 0.22; p = 0.78)	SMD 0.63 (0.14, 1.11; p = 0.01)	(1) *Socialisation* SMD 0.32 (-0.39, 1.03; p = 0.37) (2) *Communication* SMD 0.48 (-0.23, 1.20; p = 0.19)

Heterogeneity (chi²; p value; I²)	(1)-(3) Not applicable (4) Chi² = 3.60, df = 3; p = 0.31; I^2 = 17%	Not applicable	
Quality of the evidence (GRADE)	(1) Low[1,2] (2)-(3) Very low[3,4] (4) Low[2,5]	Low[2,6]	Very low[3,4]
Number of studies/participants	(1) K = 1; N = 152 (2)-(3) K = 1; N = 39 (4) K = 4; N = 245	K = 1; N = 68	K = 1; N = 31
Forest plot	1.13.4; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrator and participants were non-blind, and unclear/unknown risk of detection bias as teacher-rated and blinding of teacher not reported.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias was unclear/unknown as outcome measure based on interview with non-blind parent rather than direct behavioural observation.
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and unclear/unknown risk of detection bias as blinding of outcome assessment is unclear.
[6]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and high risk of detection bias as parent-rated and parents were non-blind and involved in the intervention. There was also a high risk of attrition bias due to a greater drop-out rate in the experimental (N = 14; 35%) than in the control (N = 5; 14%) group.

There was no evidence for statistically significant effects of either caregiver-mediated social-communication interventions or LEGO therapy (relative to SULP) on adaptive behaviour as an indirect outcome (see Table 198). There was single study evidence for a moderate indirect effect of a social skills group intervention on self-control as measured by the SSRS (see Table 198). However, the quality of the evidence was downgraded to low due to risk of bias concerns (outcome measure was parent-rated and parents non-blind and involved in the intervention and higher drop-out rate in the experimental group) and small sample size.

8.2.4 Studies considered – effect of pharmacological interventions on adaptive behaviour

Two papers from the search met the eligibility criteria for full-text retrieval. Of these, both trials provided relevant clinical evidence and were included in the review and both of these studies examined the efficacy of pharmacological interventions on adaptive behaviour as an indirect outcome (not the target of the intervention). Both studies were published in peer-reviewed journals between 2009 and 2012.

Two antipsychotic trials (MARCUS2009, OWEN2009[65]) examined effects on adaptive behaviour as an indirect outcome.

8.2.5 Clinical evidence – effect of pharmacological interventions on adaptive behaviour

Antipsychotics for adaptive behaviour as an indirect outcome

Both of the antipsychotic trials (MARCUS2009, OWEN2009) compared aripiprazole with placebo in children with autism (see Table 199). Data from MARCUS2009 also allowed for a comparison of low dose antipsychotics (5 mg/day aripiprazole) with placebo.

Table 199: Study information table for included trials of antipsychotics for adaptive behaviour

	Aripiprazole versus placebo
No. trials (N)	2 (316)
Study IDs	(1) MARCUS2009 (2) OWEN2009
Study design	(1)-(2) RCT
% female	(1) 11 (2) 12
Mean age (years)	(1) 9.7 (2) 9.3
IQ	(1)-(2) Not reported
Dose/intensity (mg/hours)	(1) Fixed doses of 5 mg/day or 10 mg/day or 15 mg/day (3 active treatment arms) (2) 2-15 mg/day
Setting	(1) Research setting (2) Not reported
Length of treatment (weeks)	(1)-(2) 8
Continuation phase (length and inclusion criteria)	(1)-(2) 8

Evidence for the effectiveness of aripiprazole and low dose aripiprazole on adaptive behaviour and the quality of the evidence is presented in Table 200 and Table 201. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

[65] See Chapter 7, Section 7.3.2 for direct outcomes from MARCUS2009 and OWEN2009.

Table 200: Evidence summary table for effects of antipsychotics on adaptive behaviour as an indirect outcome

	Aripiprazole versus placebo
Outcome	Adaptive behaviour
Outcome measure	PedsQL (change scores): (1) Total score (2) Emotional functioning (3) Social functioning (4) Cognitive functioning
Study ID	MARCUS2009 OWEN2009
Effect size (CI; p value)	(1) *Total score* SMD 0.51 (0.21, 0.80; p = 0.0007) (2) *Emotional functioning* SMD 0.41 (0.12, 0.70; p = 0.006) (3) *Social functioning* SMD 0.27 (-0.02, 0.56; p = 0.07) (4) *Cognitive functioning* SMD 0.40 (0.11, 0.69; p = 0.007)
Heterogeneity (chi²; p value; I^2)	(1) Chi² = 6.34, df = 1; p = 0.01; I^2 = 84% (2) Chi² = 1.36, df = 1; p = 0.24; I^2 = 26% (3) Chi² = 7.59, df = 1; p = 0.006; I^2 = 87% (4) Chi² = 0.49, df = 1; p = 0.48; I^2 = 0%
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2) Low[1,3] (3) Very low[1,2,4] (4) Low[1,3]
Number of studies/participants	(1)-(3) K = 2; N = 243 (4) K = 2; N = 242
Forest plot	1.14.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – risk of detection bias is unclear as blinding of parents not reported. [2]Downgraded due to very serious inconsistency as I^2 value indicates substantial to considerable heterogeneity. [3]Downgraded due to serious imprecision as N <400. [4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

Table 201: Evidence summary table for effects of antipsychotics (low dose) on adaptive behaviour as an indirect outcome

	Low dose aripiprazole versus placebo
Outcome	Adaptive behaviour
Outcome measure	PedsQL (change scores): (1) Total score (2) Emotional functioning (3) Social functioning (4) Cognitive functioning
Study ID	MARCUS2009
Effect size (CI; p value)	(1) *Total score* SMD 0.21 (-0.23, 0.65; p = 0.34) (2) *Emotional functioning* SMD 0.19 (-0.25, 0.63; p = 0.40) (3) *Social functioning* SMD 0.00 (-0.43, 0.44; p = 0.98)

	(4) *Cognitive functioning* SMD 0.32 (-0.12, 0.76; p = 0.16)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	(1)-(2) Very low[1,2] (3) Low[1,3] (4) Very low[1,2]
Number of studies/participants	K = 1; N = 80
Forest plot	1.14.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – risk of detection bias is unclear as blinding of parents not reported. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [3]Downgraded due to serious imprecision as N <400.	

There was evidence for small to moderate and statistically significant effects of aripiprazole on adaptive behaviour as measured by the PedsQL total score, and emotional functioning and cognitive functioning subscales (see Table 200). However, the quality of this evidence was low to very low due to risk of bias concerns (unclear blinding of outcome assessment), small sample size, and considerable to substantial heterogeneity (for the total score estimate). There was also evidence for statistically significant harms associated with antipsychotics, as follows: increased risk of any adverse event, increased risk of clinically relevant weight gain, continuous measure of weight gain, increased appetite, constipation, prolactin concentration, leptin change score, pulse change score, somnolence/drowsiness, fatigue, sedation, rhinitis, fever, tachycardia, drooling, and tremor (see Section 10.3.2 for adverse events associated with antipsychotics).

There were no statistically significant effects of low dose aripiprazole (5 mg/day) on adaptive behaviour as measured by the PedsQL (see Table 201).

8.2.6 Studies considered – effect of biomedical interventions on adaptive behaviour

Fourteen papers from the search met the eligibility criteria for full-text retrieval. Of these, 12 RCTs provided relevant clinical evidence and were included in the review. None of these studies examined the efficacy of psychosocial interventions on adaptive behaviour as a direct outcome (target of intervention), with all 12 providing data on adaptive behaviour as an indirect outcome. All studies were published in peer-reviewed journals between 1999 and 2011. In addition, two studies were excluded from the analysis. The reasons for exclusion were that the sample size was less than ten participants per arm or data could not be extracted due to crossover design and unavailability of first phase data. Further information about the excluded studies can be found in Appendix 12d.

Four complementary therapies trials (WONG2002, WONG2008, WONG2010A, WONG2010B[66]) examined effects on adaptive behaviour as an indirect outcome.

Two hormone trials (OWLEY1999, SANDLER1999[67]) examined effects on adaptive behaviour as an indirect outcome.

Three medical procedures studies (ADAMS2009A, GRANPEESHEH2010, ROSSIGNOL2009[68]) examined effects on adaptive behaviour as an indirect outcome.

Finally, three nutritional intervention trials (BENT2011, JOHNSON2010, WHITELEY2010[69]) examined effects on adaptive behaviour as an indirect outcome.

8.2.7 Clinical evidence – effect of biomedical interventions on adaptive behaviour

Complementary therapies for adaptive behaviour as an indirect outcome

Two of the included complementary intervention trials (WONG2010A, WONG2010B) compared acupuncture/electro-acupuncture with sham acupuncture/electro-acupuncture, and two trials (WONG2002, WONG2008) compared acupuncture/electro-acupuncture and a conventional educational programme with a conventional educational programme only (see Table 202).

In WONG2010A, acupuncture was applied to the tongue using an acupuncture needle via five acupoints for approximately 15 seconds. Sham acupuncture was applied to the tongue via the same five acupoints as the intervention group, but involved the acupuncturist touching the five points with the blunt rather than the sharp end of the needle. In WONG2010B electro-acupuncture was delivered via eight acupoints using an electro-acupuncture machine that provided electrical spacing-density stimulation for 30 minutes, and sham acupuncture was delivered in the same way but with needles only inserted to a superficial level.

In WONG2002 acupuncture was delivered with Hwato needles to five acupoints on the tongue, the acupuncture sessions lasted for less than 15 seconds and parents were present throughout. In WONG2008 five

[66] See Section 6.4.3 for direct outcomes from WONG2002 and WONG2008; see Section 8.4.7 for direct outcomes from WONG2010A and WONG2010B.
[67] See Section 6.4.5 for direct outcomes from OWLEY1999 and Section 7.4.2 for direct outcomes from SANDLER1999.
[68] See Sections 6.4.3 and 6.4.5 for direct outcomes from ADAMS2009A and GRANPEESHEH2010, respectively; see Section 7.4.2 for direct outcomes from ROSSIGNOL2009.
[69] See Section 7.4.2 for direct outcomes from BENT2011 and JOHNSON2010 and Section 6.4.5 for direct outcomes from WHITELEY2010.

acupoints were stimulated for 30 minutes per session. However, for both these studies participants in experimental and control groups were also receiving a conventional educational programme and no detail is reported about this adjunctive intervention.

Table 202: Study information table for included trials of complementary therapies for adaptive behaviour

	Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture	**Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only**
No. trials (N)	2 (109)	2 (66)
Study IDs	(1) WONG2010A (2) WONG2010B	(1) WONG2002 (2) WONG2008
Study design	(1)-(2) RCT	(1) RCT (2) RCT (crossover)
% female	(1) 14 (2) 15	(1) 3 (2) 6
Mean age (years)	(1) 6.1 (2) 9.3	(1) 7.2 (2) 7.5
IQ	(1) 62.4 (assessed using the GMDS; Griffiths, 1954) (2) Not reported	(1)-(2) Not reported
Dose/intensity (mg/hours)	(1) 0.2 hours/40 sessions (0.02 hours/week; 5 sessions/week) (2) 6 hours/12 sessions (1.5 hours week; 3 sessions/week)	(1) 0.2 hours/40 sessions (0.02 hours/week; 5 sessions/week) (2) 12 hours/24 sessions (1.5 hours/week; 3 sessions/week)
Setting	(1) Not reported (2) Hospital	(1)-(2) Not reported
Length of treatment (weeks)	(1) 8 (2) 4	(1)-(2) 8
Continuation phase (length and inclusion criteria)	(1) 8 (2) 4	(1)-(2) 8

Evidence for the effectiveness of complementary therapies on adaptive behaviour and the quality of the evidence is presented in Table 203. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 203: Evidence summary table for effects of complementary therapies on adaptive behaviour as an indirect outcome

	Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture		**Acupuncture/electro-acupuncture and conventional educational programme versus conventional educational programme only**
Outcome	Adaptive behaviour		Adaptive behaviour
Outcome measure	WeeFIM (change scores): (1) Total score (2) Self-care (3) Mobility (4) Cognition (5) Comprehension (6) Expression (7) Social interaction (8) Problem solving (9) Memory	Pediatric Evaluation Disability Inventory: (1) Self-care (functional skill) (2) Self-care (independence) (3) Mobility (functional skill) (4) Mobility (independence) (5) Social function (functional skill) (6) Social function (independence)	WeeFIM (change scores): (1) Total score (2) Self-care (3) Mobility (4) Cognition (5) Comprehension (6) Expression (7) Social interaction (8) Problem solving (9) Memory
Study ID	(1)-(4) WONG2010A WONG2010B (5)-(9) WONG2010B	WONG2010B	(1)-(4) WONG2002 WONG2008 (5)-(9) WONG2008
Effect size (CI; p value)	(1) *Total score* SMD 0.59 (0.19, 0.98; p = 0.004) (2) *Self-care* SMD 0.56 (0.17, 0.96; p = 0.005) (3) *Mobility* SMD -0.08 (-0.46, 0.31; p = 0.70) (4) *Cognition* SMD 0.48 (0.09, 0.87; p = 0.02) (5) *Comprehension* SMD 0.51 (-0.03, 1.05; p = 0.06) (6) *Expression* SMD 0.17 (-0.36, 0.70; p = 0.53) (7) *Social interaction* SMD -0.23 (-0.77, 0.30; p = 0.39)	(1) *Self-care (functional skill)* SMD -0.22 (-0.75, 0.31; p = 0.42) (2) *Self-care (independence)* SMD -0.44 (-0.97, 0.10; p = 0.11) (3) *Mobility (functional skill)* SMD -0.11 (-0.64, 0.42; p = 0.68) (4) *Mobility (independence)* SMD -0.19 (-0.72, 0.35; p = 0.49) (5) *Social function (functional skill)* SMD 0.04 (-0.49, 0.57; p = 0.87)	(1) *Total score* SMD 0.41 (-0.11, 0.93; p = 0.13) (2) *Self-care* SMD 0.16 (-0.35, 0.67; p = 0.54) (3) *Mobility* SMD 0.52 (-0.00, 1.05; p = 0.05) (4) *Cognition* SMD 0.62 (0.10, 1.14; p = 0.02) (5) *Comprehension* SMD -0.47 (-1.13, 0.19; p = 0.17) (6) *Expression* SMD 0.40 (-0.26, 1.06; p = 0.24) (7) *Social interaction* SMD 0.40 (-0.26, 1.06; p = 0.23) (8) *Problem solving*

	(8) *Problem solving* SMD -0.24 (-0.77, 0.30; p = 0.39) (9) *Memory* SMD 0.13 (-0.40, 0.67; p = 0.62)	(6) *Social function (independence)* SMD -0.14 (-0.67, 0.39; p = 0.60)	SMD 0.33 (-0.32, 0.99; p = 0.32) (9) *Memory* SMD -0.15 (-0.81, 0.50; p = 0.64)
Heterogeneity (chi²; p value; I²)	(1) Chi² = 4.44, df = 1; p = 0.04; *I²* = 77% (2) Chi² = 4.43, df = 1; p = 0.04; *I²* = 77% (3) Chi² = 1.86, df = 1; p = 0.17; *I²* = 46% (4) Chi² = 0.79, df = 1; p = 0.38; *I²* = 0% (5)-(9) Not applicable	Not applicable	(1) Chi² = 11.47, df = 1; p = 0.0007; *I²* = 91% (2) Chi² = 5.97, df = 1; p = 0.01; *I²* = 83% (3) Chi² = 10.22, df = 1; p = 0.001; *I²* = 90% (4) Chi² = 5.04, df = 1; p = 0.02; *I²* = 80% (5)-(9) Not applicable
Quality of the evidence (GRADE)	(1)-(2) Very low[1,2,3] (3) Very low[2,3,4] (4) Low[2,3] (5)-(9) Very low[3,5]	Very low[3,5]	(1)-(3) Very low[1,5,6] (4) Very low[1,2,6] (5)-(9) Very low[5,6]
Number of studies/participants	(1)-(4) K = 2; N = 105 (5)-(9) K = 1; N = 55	K = 1; N = 55	(1)-(4) K = 2; N = 64 (5)-(9) K = 1; N = 36
Forest plot	1.15.1; Appendix 13		

Note. [1]Downgraded due to very serious inconsistency – I² value indicates considerable to substantial heterogeneity.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported.
[4]Downgraded due to serious inconsistency – I² value indicates moderate heterogeneity.
[5]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[6]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and the conventional education programme differed for each participant which may introduce bias. The risk of detection bias was also unclear/unknown as all outcome measures were rated by blinded assessors, but some outcome measures involved input from parents who were not blind to treatment allocation or confounding variables and systematic review from which data was extracted does not report which outcome measures relied on non-blind parental report.

The evidence for indirect effects of acupuncture on adaptive behaviour was inconsistent. There was evidence for small to moderate and statistically significant effects of acupuncture/electro-acupuncture (relative to sham acupuncture/electro-acupuncture) on adaptive behaviour as measured by the WeeFIM total score and self-care and cognition subscales, but non-significant effects for all other subscales of the WeeFIM and all subscales of the Pediatric Evaluation Disability Inventory (see Table 203). It is also important to note that the confidence in these significant effect estimates was low to very low due to inconsistency (I² value indicates considerable to substantial heterogeneity for the meta-analyses), small sample size and selective reporting bias (follow-up data not reported). The mixed results are also observed for acupuncture/electro-acupuncture as an adjunct to a

conventional educational programme with evidence for a moderate and statistically significant effect on the cognition subscale of the WeeFIM but non-significant effects observed on all other subscales of the WeeFIM (see Table 203) and very low confidence in the significant effect estimate due to risk of bias concerns (unclear blinding of outcome assessment due to parental input), inconsistency (I^2 value indicates considerable heterogeneity) and small sample size.

Hormones for adaptive behaviour as an indirect outcome

Both of the included hormone trials (OWLEY1999, SANDLER1999) compared secretin with placebo (see Table 204), one using porcine secretin (OWLEY1999) and one using synthetic human secretin (SANDLER1999).

Table 204: Study information table for included trials of hormones for adaptive behaviour

	Secretin versus placebo
No. trials (N)	2 (116)
Study IDs	(1) OWLEY1999 (2) SANDLER1999
Study design	(1) RCT (crossover) (2) RCT
% female	(1) 14 (2) Not reported
Mean age (years)	(1) 6.7 (2) 7.5
IQ	(1) Non-verbal IQ 56.4 (assessed using DAS or MSEL) (2) 62.2 (test not reported)
Dose/intensity (mg/hours)	(1) 2 CU/kg (2) 0.4 µg/kg
Setting	(1)-(2) Not reported
Length of treatment (weeks)	(1)-(2) Single dose
Continuation phase (length and inclusion criteria)	(1) 8 (including crossover period but data were extracted only for 4 week period corresponding to the end of the first phase) (2) 4 (assessments at 1 week [post-intervention] and 4 weeks [follow-up])

Evidence for the effectiveness of secretin on adaptive behaviour and the quality of the evidence is presented in Table 205. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 205: Evidence summary table for effects of hormones on adaptive behaviour as an indirect outcome

	Secretin versus placebo
Outcome	Adaptive behaviour
Outcome measure	VABS: (1) Composite score (2) Daily living skills (3) Socialisation (4) Communication
Study ID	(1)-(3) OWLEY1999 (4) OWLEY1999 SANDLER1999
Effect size (CI; p value)	(1) *Composite score* SMD -0.08 (-0.61, 0.44; p = 0.76) (2) *Daily living skills* SMD 0.11 (-0.42, 0.63; p = 0.69) (3) *Socialisation* SMD -0.26 (-0.78, 0.27; p = 0.34) (4) *Communication* SMD -0.28 (-0.65, 0.10; p = 0.15)
Heterogeneity (chi²; p value; I^2)	(1)-(3) Not applicable (4) Chi² = 0.56, df = 1; p = 0.46; I^2 = 0%
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	(1)-(3) K = 1; N = 56 (4) K = 2; N = 112
Forest plot	1.15.2; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for statistically significant effects of secretin on adaptive behaviour as an indirect outcome as measured by the VABS (see Table 205).

Medical procedures for adaptive behaviour as an indirect outcome

One of the included medical procedure trials (ADAMS2009A) compared long-term chelation (seven rounds of DMSA therapy) with short-term chelation (one round of DMSA therapy and six rounds of placebo). The other two included medical procedure trials (GRANPEESHEH2010, ROSSIGNOL2009) compared HBOT with attention-placebo control condition (see Table 92). In ADAMS2009A participants received one screening round of DMSA (a round consisted of three doses/day for 3 days, followed by 11 days off) and children who met criteria for phase two (in particular those excreting significant heavy metals) were randomised to receive continued DMSA (six subsequent rounds) or placebo (six subsequent rounds of methyl cellulose). DMSA was compounded individually for each child from pharmaceutical grade DMSA (over 99% pure) supplied by Spectrum Chemical. To control for the strong smell of DMSA the bottles of placebo included a small slotted container that contained DMSA so that the medication smell was present. In GRANPEESHEH2010 and ROSSIGNOL2009, experimental group participants

were delivered 1.3 atm and 24% oxygen in a HBOT chamber, while control participants in GRANPEESHEH2010 were provided with free airflow through the HBOT chamber at ambient pressure and control participants in ROSSIGNOL2009 were provided with slightly pressurised room air (1.03 atm and 21% oxygen).

Table 206: Study information table for included trials of medical procedures for adaptive behaviour

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)	**HBOT versus attention-placebo**
No. trials (N)	1 (49)	2 (108)
Study IDs	ADAMS2009A	(1) GRANPEESHEH2010 (2) ROSSIGNOL2009
Study design	RCT	(1)-(2) RCT
% female	7	(1) Not reported (2) 16
Mean age (years)	6.6	(1) 6.2 (2) 4.9
IQ	Not reported	(1)-(2) Not reported
Dose/intensity (mg/hours)	Planned intensity for the experimental group of 180 mg/day (l-glutathione) and seven rounds of DMSA (each round consists of 3 days of DMSA [10 mg/kg-dose, nine doses over 3 days], followed by 11 days off [no treatment], and then repeating). For the control group one round of DMSA and six rounds of placebo planned	(1) Planned intensity of 80 hours (6-10 hours/week) (2) Planned intensity of 40 hours (10 hours/week)
Setting	Outpatient	(1) Outpatient (2) Not reported
Length of treatment (weeks)	17	(1) 10-15 (2) 4
Continuation phase (length and inclusion criteria)	17	(1) 34 (ClinicalTrials.gov reports 1-month and 3-month follow-ups but paper does not report follow-up data) (2) 4

Evidence for the effectiveness of medical procedures on adaptive behaviour and the quality of the evidence is presented in Table 207 and Table 208. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 207: Evidence summary table for effects of medical procedures (chelation) on adaptive behaviour as an indirect outcome

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)
Outcome	Adaptive behaviour
Outcome measure	PDDBI: Adaptive behaviours composite
Study ID	ADAMS2009A
Effect size (CI; p value)	SMD -0.20 (-0.84, 0.44; p = 0.54)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.15.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of chelation on adaptive behaviour as an indirect outcome as measured by the PDDBI adaptive behaviours composite score (see Table 207). It was not possible to extract any data from the paper for adverse events.

Table 208: Evidence summary table for effects of medical procedures (HBOT) on adaptive behaviour as an indirect outcome

	HBOT versus attention-placebo	
Outcome	Adaptive behaviour	Positive treatment response
Outcome measure	VABS (change scores): (1) Composite score (2) Daily living skills (3) Socialisation (4) Communication	Number of participants who were 'much improved/very improved' on CGI/PGI-I for overall functioning (1) Clinician-rated (2) Parent-rated
Study ID	GRANPEESHEH2010	ROSSIGNOL2009
Effect size (CI; p value)	(1) *Composite score* SMD -0.18 (-0.85, 0.50; p = 0.61) (2) *Daily living skills* SMD 0.11 (-0.56, 0.78; p = 0.75) (3) *Socialisation* SMD -0.38 (-1.06, 0.30; p = 0.28) (4) *Communication* SMD 0.23 (-0.45, 0.90; p = 0.51)	(1) *Clinician-rated* RR 3.90 (0.92, 16.45; p = 0.06) (2) *Parent-rated* RR 1.95 (0.68, 5.60; p =0.21)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	Low[2]
Number of studies/participants	K = 1; N = 34	K = 1; N = 56
Forest plot	1.15.3; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).		

There was no evidence for a statistically significant treatment effect of HBOT on adaptive behaviours as an indirect outcome as measured by the VABS or a parent- or clinician-reported positive treatment response defined as 'much improved/very improved' on CGI/PGI-I for overall functioning (see Table 208). There was, however, evidence from another study (SAMPANTHAVIVAT2012) for statistically significant adverse events associated with HBOT with participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotraumas than participants who received sham HBOT (see Chapter 10, Section 10.4.2, for adverse events associated with HBOT).

Nutritional interventions for adaptive behaviour as an indirect outcome

Two of the included nutritional intervention trials examined effects of an omega-3 fatty acid supplement on adaptive behaviour as an indirect outcome, one study (BENT2011) examined effects relative to placebo and one trial used a healthy-diet control comparator (JOHNSON2010). The other included nutritional intervention trial (WHITELEY2010) compared a gluten-free and casein-free diet with treatment as usual (see Table 209). In BENT2011, the omega-3 fatty acid supplement was provided as an orange-flavoured pudding packet (Coromega®, Vista, CA) and placebo pudding packets had the same orange flavour with an identical appearance and taste, but included safflower oil which has a similar texture to omega-3 fatty acids and is comprised of non-omega-3 fatty acids. While in JOHNSON2010 the omega-3 fatty acid supplement was DHA (Martek Biosciences product) capsules. Finally, in WHITELEY2010, a strict gluten-free and casein-free diet was introduced over the course of two weeks and nutritionists monitored the experimental group for the trial duration to ensure dietary compliance and nutritional intake. The experimental group was also advised to take a multivitamin supplement including calcium for the trial duration to compensate for any nutritional deficiency during the intervention.

Table 209: Study information table for included trials of nutritional interventions for adaptive behaviour

	Omega-3 fatty acids versus placebo	**Omega-3 fatty acids versus healthy diet control**	**Gluten-free and casein-free diet versus treatment as usual**
No. trials (N)	1 (27)	1 (23)	1 (72)
Study IDs	BENT2011	JOHNSON2010	WHITELEY2010
Study design	RCT	RCT	RCT
% female	11	Not reported	11
Mean age (years)	5.8	3.4	8.2
IQ	77.5 (assessed using the Stanford-Binet Intelligence Scales)	Not reported	Not reported
Dose/intensity (mg/hours)	1.3 g of omega-3 fatty acids per day (with	Planned intensity of 400 mg/day (in two	Unknown (compliance not

	1.1 g of EPA and DHA) administered as two daily doses (with 650 mg of omega-3 fatty acids, 350 mg of EPA and 230 mg of DHA per dose)	daily doses)	recorded)
Setting	Outpatient	Outpatient	Home
Length of treatment (weeks)	12	13	35 (data extracted for 8-month intervention as after this point duration was variable across participants)
Continuation phase (length and inclusion criteria)	12	13	104 (experimental group received diet and control group received treatment as usual for 8 months, at 8 months interim assessment of change in scores for the experimental group on one of several measures [ADOS, GARS, VABS, ADHD Rating Scale-IV] against pre-defined statistical thresholds as evidence of improvement, if threshold exceeded both groups allocated to receive diet and re-assessed at 20 months, if threshold not exceeded experimental and control group continued to receive their respective interventions and then re-assessed at 12 months, if experimental group exceeded threshold at 12 months both groups received diet intervention and re-assessed at 24 months, if threshold not exceed then both groups stopped trial)

Evidence for the effectiveness of nutritional interventions on adaptive behaviour and the quality of the evidence is presented in Table 210 and Table 211. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 210: Evidence summary table for effects of nutritional interventions (omega-3) on adaptive behaviour as an indirect outcome

	Omega-3 fatty acids versus placebo	**Omega-3 fatty acids versus healthy diet control**
Outcome	Adaptive skill	Frequency of attending to task/activity
Outcome measure	BASC: Adaptive skill	Behavioural observation: Attending to task/activity
Study ID	BENT2011	JOHNSON2010
Effect size (CI; p value)	SMD -0.20 (-1.00, 0.60; p = 0.63)	SMD 0.65 (-0.20, 1.50; p = 0.13)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 24	K = 1; N = 23
Forest plot	1.15.4; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for a statistically significant effect of omega-3 fatty acids (relative to placebo or a healthy diet control) on adaptive behaviours as an indirect outcome as measured by the BASC adaptive skill subscale or frequency of attending to a task/activity based on behavioural observation (see Table 210). There was also no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

Table 211: Evidence summary table for effects of nutritional interventions (gluten-free and casein-free diet) on adaptive behaviour as an indirect outcome

	Gluten-free and casein-free diet versus treatment as usual
Outcome	Adaptive behaviour
Outcome measure	VABS (change scores): (1) Daily living skills (2) Socialisation (3) Communication
Study ID	WHITELEY2010
Effect size (CI; p value)	(1) *Daily living skills* SMD 0.32 (-0.21, 0.85; p = 0.24)

	(2) *Socialisation* SMD 0.05 (-0.48, 0.58; p = 0.86) (3) *Communication* SMD -0.12 (-0.65, 0.41; p = 0.65)
Heterogeneity (chi2; p value; I2)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 55
Forest plot	1.15.4; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind and high risk of detection bias as parent-reported and non-blind to treatment allocation and other potentially confounding factors. There was also a high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group). [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of a gluten-free and casein-free diet on adaptive behaviour as an indirect outcome as measured by the VABS subscales (see Table 211). WHITELEY2010 reported adverse events associated with a gluten-free and casein-free diet and found no participants in either group reported side effects associated with the diet (see Chapter 10, Section 10.4.2, for adverse events associated with gluten-free and casein-free diet).

8.2.8 Clinical evidence summary – effect of interventions on adaptive behaviour

Based on low to very low quality evidence it is not possible to draw conclusions about the relative benefit of psychosocial interventions (behavioural interventions, cognitive-behavioural interventions, parent training, social-communication interventions) on adaptive behaviour as an indirect outcome. There was low to very low quality evidence from two studies for small to moderate effects of an antipsychotic drug (aripiprazole) on adaptive behaviour, but there was also evidence for significant harms associated with antipsychotics. Based on low to very low quality evidence it is not possible to draw conclusions about the relative benefit of biomedical interventions (complementary therapies, hormones, medical procedures, and nutritional interventions) on adaptive behaviour as an indirect outcome.

8.2.9 Economic evidence – interventions aimed at adaptive behaviour

Systematic literature review

The systematic search of the economic literature undertaken for the guideline identified 4 eligible studies on interventions for impairments in adaptive behaviour in children and young people with autism (Chasson et al., 2007; Jacobson, 1998; Motiwala et al., 2006; Peters-Scheffer et al., 2012). Three

studies were conducted in the US (Chasson et al., 2007; Jacobson, 1998; Motiwala et al., 2006) and the other one was carried out in the Netherlands (Peters-Scheffer et al., 2012). All studies were based on decision-economic modelling. Details on the methods used for the systematic review of the economic literature are described in Chapter 3; full references to the included studies and evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 16. Completed methodology checklists of the studies are provided in Appendix 15. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17, accompanying the respective GRADE clinical evidence profiles.

Chasson and colleagues (2007) estimated the net cost-savings associated with provision of EIBI to children with autism aged 4 years, resulting exclusively from improvement in children's functioning and subsequent reduction in need for special education. The study was conducted in the US (Texas) and considered only intervention costs and costs of special education (including state-budgeted, local, federal, and private); regular education costs were omitted from the analysis, as these are standard baseline costs. The time horizon of the analysis was 18 years (from 4 to 22 years of age). Resource use and cost data were based on local (state) data, personal communication and further assumptions. Estimates of clinical effectiveness were based on a non-systematic review of published studies and further assumptions made by the authors. According to these estimates, without EIBI provision all children with autism require special education for 18 years, while when they receive 3 years of EIBI only 28% of the children require special education and the remaining children can attend exclusively mainstream, regular education. The total special education cost per child with autism not receiving EIBI was $360,000 (without EIBI 100% of children receive special education), while the mean total cost per child with autism following provision of EIBI was $151,500, consisting of the intervention cost of EIBI and the special education cost for 28% of children still requiring special education. EIBI was therefore associated with a total net cost-saving of $208,500 per child (cost year not reported but it was likely 2004; no discounting was undertaken). When this figure was applied to a conservative estimate of 10,000 children with autism in Texas, it was estimated that provision of EIBI would result in a total net saving to the State of $2.09 billion.

The study is characterised by potentially serious limitations, mainly relating to the selective use of clinical effectiveness data associated with the provision of EIBI which were further modified by authors' assumptions; moreover, the study was carried out in the US and its findings are therefore only partially applicable to the UK context.

Jacobson (1998) reported the wider total net savings associated with provision of EIBI in preschool children with autism or PDD. The study was conducted in the US (Pennsylvania) and adopted a societal perspective. The authors estimated the net incremental cost of EIBI per person with autism from the age of 3 years (mean age of provision of EIBI) and up to 55 years of age. Costs were estimated for children with normal functioning following EIBI, children experiencing a partial effect of EIBI, and children where EIBI had a minimal effect. Clinical efficacy parameters were based on data derived from a non-systematic review of published literature. The authors reported overall net savings assuming different levels of EIBI effectiveness, which was expressed as the percentage of children achieving normal functioning. Net savings ranged from $656,385 for levels of normal functioning reaching 20% to $1,081,984 for levels of normal functioning reaching 50% (1996 prices). These figures were estimated assuming marginal effects, that is, children with normal range effects improved from partial effects, and those with partial effects improved from minimal effects. However, estimation of cost-savings using this methodology is underlined by the unrealistic implicit assumption that the marginal effect of normal functioning is achieved only after provision of EIBI, and that without EIBI no children achieve normal functioning. This assumption, which led to overestimation of cost-savings associated with EIBI, was considered a very serious methodological limitation, and therefore, although the study met inclusion criteria, it was not considered at guideline development.

Motiwala and colleagues (2006) conducted a modelling study to estimate the cost effectiveness of a programme of expansion of 3 years of EIBI to all eligible children with autism, aged 2-5 years, in Ontario, Canada, compared with the standard service in Ontario at the time of the analysis, which consisted of EIBI for 37% of eligible children with autism aged 2-5 years and no intervention for 63% of eligible children with autism aged 2-5 years. Expansion of EIBI was also compared with no intervention. The study adopted a public sector perspective and estimated costs starting from the preschool age and up to the age of 65 years. Costs included the cost of providing EIBI (consisting of therapists' training costs; contractual payments to service providers; salaries, benefits and overheads incurred by provincial civil servants), educational and respite service costs, costs of adult day programmes, accommodation and supported employment. Costs were estimated separately for children with autism and normal functioning, semi-dependent children with autism and very dependent children with autism. The total cost of the 3 alternative strategies was subsequently estimated based on the proportion of children with normal functioning, semi-dependent children and heavily dependent children in each strategy. The measure of outcome was the number of dependency-free years per person. Resource use and unit costs were based on provincial government data; clinical data were based on a non-systematic literature review and further assumptions.

Expansion of EIBI led to a higher number of dependency-free years per child with autism over the time horizon of the analysis (14.0), compared with standard service (11.2) and no intervention (9.6). The overall cost of expansion of EIBI, standard service, and no intervention per child with autism was $960,595, $995,074 and $1,014,315, respectively (2003 Canadian dollars, discounted at an annual rate of 3%), meaning that expansion of EIBI would produce an overall saving of $34,479 per child with autism, compared with standard service, and $53,720 per child with autism, compared with no intervention. By applying this cost-saving to the estimated population of 1,309 children with autism, aged 2-5 years, in Ontario, who at the time of the study received the standard service, the total net saving that would be accrued by expanding EIBI to all eligible children would reach $45,133,011. Results were sensitive to the EIBI efficacy (expressed as the proportion of children that achieved normal functioning following EIBI) and the discount rate used.

The study is characterised by potentially serious limitations relating to the assumptions made at the estimation of the clinical parameters of the economic model; furthermore, as it was conducted from a Canadian public sector perspective, it is only partially applicable to the UK setting.

Peters-Scheffer and colleagues (2012) conducted a cost analysis to estimate the cost savings associated with provision of EIBI – in addition to treatment as usual (TAU) – to children with autism of preschool age in the Netherlands. The comparator of the analysis was TAU alone. The study adopted a public service perspective and estimated costs starting from the preschool age and up to the age of 65 years. Cost elements included implementation of EIBI (personnel, capital assets, transportation, materials and supplies), speech therapy and physiotherapy, educational services, daytime activities and care, social benefits for parents, payments for future adult living expenses, day programs or supported work and sheltered environment services. Like Motiwala and colleagues (2006), the study estimated costs for children with autism and normal functioning, semi-dependent children with autism and very dependent children with autism, and subsequently estimated costs for EIBI and TAU based on the proportion of children achieving normal functioning, semi-dependent children and heavily dependent children following EIBI and TAU, respectively. Resource use and unit costs were based on national data and further assumptions; clinical data were based on a review of meta-analyses, selection of the reported data according to their applicability to the Dutch setting, and further assumptions.

EIBI and TAU were associated with an overall cost per child with autism up to the age of 65 years of €2,578,746 and €3,681,813, respectively, meaning that EIBI resulted in an overall cost-saving of €1,103,067 (cost year not reported but it was likely 2011; discounting was not applied). The authors reported that if these cost-savings per child were extended to the total number of children with autism born every year in the Netherlands (approximately 1092

to 1820 children), the estimated cost savings would reach €109.2–€182 billion, excluding costs associated with inflation.

The study is characterised by potentially serious limitations relating to the assumptions made at the selection of the data used to populate the economic model, and is only partially applicable to the UK setting since it was undertaken in the Netherlands.

Overall conclusion from economic evidence

Although the studies included in the systematic literature review suggested that provision of EIBI to pre-school children with autism may result in important cost-savings, all studies suffered from potentially serious methodological limitations, especially regarding the identification and selective use of clinical effectiveness data, which may have significantly affected the study results and conclusions. Moreover, none of the studies identified in the review were conducted in the UK, and therefore their applicability to the NICE context is limited.

8.2.10 From evidence to recommendations – interventions aimed at adaptive behaviour

There was no evidence to suggest that any of the interventions aimed at adaptive behaviour would be clinically effective given that none of the evidence reviewed met the GDG criteria for recommendation (see Chapter 3) of being a direct outcome of the intervention, being amenable to meta-analysis (K>2) and outcome assessment being blinded. Existing economic evidence on psychosocial interventions is limited, flawed, and only partially applicable to the UK context. Based on the limited and low quality evidence for these aimed at adaptive behaviour the GDG concluded that there was insufficient evidence to make a recommendation about the use of psychosocial, pharmacological or biomedical interventions for adaptive behaviour in children and young people with autism.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

8.3 SPEECH AND LANGUAGE PROBLEMS

8.3.1 Introduction

Although communication impairments, in the broadest sense, are a core deficit in autism, the level of *structural* language abilities varies widely and some children have a relative strength in verbal abilities and literacy

development. However, many children with autism show significant delays in the acquisition of language and if spoken language is not achieved by 6 years then the prognosis for later speech development is poor (Boucher, 2012). Recent research suggests that around 10% of individuals with autism fail to develop any functional speech (Hus et al., 2007). These tend to be the children who also have severe intellectual disability although discrepancies between language and intellectual skills can occur. Besides delay in language onset, about one third of children with autism are reported by parents to have lost early words in the second year of life. Loss of words at this stage is considered to be a 'red flag' for possible autism (Pickles et al., 2009). Although the majority of individuals with autism do develop speech, core deficits in speech and communication tend to persist, even in those with good spoken language.

Receptive language skills are typically more impaired than expressive language (Boucher, 2012; Hudry et al, 2010). Other features of language disorder include poor vocabulary, problems with grammar and discourse, and speech impairments. Moreover, most individuals with autism, even those who have apparently good use and understanding of language, are likely to have problems with abstract concepts, and with reciprocal, flexible and socially appropriate communication that continue to affect their education, social and working lives. When children with autism have problems with phonology and/or syntax they may be diagnosed as having an additional language or speech disorder.

Current practice

Since communication impairment is a central component of autism most professionals working with children with autism will consider the development of communication and language to be an essential part of their remit.

Specialist education programmes incorporate communication goals and review progress on a regular basis. Speech and language therapists work with children and young people across the entire age and ability range. A key element of the role involves working with colleagues and parents to establish appropriate aims for developing communication. Targets depend on the current competence and expected outcome for each individual. These can range from enhancing an individual's understanding and use of pragmatic language functions in social and work contexts to assisting relevant professionals and the family of an individual with profound difficulties to recognise and respond to unusual ways of communicating in a consistent way that promotes more effective communicative function.

For some children and young people it is necessary to introduce an augmentative or alternative form of communication. This can be 'low tech' (that is, use of manual signs or a picture system) or 'high tech' (that is, use of electronic systems, using visual images, writing or voice output

communication aide [VOCA]). However, in most children and young people impairments in the functional use of language do not arise from problems with speech or expressive skills and will therefore affect any system of communication, including augmentative systems.

8.3.2 Studies considered – psychosocial interventions aimed at speech and language

Fifty-one papers from the search met the eligibility criteria for full-text retrieval. Of these, 21 RCTs provided relevant clinical evidence and were included in the review. Six of these studies examined the efficacy of psychosocial interventions on speech and language as a direct outcome (target of intervention), and 15 provided data on speech and language as an indirect outcome. All studies were published in peer-reviewed journals between 1998 and 2013. In addition, 30 studies were excluded from the analysis. The most common reasons for exclusion were that the study was a systematic review with no new useable data and any meta-analysis results were not appropriate to extract, group allocation was non-randomised, or sample size was too small (less than ten participants per arm). Further information about both included and excluded studies can be found in Appendix 12d.

Two AAC intervention trials (HOWLIN2007, YODER2006B [one trial reported across two papers: Yoder & Lieberman, 2010; Yoder & Stone, 2006) examined effects on speech and language as a direct outcome.

Two arts-based intervention trials (GATTINO2011, LIM2010 [Lim, 2010]) examined effects on speech and language as a direct outcome.

Four behavioural intervention trials (DAWSON2010, ROBERTS2011, ROGERS2012, SMITH2000[70]) examined effects on speech and language as an indirect outcome.

One educational intervention trial (WHALEN2010) examined effects on speech and language as a direct outcome, and one study (STRAIN2011[71]) examined effects on speech and language as an indirect outcome.

One parent training trial (WELTERLIN2012) examined direct effects on speech and language, and three trials (DREW2002, JOCELYN1998, TONGE2006[72]) examined indirect effects of parent training on speech and language.

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[70] See Section 8.2.3 for direct outcomes from DAWSON2010, ROBERTS2011 and SMITH2000; see Section 8.4.3 for direct outcomes from ROGERS2012.
[71] See Section 6.2.3 for direct outcomes from STRAIN2011.
[72] See Section 6.2.5 and Section 6.2.3 for direct outcomes from DREW2002 and JOCEYLN1998, respectively; see Section 9.2.2 for direct outcomes from TONGE2006.

Finally, seven social-communication intervention trials (ALDRED2001, CARTER2011, GREEN2010, KASARI2006, LANDA2011, LOPATA2010, SCHERTZ2013[73]) examined effects on speech and language as an indirect outcome.

8.3.3 Clinical evidence – effect of psychosocial interventions on speech and language

AAC interventions for speech and language as a direct outcome

One of the included AAC intervention trials (HOWLIN2007) was a three-armed trial comparing PECS training (Frost & Bondy, 2002) for teachers (ITG or DTG) with treatment as usual in children with autism. The other included AAC intervention trial (YODER2006B) compared PECS with another active intervention; Responsive Education and Prelinguistic Milieu Training (RPMT) (see Table 30).

In HOWLIN2007,PECS teacher training began with a 2-day workshop (13 hours of training) that staff (4-6 per class; mean = 5) and parents (0-7 per class; mean = 3) attended. Training followed the PECS manual (Frost & Bondy, 2002). PECS is an augmentative communication system where children are taught to exchange a picture card for something they like and want. The workshop was followed (a week later) by an active training period involving six half-day consultation visits over five months to each class. These visits were intended to encourage teachers to facilitate children's use of PECS in various sessions during the school day and PECS consultants recommended and demonstrated strategies to teachers, monitored teachers' progress and provided feedback including written summaries, agreed action points and future goals. It was not possible to analyse the data from this study using conventional pair-wise methodology as data came from three groups (ITG, DTG and no treatment) across three time points (time 1 [baseline], time 2 which was post-intervention for ITG and waitlist for DTG, and time 3 which was follow-up for ITG and post-intervention for DTG), and there were statistically significant baseline differences between groups (DTG children had a significantly higher ADOS language impairment score [mean=3.4] than those in the ITG [2.7] and no treatment [2.5] and children in the ITG had a significantly higher non-verbal developmental quotient [25.9] than children in the DTG [22.7]). As the authors report the OR results from a multilevel ordinal regression model that corrects for baseline differences by taking into account within-child and within-class correlations, these values were extracted and entered into the data analysis using the Generic Inverse Variance method.

In YODER2006B, the intervention was manualised (Bondy & Frost, 1994) with the exception that training was implemented three times a week for

[73] See Section 6.2.5 for direct outcomes from ALDRED2001, CARTER2011, GREEN2010, KASARI2006, LANDA2011, LOPATA2010, SCHERTZ2013.

20 minutes rather than throughout the day. The PECS curriculum has six phases, beginning with the physically prompted exchange of a single picture without distracter pictures and ending with the exchange of a sentence strip in response to 'What do you see?' Picture symbols were Mayer-Johnson line drawings closely resembling objects used during training sessions. The intervention also included a parent component involving demonstration and discussion of strategies to promote PECS use outside of treatment sessions. The control active intervention condition, RPMT, was aimed at gestures, vocalisations and eye gaze and involved establishing highly engaging play routines and using the least intrusive prompting procedures to target specific prelinguistic communication behaviours. There was also a parent component which involved supporting parents in the use of responsive play and communication strategies (following Hanen centre curriculum [Sussman 2001]). The main differences between the two active interventions were in: Positioning (RPMT on floor and PECS mostly in chair); adult to child ratios (RPMT 1:1 and PECS 2:1 for Phases 1, 2 and 4, and 1:1 for 3, 5 and 6); behaviours taught (gestures, gaze, vocalisations and words for RPMT and picture exchange and words for PECS); general teaching approach (incidental teaching for RPMT and discrete trial for PECS); relative consistency of linguistic mapping (moderate for RPMT and high for PECS); when word use was explicitly prompted (after meeting prelinguistic fluency criteria for RPMT and after Phase 3 for PECS); types of prompts for spoken communication ('mands' and explicit imitation prompts for RPMT and fill-in-the-blank prompts for PECS); and consequences for word use (expansions, repetition and compliance for RPMT and repetition and compliance for PECS).

Table 212: Study information table for included trial of AAC intervention for speech and language

	PECS training for teachers versus treatment as usual	**PECS versus RPMT**
No. trials (N)	1 (88)	1 (36)
Study IDs	HOWLIN2007	YODER2006B
Study design	RCT	RCT
% female	13	14
Mean age (years)	6.8	2.8
IQ	Not reported (100% LD)	51 (assessed using the MSEL)
Dose/intensity (mg/hours)	Planned intensity was approximately calculated at 32.5 hours with an initial 2-day workshop (13 hours) followed by six half-day consultations over 5 months	Actual mean intensity for children components of 20 hours (0.8 hours/week). Actual mean intensity for parent training: 10.6 hours for RPMT group and 7.9 hours for PECS group.
Setting	School (specialist education)	University clinic
Length of treatment (weeks)	24	26
Continuation phase (length and inclusion criteria)	Mean interval between time 1 (baseline) and time 3 (follow-up for ITG and post-treatment	52 (including 6-month post-intervention follow-up)

	for DTG) of: 78 weeks (for ITG); 63 weeks (for DTG); 65 weeks (for no treatment control)	

Evidence for the effectiveness of AAC interventions on speech and language and the quality of the evidence is presented in Table 213 and Table 214. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was single study evidence for moderate to large and statistically significant effects of PECS teacher training (relative to treatment as usual) on frequency of child communicative initiations and PECS symbol use as measured by the odds of being in a higher ordinal category based on study-specific behavioural observation (see Table 213). However, these effects were transient and were non-significant at the 10-month post-intervention follow-up. In addition, the confidence in the statistically significant effects was low due to risk of bias concerns (non-blind outcome assessment) and small sample size. There were also non-significant effects observed on speech/vocalisation use as measured by behavioural observation, and receptive and expressive language as measured by the BPVS and EOWPVT (see Table 213).

There was also single study evidence for a large and statistically significant effect of PECS (relative to RPMT) on the number of picture exchanges as measured by the ESCS-Abridged (see Table 214). However, the quality of this evidence was low due to small sample size and high risk of selective reporting bias (no 6-month post-intervention follow-up data reported for this outcome measure). The evidence was also inconsistent with non-significant effects observed for frequency of non-imitative spoken acts and number of different non-imitative words as measured by behavioural observation (see Table 214).

Table 213: Evidence summary table for effects of AAC intervention (PECS versus treatment as usual) on speech and language as a direct outcome

	PECS training for teachers versus treatment as usual				
Outcome	Spontaneous child communicative initiations	PECS use	Speech/vocalisation use	Receptive language	Expressive language
Outcome measure	Odds of being in a higher initiation category based on behavioural observation of frequency of child communicative initiations at: (1) Post-intervention (2) 10-month post-intervention follow-up	Odds of being in a higher initiation category based on behavioural observation of frequency of use of PECS symbols at: (1) Post-intervention (2) 10-month post-intervention follow-up	Odds of being in a higher initiation category based on behavioural observation of frequency of speech (including non-word vocalisations) at: post-intervention	Odds of being in a higher category on BPVS at post-intervention	Odds of being in a higher category on EOWPVT at post-intervention
Study ID	HOWLIN2007				
Effect size (CI; p value)	(1) OR 2.73 (1.22, 6.09; p = 0.01) (2) OR 1.08 (0.30, 3.89; p = 0.91)	(1) OR 3.90 (1.75, 8.69; p = 0.0009) (2) OR 1.56 (0.46, 5.30; p = 0.48)	OR 1.10 (0.46, 2.63; p = 0.83)	OR 1.54 (0.52, 4.55; p = 0.43)	OR 1.01 (0.89, 1.15; p = 0.88)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	(1) Low[1,2] (2) Very low[1,3]		Very low[1,3]		Low[1,2]
Number of studies/participants	(1) K = 1; N = 84 (2) K = 1; N = 53		K = 1; N = 84		
Forest plot	1.16.1; Appendix 13				

Note. [1]Downgraded for serious bias – high risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind.
[2]Downgraded due to serious imprecision as number of events <300.
[3]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm.

Table 214: Evidence summary table for effects of AAC intervention (PECS versus RPMT) on speech and language as a direct outcome

	PECS versus RPMT		
Outcome	Frequency of non-imitative spoken acts	Number of different non-imitative words	Number of picture exchanges
Outcome measure	Behavioural observation (semistructured free-play with examiner): Frequency of non imitative spoken acts at: (1) Post-intervention (2) 6-month post-intervention follow-up	Behavioural observation (semistructured free-play with examiner): Number of different non imitative words at: (1) Post-intervention (2) 6-month post-intervention follow-up	ESCS-Abridged: Number of picture exchanges at: (1) Post-intervention
Study ID	YODER2006B		
Effect size (CI; p value)	(1) *Post-intervention* SMD 0.61 (-0.06, 1.28; p = 0.07) (2) *6-month follow-up* SMD 0.03 (-0.62, 0.68; p = 0.93)	(1) *Post-intervention* SMD 0.49 (-0.18, 1.15; p = 0.15) (2) *6-month follow-up* SMD 0.08 (-0.57, 0.74; p = 0.81)	(1) *Post-intervention* SMD 0.80 (0.12, 1.48; p = 0.02)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2]		Low[3,4]
Number of studies/participants	K = 1; N = 36		
Forest plot	1.16.1; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance bias as intervention administrators were non-blind and comparison groups did not receive the same care apart from the intervention studied (parents in the RPMT group chose to receive more hours of training [mean: 10.6 hours] than parents in the PECS group [mean 7.9 hours]. In addition, the number of hours of 'other intervention' increased between the treatment and follow-up periods, and this increase was greater for the PECS group [4 hours] than for the RPMT group [-0.3 hours]). There was also a high risk of response bias as participants were non-blind and detection bias as identity and blinding of outcome assessors is not reported.

[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

[3]Downgraded due to serious imprecision as N <400.

[4]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as only post-intervention (and not 6-month post-intervention follow-up) reported for the only outcome where significant treatment effects observed (number of picture exchanges as assessed by the ESCS-Abridged)

Arts-based interventions for speech and language as a direct outcome

The included arts-based intervention trials (GATTINO2011, LIM2010) compared music therapy with waitlist or treatment as usual control (see Table 34). In GATTINO2011, RMT (Gallardo, 2004) was compared with waitlist control. This intervention was based on psychodynamic principles (free association, unconscious conflicts, drive component, transference and counter-transference) and aimed to help participants through interactions with the music therapist based around music, for instance, singing, composing, improvising and playing musical games. The music therapist began each session by providing various instruments on the floor or table and allowed the participant to select one or several instruments and the focus was on the actions of the participant with the music therapist taking a non-directive role and prioritising participant initiatives and behavioural observation. This intervention also involved a parent component with parents being encouraged to attend some sessions so that the therapist could observe how the child interacts with his/her family through musical activities. In LIM2010 there were two active intervention arms (compared with treatment as usual), developmental speech and language training through music and speech therapy. In the developmental speech and language training through music condition, 36 target words were included in six songs composed by the investigator that were presented to participants on video. Pictures from PECS for each of the 36 target words were also presented by the singer as she sang the congruent target word and each song was presented twice in the music video. The speech therapy active intervention comparison condition used exactly the same training stimuli and format as the developmental speech and language training through music condition with the exception that instead of six songs, the same texts were presented as six stories in the speech therapy condition.

Table 215: Study information table for included trials of arts-based interventions for speech and language

	Music therapy versus treatment as usual
No. trials (N)	2 (74)
Study IDs	(1) GATTINO2011 (2) LIM2010
Study design	(1)-(2) RCT
% female	(1) 0 (2) Not reported
Mean age (years)	(1) 9.8 (2) 4.7
IQ	(1) Not reported (based on N = 22 27% LD as assessed using the Raven's Coloured Progressive Matrices for Children [Pasquali et al., 2002]) (2) Not reported
Dose/intensity (mg/hours)	(1) Planned intensity was 8 hours (16 weekly sessions; 0.5 hours/week)

	(2) 1.8 hours for music therapy and 1.1 hours for speech therapy (across 12 training sessions and 4 days)
Setting	(1) Outpatient (2) Not reported
Length of treatment (weeks)	(1) 30 (due to school activities and vacations, the 16 sessions were completed over seven months) (2) 0.6 weeks (4 days)
Continuation phase (length and inclusion criteria)	(1) 30 (2) 0.6 weeks (4 days)

Evidence for the effectiveness of music therapy on speech and language and the quality of the evidence is presented in Table 216. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 216: Evidence summary table for effects of arts-based interventions on speech and language as a direct outcome

	Music therapy versus treatment as usual		
Outcome	Verbal communication	Non-verbal communication	Expressive language
Outcome measure	CARS-BR: Verbal communication	CARS-BR: Non-verbal communication	Verbal Production Evaluation Scale: Production of target words (1) Music therapy (2) Speech therapy
Study ID	GATTINO2011		LIM2010
Effect size (CI; p value)	SMD -0.09 (-0.89, 0.71; p = 0.83)	SMD 0.35 (-0.45, 1.16; p = 0.39)	(1) *Music therapy* SMD 1.22 (0.45, 1.99; p = 0.002) (2) *Speech therapy* SMD 1.09 (0.33, 1.84; p = 0.005)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]		Moderate[2]
Number of studies/participants	K = 1; N = 24		K = 1; N = 32
Forest plot	1.16.2; Appendix 13		
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to serious imprecision as N <400.			

There was no evidence for statistically significant effects of RMT on verbal or non-verbal communication as measured by the CARS-BR (see Table 216). There was, however, single study moderate quality evidence for large and statistically significant effects of both music therapy (developmental speech and language training through music) and speech therapy on expressive

language as measured by the study-specific Verbal Production Evaluation Scale (see Table 216). Direct comparison between the two active intervention arms (music and speech therapy) revealed no statistically significant difference between them (SMD 0.09 [-0.56, 0.74]; Test for overall effect: $Z = 0.27$, $p = 0.79$).

Behavioural interventions for speech and language as an indirect outcome

One of the included behavioural intervention trials (DAWSON2010) compared EIBI (Early Start Denver Model [ESDM]) with treatment as usual and another behavioural intervention trial (ROGERS2012) compared EBI (P-ESDM) with treatment as usual. One of the behavioural intervention studies (SMITH2000) compared EIBI with parent training. Finally, the remaining included behavioural intervention trial (ROBERTS2011) compared a home-based EBI programme with a centre-based EBI programme (see Table 189). See section 8.2.3 for further intervention details.

Evidence for the effectiveness of behavioural interventions on speech and language and the quality of the evidence is presented in Table 217 and Table 218. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was no evidence for statistically significant effects of EIBI or EBI (relative to treatment as usual or parent training) on receptive or expressive language as measured by the MSEL, CDIs or RDLS (see Table 217). There was also no evidence for a statistically significant effect of home-based EBI (relative to centre-based EBI) on receptive or expressive language as measured by the RDLS or everyday language functioning as measured by the pragmatics Profile of Everyday Conversation (see Table 218).

Table 217: Evidence summary table for effects of behavioural interventions (EIBI) on speech and language as an indirect outcome

	EIBI (ESDM) versus treatment as usual		**EBI (P-ESDM) versus treatment as usual**	**EIBI versus parent training**		
Outcome	Receptive language	Expressive language	Speech and language	Receptive language	Expressive language	Receptive and expressive language
Outcome measure	MSEL: Receptive language	MSEL: Expressive language	CDIs' subscales: (1) Phrases understood (2) Vocabulary comprehension (3) Vocabulary production (4) Total gestures produced	RDLS: Comprehension	RDLS: Expressive language	RDLS: total
Study ID	DAWSON2010		ROGERS2012	SMITH2000		
Effect size (CI; p value)	SMD 0.60 (-0.00, 1.20; p = 0.05)	SMD 0.55 (-0.05, 1.15; p = 0.07)	(1) *Phrases understood* SMD -0.23 (-0.63, 0.16; p = 0.25) (2) *Vocabulary comprehension* SMD -0.19 (-0.58, 0.21; p = 0.35) (3) *Vocabulary production* SMD 0.05 (-0.35, 0.45; p = 0.81) (4) *Total gestures produced* SMD -0.13 (-0.53, 0.26; p = 0.51)	SMD 0.48 (-0.28, 1.23; p = 0.21)	SMD 0.36 (-0.39, 1.11; p = 0.35)	SMD 0.63 (-0.13, 1.39; p = 0.11)

Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]	(1)-(2) Very low[1,2] (3) Low[2,3] (4) Very low[1,2]	Low[1]
Number of studies/participants	K = 1; N = 45	K = 1; N = 98	K = 1; N = 28
Forest plot	1.16.3; Appendix 13		

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and high risk of detection bias as come measure was parent-rated and parents were non-blind and involved in the intervention.
[3]Downgraded due to serious imprecision as N <400.

Table 218: Evidence summary table for effects of behavioural interventions (EBI) on speech and language as an indirect outcome

	Home-based EBI versus centre-based EBI		
Outcome	Receptive language	Expressive language	Everyday language functioning
Outcome measure	RDLS: Comprehension	RDLS: Expressive language	Pragmatics Profile of Everyday Communication: total Q range
Study ID	ROBERTS2011		
Effect size (CI; p value)	SMD -0.42 (-0.96, 0.13; p = 0.13)	SMD -0.26 (-0.80, 0.28; p = 0.35)	SMD -0.52 (-1.06, 0.01; p = 0.05)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]		Very low[1,2]
Number of studies/participants	K = 1; N = 53		K = 1; N = 56
Forest plot	1.16.3; Appendix 13		

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias in unclear/unknown as although the outcome assessors were blinded, this outcome measure was based on interview with parent and parents were non-blind and were part of the intervention.

Educational interventions for speech and language as a direct or indirect outcome

One of the educational intervention trials (WHALEN2010) compared combined computer-assisted educational intervention (TeachTown: Basics) and IBI day class programmes (Intensive Comprehensive Autism Programs) with IBI day class programmes only and examined effects on speech and language as a direct outcome. The other included educational intervention trial (STRAIN2011) compared direct training of the LEAP approach with a LEAP intervention manual-only control and examined effects on speech and language as an indirect outcome (see Table 45).

In WHALEN2010, all participants attended Intensive Comprehensive Autism Programs for 27-30 hours per week where children were taught in classes of no more than eight with an adult to child ratio of 1:2 using an ABA approach (typically discrete trials) to target language/communication, sensory issues, and behaviour within a classroom organised according to TEACCH principles. In addition to this IBI intervention, participants in the experimental group also received computer-assisted instruction (using the TeachTown: Basics program). This computer-assisted instruction intervention included computer lessons and off-computer natural environment activities to target additional skills and encourage generalisation. The computer lessons

incorporated the basic principles of ABA with teaching in a discrete trial format and reinforcement for correct responses, and for the off-computer activities the techniques used followed the principles of pivotal response training. The computer lessons aimed to improve receptive language (including vocabulary, school readiness such as play and classroom vocabulary, semantics and community life such as body parts and environmental sounds), social understanding (including knowledge of eye gaze, joint attention, face matching and emotion recognition), life skills (including awareness and regulation, functional skills such as time telling and self-awareness such as food and clothing vocabulary), and academic/cognitive skills (including math, reading, categorisation and problem solving). Off-computer activities additionally targeted expressive language, play, imitation, social interaction, motor skills and daily living skills. This study also examined whether treatment effects were mediated by age (preschool and K-1 subgroups) and subgroups were retained and examined in the analysis.

Core components of the LEAP intervention in STRAIN2011 included: Social skills training for typically-developing peers to facilitate the social and communicative competence of their class peers with autism; Teacher training (in: LEAP programme; autism; classroom organisation and management; teaching strategies; teaching communication skills; providing positive behavioural guidance; monitoring progress and collecting data on individual education plan goals, and promoting social interactions with typically-developing peers); Family skills training of adult family members in behavioural teaching strategies. In the control condition preschool staff were provided with intervention manuals and related written materials but not with any direct training

Table 219: Study information table for included trials of educational interventions for speech and language

	Combined TeachTown and IBI versus IBI-only	**LEAP training versus manual-only control**
No. trials (N)	1 (47; 8 classrooms)	1 (294)
Study IDs	WHALEN2010	STRAIN2011
Study design	RCT	RCT
% female	Not reported	Not reported
Mean age (years)	Not reported	4.2
IQ	Not reported	61 (assessed using the MSEL – early-learning composite score)
Dose/intensity (mg/hours)	351 (preschool)/390 (Kindergarten and first grade) for IBI (of which 43.33 for computer-assisted intervention)	23 full days of training
Setting	Educational (Intensive	Educational

	Comprehensive Autism Programs)	
Length of treatment (weeks)	13	104
Continuation phase (length and inclusion criteria)	13	104

Evidence for the effectiveness of educational interventions on speech and language and the quality of the evidence is presented in Table 220 and Table 221. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 220: Evidence summary table for effects of educational intervention (TeachTown) on speech and language as a direct outcome

	Combined TeachTown and IBI versus IBI-only			
Outcome	Receptive language		Expressive language	
Outcome measure	PPVT-III: total for: (1) Preschool subgroup (2) Kindergarten and first grade subgroup	Brigance Inventory of Early Development: Receptive language for: (1) Preschool subgroup (2) Kindergarten and first grade subgroup	Expressive Vocabulary Test: total for: (1) Preschool subgroup (2) Kindergarten and first grade subgroup	Brigance Inventory of Early Development: Expressive language for: (1) Preschool subgroup (2) Kindergarten and first grade subgroup
Study ID	WHALEN2010			
Effect size (CI; p value)	(1)+(2) SMD 0.33 (-0.25, 0.92; p = 0.26) (1) *Preschool* SMD 0.40 (-0.43, 1.22; p = 0.35) (2) *Kindergarten and first grade* SMD 0.27 (-0.55, 1.09; p = 0.52)	(1)+(2) SMD 0.09 (-0.49, 0.67; p = 0.77) (1) *Preschool* SMD -0.02 (-0.84, 0.80; p = 0.96) (2) *Kindergarten and first grade* SMD 0.20 (-0.62, 1.02; p = 0.64)	(1)+(2) SMD 0.27 (-0.31, 0.85; p = 0.36) (1) *Preschool* SMD 0.33 (-0.50, 1.15; p = 0.43) (2) *Kindergarten and first grade* SMD 0.22 (-0.60, 1.04; p = 0.60)	(1)+(2) SMD 0.01 (-0.57, 0.59; p = 0.97) (1) *Preschool* SMD 0.07 (-0.75, 0.89; p = 0.87) (2) *Kindergarten and first grade* SMD -0.05 (-0.87, 0.77; p = 0.91)
Heterogeneity (chi²; p value; I²)	Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), *I²* = 0%	Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), *I²* = 0%	Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), *I²* = 0%	Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), *I²* = 0%
Quality of the evidence (GRADE)	Very low[1,2]	Very low[2,3]	Very low[1,2]	Very low[2,3]
Number of studies/ participants	K = 1; N = 46			
Forest plot	1.16.4; Appendix 13			
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. Risk of detection bias is				

unclear/unknown as the identity and blinding of outcome assessors not reported.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. Risk of detection bias is unclear/unknown as the identity and blinding of outcome assessors not reported. In addition, for the Brigance Inventory of Child Development scale there are no independent reliability and/or validity data reported.

Table 221: Evidence summary table for effects of educational intervention (LEAP) on speech and language as an indirect outcome

	LEAP training versus manual-only control		
Outcome	Receptive and expressive language	Receptive language	Expressive language
Outcome measure	PLS-4: total	MSEL: Receptive Language Age (in months)	MSEL: Expressive Language Age (in months)
Study ID	STRAIN2011		
Effect size (CI; p value)	SMD 0.94 (0.70, 1.19; p <0.00001)	SMD 1.10 (0.85, 1.35; p <0.00001)	SMD 0.49 (0.25, 0.73; p <0.0001)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1,2]		
Number of studies/participants	K = 1; N = 294		
Forest plot	1.16.4; Appendix 13		
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported. [2]Downgraded due to serious imprecision as N <400.			

There was no evidence for statistically significant effects of the TeachTown intervention (as an adjunct to IBI programme) on receptive or expressive language, and no evidence that treatment effect was mediated by age (see Table 220). There was, however, evidence for large and statistically significant indirect effects of LEAP training (relative to manual-only control) on total language score as measured by the PLS-4 and receptive language as measured by the MSEL, and evidence for a small effect on expressive language as measured by the MSEL (see Table 221). However, confidence in these effect estimates was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size.

Parent training for speech and language as a direct or indirect outcome

Three of the included parent training trials compared parent training with treatment as usual; one (WELTERLIN2012) examined effects on speech and language as a direct outcome and two (DREW2002, TONGE2006) examined

indirect effects on speech and language. The other included parent training trial (JOCELYN1998) compared parent and day care staff training with standard day care and examined effects on speech and language as an indirect outcome (see Table 222).

In WELTERLIN2012, the home TEACCH programme incorporated parent training in how to teach specific cognitive, fine motor, and language skills to their child. The intervention began with the clinician teaching the child the specific skills and modelling appropriate prompting behaviour and teaching environment set-up for the parents. Parents were also provided with education about autism and intervention strategies and assigned written homework and requested to practice applying new skills in between intervention sessions. From week eight onwards, parents took over the active teaching of their child and the clinician provided coaching and feedback.

In DREW2002 the parent training intervention emphasised the development of joint attention and joint action routines, and included advice about behaviour management. Speech and language therapists described developmental principles to parents and then monitored and provided feedback on implementation. Parents were instructed on how to teach joint attention behaviours such as pointing and gaze switching, including the use of visual supports for spoken language and techniques were implemented in allocated times for activities (for instance, joint play times) but also integrated into everyday routines, such as mealtimes, dressing and bedtimes. Instruction in behaviour management techniques followed a similar structure and included instruction in the principles of reinforcement, interrupting unwanted behaviours and encouraging alternative behaviours through joint action routines.

See section 8.2.3 for further details about the parent training intervention in TONGE2006 and JOCELYN1998.

Evidence for the effectiveness of parent training on speech and language and the quality of the evidence is presented in Table 223. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 222: Study information table for included trials of parent training for speech and language

	Parent training versus treatment as usual	Parent and day-care staff training versus standard day-care
No. trials (N)	3 (149)	1 (36)
Study IDs	(1) DREW2002 (2) TONGE2006 (3) WELTERLIN2012	JOCELYN1998
Study design	(1)-(3) RCT	RCT
% female	(1) 21 (2) 16 (3) 10	3
Mean age (years)	(1) 1.9 (2) 3.9 (3) 2.5	3.6
IQ	(1) Non-verbal IQ 77.1 (assessed using the D and E subscales of the Griffiths Scale of Infant Development; Griffiths, 1986) (2) 59.2 (assessed using the PEP-R – developmental quotient) (3) 55.4 (assessed using MSEL – developmental quotient)	PIQ 63.1 (assessed using LIPS; Leiter, 1948)
Dose/intensity (mg/hours)	(1) Planned intensity was 26 hours (3 hours/6 weeks, equating to 0.5 hours/week) (2) 25 hours (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions) (3) Planned intensity was 18 hours (1.5 hour/week)	50 hours (3 hours/week of educational seminars for 5 weeks and 3 hours/week of on-site day-care staff consultation for 10 weeks, and three parent-staff review meetings at day care centre [estimated at 3 hours] and 2 in-home visits [estimated at 2 hours]; equating to 4 hours/week)
Setting	(1) Home (2) Not reported (3) Home	Outpatient, educational (day care centre) and home-based
Length of treatment (weeks)	(1) 52 (2) 20 (3) 12	12
Continuation phase (length and inclusion criteria)	(1) 52 (2) 46 (including 6-month post-intervention follow-up) (3) 12	12

Table 223: Evidence summary table for effects of parent training on speech and language as a direct or indirect outcome

	Parent training versus treatment as usual				**Parent and day-care staff training versus standard day care**
Outcome	Receptive language	Expressive language	Overall language rating	Total gestures produced	Language
Outcome measure	(1) MSEL: Receptive language (direct outcome) (2) CDIs: Vocabulary Comprehension (indirect outcome) (3) RDLS: Comprehension (indirect outcome; 6-month follow-up; PEC+PEBM combined)	(1) MSEL: Expressive language (direct outcome) (2) CDIs: Vocabulary Production (indirect outcome) (3) RDLS: Expressive language (indirect outcome; 6-month follow-up; PEC+PEBM combined)	Dichotomous: Number of participants with overall language rating based on ADI-R (indirect outcome): (1) Non-verbal (<5 words) (2) Single word speech (3) Phrase speech	CDIs: total gestures produced (indirect outcome)	EIDP/PSDP: Language (developmental age) (indirect outcome)
Study ID	(1) WELTERLIN2012 (2) DREW2002 (3) TONGE2006		DREW2002		JOCELYN1998
Effect size (CI; p value)	(1)+(2)+(3) SMD -0.20 (-0.54, 0.14; p = 0.24) (1) *MSEL (direct outcome)* SMD 0.09 (-0.78, 0.97; p = 0.83) (2) *CDIs (indirect outcome)* SMD 0.71 (-0.12, 1.54; p = 0.09) (3) *RDLS (indirect outcome)* SMD -0.50 (-0.91, -0.08; p = 0.02)	(1)+(2)+(3) SMD -0.14 (-0.48, 0.20; p = 0.42) (1) *MSEL (direct outcome)* SMD -0.15 (-1.03, 0.73; p = 0.73) (2) *CDIs (indirect outcome)* SMD 0.56 (-0.26, 1.38; p = 0.18) (3) *RDLS (indirect outcome)* SMD -0.31 (-0.72, 0.10; p = 0.14)	(1) *Non-verbal* RR 0.44 (0.19, 1.05; p = 0.07) (2) *Single word* RR 1.67 (0.51, 5.46; p = 0.40) (3) *Phrase* RR 7.00 (0.40, 122.44; p = 0.18)	SMD 0.58 (-0.24, 1.40; p = 0.16)	SMD 0.66 (-0.03, 1.34; p = 0.06)
Heterogeneity (chi²; p value; I²)	Chi² = 7.01, df = 2 (P = 0.03); *I²* = 71%	Chi² = 3.44, df = 2 (P = 0.18); *I²* = 42%	Not applicable		

Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,4,5]	Very low[6,7]	Very low[3,6]	Low[3]
Number of studies/participants	K = 3; N = 147		K = 1; N = 24		K = 1; N = 35
Forest plot	1.16.5; Appendix 13				

Note. [1]Downgraded for serious risk of bias -High risk of selection bias as baseline differences in TONGE2006 between groups on this outcome measure.
[2]Downgraded due to very serious inconsistency – I^2 value indicates considerable heterogeneity.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded due to serious inconsistency – I^2 value indicates moderate heterogeneity.
[5]Downgraded due to serious imprecision as N <400.
[6]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as outcome measure relies on parental report and parents were non-blind and involved in the intervention.
[7]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

There was no evidence for statistically significant effects of parent training (relative to treatment as usual) on receptive language, expressive language or total gestures produced, as measured by the MSEL, RDLS or CDIs. There was also no evidence for statistically significant effects of parent training on overall language rating based on the ADI-R (see Table 223). Due to significant baseline group differences it was not possible to compare effects in the two active intervention arms for TONGE2006 and data from the two groups (PEBM and PEC) were combined to be entered into meta-analysis. There was also no evidence for a statistically significant effect of parent and day-care staff training (relative to standard day-care) on language as measured by the EIDP/PSDP (see Table 223).

Social-communication interventions for speech and language as an indirect outcome

Four of the included social-communication intervention trials (ALDRED2001, CARTER2011, GREEN2010, SCHERTZ2013) compared caregiver-mediated social-communication interventions with treatment as usual. One of the included social-communication intervention trials (LOPATA2010) compared a social skills group with treatment as usual. The remaining two social-communication intervention trials (KASARI2006, LANDA2011) compared joint attention training and EBI/EIBI with EBI/EIBI only (see Table 224).

See section 8.2.3 for further detail about the caregiver-mediated social-communication interventions (ALDRED2001, CARTER2011, GREEN2010, SCHERTZ2013).

In LOPATA2010, the social skills group intervention (Lopata et al., 2008) was delivered to children (grouped by age) and targeted outcomes were social skills, emotion recognition and interpretation of non-literal language. Teaching techniques included direct instruction, modelling, role play, performance feedback, team-working to complete task or solve problem, a response-cost reinforcement system, and homework assignments. There were also weekly concurrent parent training sessions that focused on increasing understanding of autism and of the intervention that their child was taking part in, and on teaching parents strategies to encourage generalisation.

In KASARI2006 all participants in the study (experimental and control groups) were already participating in an EIBI preschool programme which was based on ABA principles and followed a typical preschool curriculum but with staff to participant ratios of 1:1 for 6 hours a day. In addition, the experimental group was given a joint attention training intervention. This intervention was aimed at increasing joint attention initiation (including coordinated joint looking, showing, giving to share, proximal and distal pointing) and responding to joint attention attempts (including following proximal and distal points). Each session of the joint attention intervention followed the same format with five minutes of a direct-instruction table

activity where principles of ABA were used to prime the appropriate joint attention response using techniques such as positive reinforcement and hierarchical prompting (verbal prompt, model, physical prompt). The following 20 minutes of the session involved a move to naturalistic milieu instruction on the floor where the same goal was targeted but this time instruction was more child-driven and included techniques such as following the child's lead and interest in activities, talking about what the child was doing, repeating back and expanding child utterances, giving corrective feedback, sitting close to and making eye-contact with the child, and making environmental adjustments to engage the child. In LANDA2011, participants in both the control group and the experimental group received behavioural intervention using the Assessment, Evaluation, and Programming System for Infants and Children (Bricker, 2002) curriculum. This intervention involved techniques such as discrete trial teaching and pivotal response training and AAC techniques (including visual cues and schedules) to target child-initiated intentional communication and diverse object play. The intervention administrator followed the child's lead and expanded language and play behaviour. Both control and experimental interventions also included parent education classes (38 hours) focusing on behavioural strategies for enhancing child development and for behaviour management, and coping and advocacy, and home-based parent training (9 hours) focusing on techniques for improving communication and adaptive behaviour. Both experimental and control interventions included goals for joint attention and imitation. However, the experimental group differed from the control group in the number of orchestrated opportunities to respond to and initiate joint attention and imitate others during social interaction and the number of opportunities afforded by the physical environment for initiating and responding to joint attention and for sharing positive affect, and there was a more discrete breakdown of social targets for the experimental curriculum. Evidence for the effectiveness of social-communication interventions on speech and language and the quality of the evidence is presented in Table 225.

The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 224: Study information table for included trials of social-communication interventions for speech and language

	Caregiver-mediated social-communication intervention versus treatment as usual	**Social skills group versus treatment as usual**	**Joint attention training and EBI/EIBI versus EBI/EIBI only**
No. trials (N)	4 (265)	1 (36)	2 (87)
Study IDs	(1) ALDRED2001 (2) CARTER2011 (3) GREEN2010 (4) SCHERTZ2013	LOPATA2010	(1) KASARI2006 (2) LANDA2011
Study design	(1)-(4) RCT	RCT	(1)-(2) RCT

% female	(1) 11 (2) Not reported (3) 9 (4) Not reported	6	(1) 19 (2) 21
Mean age (years)	(1) Median 4-4.3 (2) 1.8 (3) 3.8 (4) 2.2	9.5	(1) 3.6 (2) 2.4
IQ	(1)-(2) Not reported (3) Non-verbal IQ age equivalent: 26.2 months (assessed using the MSEL) (4) Not reported	103 (assessed using the WISC-IV Short form)	(1) 55.4 (assessed using the MSEL) (2) Not reported
Dose/intensity (mg/hours)	(1) Not reported (parents and children attended monthly intervention sessions for 6 months, followed by a further 6 months of less frequent maintenance sessions) (2) Hours of intervention not reported (intervention consisted of eight group parent-training sessions and three individualised parent–child sessions) (3) 28 (4) Not reported	Planned intensity of 204 hours (41 hours/week, consisting of 5 1.2 hour-sessions a day every day for 5 weeks)	(1) Combined joint attention training and EIBI: 194.3 (32 hours/week); EIBI only:180 hours (30 hours/week) (2) 205.7 hours for experimental group and 196.2 hours for the control group (8 hours/week)
Setting	(1) Not reported (2) Clinic and home (3) Outpatient (4) Home	College campus	(1) Outpatient (2) Educational (Kennedy Krieger classroom)
Length of treatment (weeks)	(1) 52 (2) 15 (3) 56 (4) 17-52 (mean: 30)	5	(1) 5-6 (2) 26
Continuation phase (length and inclusion criteria)	(1) 52 (2) 39 (with post-intervention assessments at 22 weeks and follow-up assessments at 39 weeks) (3) 56 (4) 60 (including 4-8-week post-intervention follow-up assessments)	6 (post-intervention assessments completed during the 5 days following treatment)	(1) 52 (includes 6-month and 1-year post-intervention follow-ups) (2) 52 (includes 6-month post-intervention follow-up)

Table 225: Evidence summary table for effects of social-communication interventions on speech and language as an indirect outcome

	Caregiver-mediated social-communication intervention versus treatment as usual		**Social skills group versus treatment as usual**	**Joint attention training and EBI/EIBI versus EBI/EIBI only**	
Outcome	Receptive language	Expressive language	Idiomatic language	Receptive language	Expressive language
Outcome measure	(1) Clinician-rated (PLS-3/MSEL/MSEL age [months]) (2) Parent-rated (CDIs)		Comprehensive Assessment of Spoken Language: Idiomatic language	RDLS or MSEL at: (1) Post-intervention (2) 6-month post-intervention follow-up (3) 12-month post-intervention follow-up	
Study ID	(1) CARTER2011 GREEN2010 SCHERTZ2013 (2) ALDRED2001 GREEN2010		LOPATA2010	(1)-(2) KASARI2006 LANDA2011 (3) KASARI2006	
Effect size (CI; p value)	(1) *Clinician-rated* SMD 0.04 (-0.23, 0.30; p = 0.79) (2) *Parent-rated* SMD 0.16 (-0.13, 0.45; p = 0.29)	(1) *Clinician-rated* SMD 0.03 (-0.23, 0.29; p = 0.83) (2) *Parent-rated* SMD 0.05 (-0.24, 0.34; p = 0.75)	SMD 0.05 (-0.62, 0.73; p = 0.88)	(1) *Post-intervention* SMD 0.27 (-0.16, 0.69; p = 0.22) (2) *6-month follow-up* SMD 0.23 (-0.20, 0.65; p = 0.30) (3) *12-month follow-up* SMD 0.36 (-0.31, 1.02; p = 0.29)	(1) *Post-intervention* SMD 0.19 (-0.23, 0.62; p = 0.38) (2) *6-month follow-up* SMD 0.29 (-0.14, 0.72; p = 0.19) (3) *12-month follow-up* SMD 0.57 (-0.10, 1.25; p = 0.09)
Heterogeneity (chi²; p value; I²)	(1) Chi² = 1.50, df = 2; p = 0.47; *I²* = 0%(2) Chi² = 0.20, df = 1 (P = 0.65); *I²* = 0%	(1) Chi² = 1.05, df = 2; p = 0.59; *I²* = 0%(2) Chi² = 0.01, df = 1 (P = 0.91); *I²* = 0%	Not applicable	(1) Chi² = 0.53, df = 1 (P = 0.46); *I²* = 0% (2) Chi² = 0.01, df = 1 (P = 0.91); *I²* = 0% (3) Not applicable	(1) Chi² = 0.05, df = 1 (P = 0.82); *I²* = 0% (2) Chi² = 0.03, df = 1 (P = 0.86); *I²* = 0% (3) Not applicable
Quality of the evidence (GRADE)	(1) Moderate[1] (2) Low[1,2]		Very low[3,4]	Low[4]	

Number of studies/participants	(1) K = 3; N = 225 (2) K = 2; N = 180	K = 1; N = 34	(1)-(2) K = 2; N = 85 (3) K = 1; N = 36
Forest plot	1.16.6; Appendix 13		

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as this outcome measure was parent-rated and parents were non-blind.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as researcher-rated and researchers were non-blind and no reliability or validity data for the use of this scale in this age group (only for >11 years).
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

There was no evidence for a statistically significant effect of caregiver-mediated social-communication interventions on clinician-rated or parent-rated receptive or expressive language as measured by the PLS-3, MSEL or CDIs. There was also no evidence for a statistically significant effect of a social skills group intervention on idiomatic language as measured by the Comprehensive Assessment of Spoken Language. Finally, there was no evidence for statistically significant effects of JA training (as an adjunct to EBI/EIBI) on receptive or expressive language as measured by the MSEL or RDLS at post-intervention or 6-month or 12-month post-intervention follow-up (see Table 225).

8.3.4 Studies considered – pharmacological interventions aimed at speech and language

Only one pharmacological intervention study met criteria for full-text retrieval, but this study could not be included in the review as data could not be extracted due to crossover design and unavailability of either first phase data or results of paired-sample t-tests.

8.3.5 Studies considered – biomedical interventions aimed at speech and language

Seventeen papers from the search met the eligibility criteria for full-text retrieval. Of these, 16 RCTs provided relevant clinical evidence and were included in the review. Two of these studies examined the efficacy of biomedical interventions on speech and language as a direct outcome (target of intervention), and 14 provided data on speech and language as an indirect outcome. All studies were published in peer-reviewed journals between 1996 and 2011. In addition, one study was excluded from the analysis as the sample size was less than ten participants per arm for analysis due to the crossover design. Further information about both included and excluded studies can be found in Appendix 12d.

Two complementary therapies trials (ALLAM2008 [Allam et al., 2008], ZHOU2008 [Zhou & Zhang, 2008]) examined effects on speech and language as a direct outcome. One of these was a foreign language paper (ZHOU2008); however, data and study characteristics were extracted from a systematic review (Cheuk et al., 2011). An additional two complementary intervention trials (WONG2010A, WONG2010B[74]) examined indirect effects on speech and language.

Four hormone trials (DUNNGEIER2000, MOLLOY2002, OWLEY1999, UNIS2002[75]) examined effects on speech and language as an indirect outcome.

[74] See Section 8.4.7 for direct outcomes from WONG2010A and WONG2010B.
[75] See Sections 6.4.3 and 6.4.5 for direct outcomes from DUNNGEIER2000 and MOLLOY2002, and OWLEY1999 and UNIS2002, respectively.

Two medical procedures trials (ADAMS2009A, GRANPEESHEH2010[76]) examined effects on speech and language as an indirect outcome.

Four nutritional intervention trials (ADAMS2011, BENT2011, CHEZ2002, JOHNSON2010[77]) examined indirect effects on speech and language.

Finally, two sensory intervention trials (BETTISON1996, KOUIJZER2010[78]) examined effects on speech and language as an indirect outcome.

8.3.6 Clinical evidence – effect of biomedical interventions on speech and language

Complementary interventions for speech and language as a direct or indirect outcome

Two of the included complementary intervention trials (ALLAM2008, ZHOU2008) compared acupuncture/acupressure and language therapy with language therapy only, and examined effects on speech and language as a direct outcome. The other two included complementary intervention trials (WONG2010A, WONG2010B) compared acupuncture/electro-acupuncture with sham acupuncture/electro-acupuncture and examined indirect effects on speech and language (see Table 226).

In ALLAM2008, both the intervention group and the control group received language therapy delivered by a language therapist that used individualised sessions to target attention and verbal ability. The experimental group also received scalp acupuncture through eight acupoints including the temples, cerebrum and aphasia points, for 20 minutes at a time. In ZHOU2008 both experimental and control groups received language therapy; however, no further detail is reported in the English-language review by Cheuk and colleagues (2011) that was included in this guideline under the study ID ZHOU2008 with regard to the language therapy. The experimental group also received acupressure that was applied to three acupoints on the thumb 100 times each, and then to six acupoints on the fingers 100 times each, and finally to five further acupoints 100 times each. In between the acupressure, areas of the face and head were massaged for several minutes and each session lasted around 45 minutes.

See Section 8.2.7 for further details about the intervention in WONG2010A and WONG2010B.

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[76] See Sections 6.4.3 and 6.4.5 for direct outcomes from ADAMS2009A and GRANPEESHEH2010, respectively.
[77] See Section 6.4.3 for direct outcomes from ADAMS2011 and CHEZ2002; see Section 7.4.2 for direct outcomes from BENT2011 and JOHNSON2010.
[78] See Section 8.5.6 for direct outcomes from BETTISON1996; see Section 6.4.3 for direct outcomes from KOUIJZER2010.

Table 226: Study information table for included trials of complementary therapies for speech and language

	Acupuncture/acupressure and language therapy versus language therapy only	Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture
No. trials (N)	2 (50)	2 (109)
Study IDs	(1) ALLAM2008 (2) ZHOU2008	(1) WONG2010A (2) WONG2010B
Study design	(1)-(2) RCT	(1)-(2) RCT
% female	(1) 40 (2) 27	(1) 14 (2) 15
Mean age (years)	(1) Not reported (2) 5.7	(1) 6.1 (2) 9.3
IQ	(1)-(2) Not reported	(1) 62.4 (assessed using the GMDS; Griffiths, 1954) (2) Not reported
Dose/intensity (mg/hours)	(1) Acupuncture: 16.7 hours/50 sessions (0.7 hours/week; 2 sessions/week) (cycles of 2 months of acupuncture, followed by a 2 week rest for the duration of the treatment period). Language therapy was delivered to both groups twice a week for the duration of the treatment period. No further intensity details are reported. (2) Acupressure: 97.5-146.25 hours (3.75 hours/week; 5 sessions/week)	(1) 0.2 hours/40 sessions (0.02 hours/week; 5 sessions/week) (2) 6 hours/12 sessions (1.5 hours week; 3 sessions/week)
Setting	(1) Academic (2) Not reported	(1) Not reported (2) Hospital
Length of treatment (weeks)	(1) 39 (2) 26-39	(1) 8 (2) 4
Continuation phase (length and inclusion criteria)	(1) 39 (2) 39	(1) 8 (2) 4

Evidence for the effectiveness of complementary therapies on speech and language and the quality of the evidence is presented in Table 227. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 227: Evidence summary table for effects of complementary therapies on speech and language as a direct or indirect outcome

	Acupuncture/acupressure and language therapy versus language therapy only			**Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture**	
Outcome	Language and attention (direct outcome)	Positive treatment response (direct outcome)		Receptive language (indirect outcome)	Expressive language (indirect outcome)
Outcome measure	Arabic Language Test: (1) Receptive semantics (2) Expressive semantics (3) Attention level	Frequency of improvement in basic developmental assessment: (1) Vocalisation (2) Babbling (3) Speech	Frequency of improvement on CRRC sign-significance relations scale: (1) Speech comprehension (2) Speech expression (3) Speech imitation (4) Vocabulary comprehension (5) Vocabulary expression (6) Phrase comprehension (7) Phrase expression (8) Communication attitude	RDLS: Comprehension (change score): (1) Comprehension score (2) Comprehension age (years)	RDLS: Expression (change score): (1) Expression score (2) Expression age (years)
Study ID	ALLAM2008	ZHOU2008		(1) WONG2010A (2) WONG2010A WONG2010B	
Effect size (CI; p value)	(1) *Receptive semantics* SMD 0.66 (-0.24, 1.57; p = 0.15) (2) *Expressive semantics* SMD -0.08 (-0.96, 0.79; p = 0.85) (3) *Attention level* SMD 0.36 (-0.53, 1.24; p = 0.43)	(1) *Vocalisation* RR 0.44 (0.04, 4.32; p = 0.48) (2) *Babbling* RR 0.44 (0.09, 2.04; p = 0.29) (3) *Speech* RR 3.50 (0.89, 13.82; p = 0.07)	(1) *Speech comprehension* RR 0.87 (0.32, 2.40; p = 0.80) (2) *Speech expression* RR 1.17 (0.31, 4.34; p = 0.82) (3) *Speech imitation* RR 0.44 (0.04, 4.32; p = 0.48) (4) *Vocabulary comprehension* RR 9.71 (0.58, 161.31; p = 0.11)	(1) *Comprehension score* SMD -0.18 (-0.73, 0.38; p = 0.53) (2) *Comprehension age* SMD 0.39 (0.00, 0.78; p = 0.05)	(1) *Expression score* SMD 0.42 (-0.14, 0.98; p = 0.14) (2) *Expression age* SMD 0.11 (-0.28, 0.49; p = 0.59)

			(5) *Vocabulary expression* RR 9.71 (0.58, 161.31; p = 0.11) (6) *Phrase comprehension* RR 2.65 (0.12, 60.21; p = 0.54) (7) *Phrase expression* RR 2.65 (0.12, 60.21; p = 0.54) (8) *Communication attitude* RR 1.64 (1.02, 2.63; p = 0.04)		
Heterogeneity (chi²; p value; I^2)	Not applicable			(1) Not applicable (2) Chi² = 1.12, df = 1; p = 0.29; I^2 = 11%	(1) Not applicable (2) Chi² = 0.11, df = 1; p = 0.74; I^2 = 0%
Quality of the evidence (GRADE)	Very low[1,2]	Very low[1,3]	(1)-(7) Very low[1,3] (8) Low[1,4]	(1) Low[2] (2) Low[5,6]	
Number of studies/participants	K = 1; N = 20	K = 1; N = 30		(1) K = 1; N = 50 (2) K = 2; N = 105	
Forest plot	1.17.1; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported and no independent reliability or validity data for this outcome measure.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)
[3]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[4]Downgraded due to serious imprecision as number of events <300.
[5]Downgraded due to serious imprecision as N <400.
[6]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias in WONG2010B as trial protocol includes a follow-up but no follow-up data reported.

There was single study evidence for a moderate and statistically significant effect of acupressure (as an adjunct to language therapy) on a dichotomous measure of positive treatment response for communication attitude as defined by showing an improvement on the CRRC sign-significance relations scale (see Table 227), with participants who received acupressure and language therapy being over one and a half times more likely to show an improvement in their communication attitude than participants receiving language therapy only. However, the quality of the evidence was low due to risk of bias concerns (unclear blinding of outcome assessment and no independent reliability or validity data for outcome measure) and small sample size. There was also a statistically significant small effect from a meta-analysis with two studies of acupuncture/electro-acupuncture (relative to sham acupuncture/electro-acupuncture) on comprehension age as measured by the RDLS as an indirect outcome (see Table 227). However, the quality of this evidence is low due to small sample size and high risk of selective reporting bias (trial protocol includes a follow-up but no follow-up data reported). Moreover, the number of non-significant effects for both comparisons far outweighs these two significant results with evidence for non-significant effects of acupuncture/acupressure (as an adjunct to language therapy) on language and attention as measured by the Arabic Language Test, positive treatment response as measured by frequency of improvement in basic developmental assessment, and positive treatment response as measured by frequency of improvement on CRRC sign-significance relations scale for seven of the eight subscales. There were also non-significant effects of acupuncture/electro-acupuncture (relative to sham acupuncture/electro-acupuncture) on comprehension score, and expression score and expression age as measured by the RDLS (see Table 227).

Hormones for speech and language as an indirect outcome

The entire four included hormone trials (DUNNGEIER2000, MOLLOY2002, OWLEY1999, UNIS2002) compared secretin and placebo (see Table 228). DUNNGEIER2000 and OWLEY1999 used porcine secretin and MOLLOY2002 used synthetic human secretin. UNIS2002 was a three-armed trial comparing porcine secretin, synthetic porcine secretin and placebo. For data analysis with this study, initial comparisons tested for significant differences between the two active intervention arms (porcine secretin and synthetic porcine secretin) and as there were no significant differences between these two groups, data was combined for meta-analysis.

Table 228: Study information table for included trials of hormones for speech and language

	Secretin versus placebo
No. trials (N)	4 (283)
Study IDs	(1) DUNNGEIER2000 (2) MOLLOY2002 (3) OWLEY1999 (4) UNIS2002
Study design	(1) RCT (2)-(3) RCT (crossover) (4) RCT
% female	(1) 7 (2) 12 (3) 14 (4) Not reported
Mean age (years)	(1) 5.1 (2) 6.2 (3) 6.7 (4) 6.5
IQ	(1)-(2) Not reported (3) Non-verbal IQ 56.4 (assessed using DAS or MSEL) (4) Not reported
Dose/intensity (mg/hours)	(1) 2 CU/kg (up to 75 CU) (2)-(3) 2 CU/kg (4) 2 CU/kg of porcine secretin or 0.4 µg/kg of synthetic porcine secretin
Setting	(1)-(3) Not reported (4) Academic
Length of treatment (weeks)	(1)-(4) Single dose
Continuation phase (length and inclusion criteria)	(1) 3 (2) 12 (including crossover period but data were extracted only for 6 week period corresponding to the end of the first phase) (3) 8 (including crossover period but data were extracted only for 4 week period corresponding to the end of the first phase) (4) 4

Evidence for the effectiveness of secretin on speech and language and the quality of the evidence is presented in Table 229. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 229: Evidence summary table for effects of hormones on speech and language as an indirect outcome

	Secretin versus placebo				
Outcome	Receptive language	Expressive language	Receptive and expressive language	Vocabulary	Positive treatment response
Outcome measure	PLS-3 (change score) or MSEL or PPVT-III/MSEL (language age in months; change score)	PLS-3 (change score) or behavioural observation (mean length of utterance) or EOWPVT-R (change score)	PLS-3: total (change score)	Behavioural observation: Type/Token Ratio or CDIs: Vocabulary (change score)	Number of participants showing ≥4 points improvement on PLS-3 total score
Study ID	DUNNGEIER2000 MOLLOY2002 OWLEY1999		DUNNGEIER2000	MOLLOY2002 UNIS2002	DUNNGEIER2000
Effect size (CI; p value)	SMD -0.02 (-0.31, 0.27; p = 0.89)	SMD -0.16 (-0.43, 0.11; p = 0.25)	SMD 0.28 (-0.15, 0.71; p = 0.20)	SMD -0.06 (-0.43, 0.31; p = 0.75)	RR 1.63 (0.83, 3.23; p = 0.16)
Heterogeneity (chi²; p value; I²)	Chi² = 3.85, df = 2; p = 0.15; I^2 = 48%	Chi² = 1.93, df = 2; p = 0.38; I^2 = 0%	Not applicable	Chi² = 0.84, df = 1; p = 0.36; I^2 = 0%	Not applicable
Quality of the evidence (GRADE)	Low[1,2]	Moderate[2]	Low[3]	Moderate[2]	Low[4]
Number of studies/participants	K = 3; N = 187	K = 3; N = 212	K = 1; N = 85	K = 2; N = 115	K = 1; N = 95
Forest plot	1.17.2; Appendix 13				

Note. [1]Downgraded due to serious inconsistency – I^2 value indicates moderate heterogeneity.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

An initial analysis compared porcine secretin with synthetic porcine secretin as examined in the two active intervention arms in UNIS2002. There were no significant differences between these conditions for expressive language as measured by the EOWPVT-R (SMD 0.49 [-0.06, 1.05]; Test for overall effect: Z = 1.73, p = 0.08) or for vocabulary as measured by the CDIs (SMD 0.08 [-0.52, 0.68]; Test for overall effect: Z = 0.26, p = 0.80). As a result data from these two groups were combined and entered into a meta-analysis.

There was no evidence for statistically significant effects of secretin on receptive or expressive language or vocabulary (see Table 229).

Medical procedures for speech and language as an indirect outcome

One of the included medical procedure trials (ADAMS2009A) compared long-term chelation (seven rounds of DMSA therapy) and short-term chelation (one round of DMSA therapy and six rounds of placebo), and the other included medical procedure trials (GRANPEESHEH2010) involved a comparison between HBOT and attention-placebo control condition (see Table 230). See section 8.2.7 for further details about interventions.

Table 230: Study information table for included trials of medical procedures for speech and language

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)	**HBOT versus attention-placebo**
No. trials (N)	1 (49)	1 (46)
Study IDs	ADAMS2009A	GRANPEESHEH2010
Study design	RCT	RCT
% female	7	Not reported
Mean age (years)	6.6	6.2
IQ	Not reported	Not reported
Dose/intensity (mg/hours)	Planned intensity for the experimental group of 180 mg/day (l-glutathione) and seven rounds of DMSA (each round consists of 3 days of DMSA [10 mg/kg-dose, nine doses over 3 days], followed by 11 days off [no treatment], and then repeating). For the control group one round of DMSA and six rounds of placebo planned	Planned intensity of 80 hours (6-10 hours/week)
Setting	Outpatient	Outpatient
Length of treatment (weeks)	17	10-15
Continuation phase (length and inclusion criteria)	17	34 (ClinicalTrials.gov reports 1-month and 3-month follow-ups but paper does not report follow-up data)

Evidence for the effectiveness of medical procedures on speech and language and the quality of the evidence is presented in Table 231 and Table 232. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 231: Evidence summary table for effects of medical procedures (chelation) on speech and language as an indirect outcome

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)
Outcome	Receptive and expressive language
Outcome measure	PDDBI: (1) Semantic pragmatic problems (2) Expressive language (3) Learning, memory and receptive language
Study ID	ADAMS2009A
Effect size (CI; p value)	(1) *Semantic pragmatic problems* SMD 0.44 (-0.20, 1.09; p = 0.18) (2) *Expressive language* SMD -0.26 (-0.91, 0.38; p = 0.42) (3) *Learning, memory and receptive language* SMD -0.12 (-0.76, 0.52; p = 0.71)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.17.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of chelation on speech and language as measured by the PDDBI (see Table 231).

Table 232: Evidence summary table for effects of medical procedures (HBOT) on speech and language as an indirect outcome

	HBOT versus attention-placebo
Outcome	Receptive language
Outcome measure	PPVT-III: total (change score)
Study ID	GRANPEESHEH2010
Effect size (CI; p value)	SMD -0.45 (-1.22, 0.31; p = 0.25)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 27
Forest plot	1.17.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of HBOT on receptive language as measured by the PPVT-III (see Table 232). There was, however, evidence from another study (SAMPANTHAVIVAT2012) for statistically significant adverse events associated with HBOT with

participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotraumas than participants who received sham HBOT (see Chapter 10, Section 10.4.2, for adverse events associated with HBOT).

Nutritional interventions for speech and language as an indirect outcome

Two of the included nutritional intervention trials examined effects of an omega-3 fatty acid supplement, one study (BENT2011) examined effects relative to placebo and one trial used a healthy-diet control comparator (JOHNSON2010). One study (ADAMS2011) compared a multivitamin/ mineral supplement with placebo, and one study (CHEZ2002) compared an L-carnosine supplement with placebo (see Table 233). See section 8.2.7 for further details about interventions in BENT2011 and JOHNSON2010. In ADAMS2011 the multivitamin and mineral supplement included most vitamins and minerals (with the exception of vitamin K, copper and iron) and was provided as a liquid (with a cherry flavour). Dosage levels of nutrients in the supplement were selected to be significantly higher than recommended daily allowance levels, but were either at or below the Tolerable Upper Limit. In CHEZ2002 the L-carnosine and placebo pills were contained by a gelatin capsule and parents were instructed to mix the powder with food or drink. In JOHNSON2010 the omega-3 fatty acid supplement was DHA (Martek Biosciences product) capsules.

Table 233: Study information table for included trials of nutritional interventions for speech and language

	Omega-3 fatty acids versus placebo	**Omega-3 fatty acids versus healthy diet control**	**Multivitamin/ mineral supplement versus placebo**	**L-carnosine supplement versus placebo**
No. trials (N)	1 (27)	1 (23)	1 (141)	1 (31)
Study IDs	BENT2011	JOHNSON2010	ADAMS2011	CHEZ2002
Study design	RCT	RCT	RCT	RCT
% female	11	Not reported	11	32
Mean age (years)	5.8	3.4	10.8	7.5
IQ	77.5 (assessed using the Stanford-Binet Intelligence Scales)	Not reported	Not reported	Not reported
Dose/intensity (mg/hours)	1.3 g of omega-3 fatty acids per day (with 1.1 g of EPA and DHA) administered as two daily doses (with 650 mg of omega-3 fatty	Planned intensity of 400 mg/day (in two daily doses)	One dose a day at lunchtime[1]	Planned intensity of 800 mg/day (in two daily doses of 400 mg)

	acids, 350 mg of EPA and 230 mg of DHA per dose)			
Setting	Outpatient	Outpatient	Outpatient	Outpatient
Length of treatment (weeks)	12	13	13	8
Continuation phase (length and inclusion criteria)	12	13	13	8
Note. [1] Formulation of vitamin/mineral supplement based on 60 lb which was adjusted up or down according to body weight up to a maximum of 100 lb: 1000 IU vitamin A; 600 mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70 mg mixed tocopherols; 20 mg B1, 20 mg B2, 15 mg niacin and 10 mg niacinamide B3; 15 mg B5; 40 mg B6; 500 mcg B12; 100 mcg folic acid; 550 mcg folinic acid; 150 mcg biotin; 250 mcg choline; 100 mcg inositol; 3.6 mg mixed carotenoids; 50 mg coenzyme Q10; 50 mg N-acetylcysteine; 100 mg calcium; 70 mcg chromium; 100 mcg iodine; 500 mcg lithium; 100 mg magnesium; 3 mg manganese; 150 mcg molybdenum; 50 mg potassium; 22 mcg selenium; 500 mg sulphur; 12 mg zinc.				

Evidence for the effectiveness of nutritional interventions on speech and language and the quality of the evidence is presented in Table 234, Table 235 and Table 236. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 234: Evidence summary table for effects of nutritional interventions (omega-3) on speech and language as an indirect outcome

	Omega-3 fatty acids versus placebo		**Omega-3 fatty acids versus healthy diet control**	
Outcome	Receptive language	Expressive language	Receptive language	Expressive language
Outcome measure	PPVT-III: total	Expressive Vocabulary Test: total	MSEL: Receptive language	MSEL: Expressive language
Study ID	BENT2011		JOHNSON2010	
Effect size (CI; p value)	SMD -0.52 (-1.32, 0.28; p = 0.20)	SMD -0.69 (-1.51, 0.12; p =0.09)	SMD 0.21 (-0.61, 1.04; p = 0.61)	SMD 0.36 (-0.47, 1.19; p = 0.40)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Low[1]		Very low[1,2]	
Number of studies/participants	K = 1; N = 25		K = 1; N = 23	
Forest plot	1.17.4; Appendix 13			
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded.				

There was no evidence for a statistically significant effect of omega-3 fatty acids (relative to placebo or healthy diet control) on receptive or expressive language (see Table 234).

Table 235: Evidence summary table for effects of nutritional interventions (multivitamin/mineral) on speech and language as an indirect outcome

	Multivitamin/ mineral supplement versus placebo	
Outcome	Receptive language	Expressive language
Outcome measure	PGI-R: Receptive language improvement	PGI-R: Expressive language improvement
Study ID	ADAMS2011	
Effect size (CI; p value)	SMD 0.43 (0.04, 0.82; p = 0.03)	SMD 0.37 (-0.02, 0.76; p = 0.06)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Moderate[1]	Low[2]
Number of studies/participants	K = 1; N = 104	
Forest plot	1.17.4; Appendix 13	
Note. [1]Downgraded due to serious imprecision as N <400. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was moderate quality evidence for a small and statistically significant indirect effect of a multivitamin/mineral supplement on receptive language, but a non-significant effect on expressive language as measured by the PGI-R (see Table 235), when compared to placebo.

Table 236: Evidence summary table for effects of nutritional interventions (L-carnosine) on speech and language as an indirect outcome

	L-carnosine supplement versus placebo	
Outcome	Receptive language	Expressive language
Outcome measure	Receptive One Word Picture Vocabulary Test: total: (1) Raw score (2) Age-adjusted score	EOWPVT: total: (1) Raw score (2) Age-adjusted score
Study ID	CHEZ2002	
Effect size (CI; p value)	(1) *Raw score* SMD 0.25 (-0.46, 0.96; p =0.49) (2) *Age-adjusted score* SMD 0.20 (-0.50, 0.91; p = 0.57)	(1) *Raw score* SMD 0.20 (-0.51, 0.91; p = 0.58) (2) *Age-adjusted score* SMD 0.21 (-0.50, 0.92; p = 0.57)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 31	
Forest plot	1.17.4; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for a statistically significant effect of an L-carnosine supplement on receptive or expressive language as measured by the Receptive One Word Picture Vocabulary Test/EOWPVT (see Table 236).

Sensory interventions for speech and language as an indirect outcome

One of the included sensory intervention trials (BETTISON1996) compared auditory integration training with an attention-placebo condition. The other included sensory intervention trial (KOUIJZER2010) compared neurofeedback with treatment as usual (see Table 100). In BETTISON1996, the auditory integration training was based on the method of Berard (1993). Experimental group participants listened to filtered and modulated music that was specially modified for each participant based on their pre-test audiogram. While participants in the control group listened to the same music for the same number of sessions as the experimental group; however, for the control group the music was unmodified (structured listening condition). In KOUIJZER2010, the neurofeedback intervention involved recording participants' electroencephalographic activity, showing them their oscillatory brain activity as it is recorded (using bar graphs to reflect the amplitude of a particular frequency) and training the participant to 'move up or down' their brain activity while observing the amplitude of their own brain waves. The targeted oscillatory activity was to reduce theta activity over frontal and central electrodes.

Table 237: Study information table for included trials of sensory interventions for speech and language

	Auditory integration training versus attention-placebo (structured listening)	**Neurofeedback versus treatment as usual**
No. trials (N)	1 (80)	1 (20)
Study IDs	BETTISON1996	KOUIJZER2010
Study design	RCT	RCT
% female	18	15
Mean age (years)	Not reported	9.3
IQ	PIQ 76 (as assessed using the LIPS)	Not reported (but inclusion criteria IQ ≥80)
Dose/intensity (mg/hours)	10 hours (7 hours/week)	Planned intensity was an estimated 18.7 hours (40 sessions; 0.9 hour/week)
Setting	Educational	Educational (specialist)
Length of treatment (weeks)	1.4	20
Continuation phase (length and inclusion criteria)	52 (follow-up assessments at 1 month, 3 months, 6 months and 1 year)	46 (but data cannot be extracted for 6-month post-intervention follow-up)

Evidence for the effectiveness of sensory interventions on speech and language and the quality of the evidence is presented in Table 238 and Table 239. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 238: Evidence summary table for effects of sensory interventions (auditory integration training) on speech and language as an indirect outcome

	Auditory integration training versus attention-placebo (structured listening)
Outcome	Receptive language
Outcome measure	PPVT: total at: (1) 3-month post-intervention follow-up (2) 6-month post-intervention follow-up (3) 12-month post-intervention follow-up
Study ID	BETTISON1996
Effect size (CI; p value)	(1) *3-month follow-up* SMD -0.24 (-0.68, 0.20; p = 0.28) (2) *6-month follow-up* SMD -0.32 (-0.76, 0.12; p = 0.16) (3) *12-month follow-up* SMD -0.50 (-0.94, -0.05; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	(1)-(2) Low[1] (3) Moderate[2]
Number of studies/participants	K = 1; N = 80
Forest plot	1.17.5; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to serious imprecision as N <400.	

There was single study moderate quality evidence for a placebo effect with auditory integration training on receptive language as measured by the PPVT at 12-month post-intervention follow-up (see Table 238). Effects were non-significant at 3-month and 6-month post-intervention follow-ups. Narrative review of this negative treatment effect suggests improvement in both groups but greater improvement in the attention-placebo control condition (structured listening) than in the auditory integration training condition.

Table 239: Evidence summary table for effects of sensory interventions (neurofeedback) on speech and language as an indirect outcome

	Neurofeedback versus treatment as usual			
Outcome	Speech production	Syntax	Semantics	Coherence
Outcome measure	CCC-2: Speech production (1) Parent-rated (2) Teacher-rated	CCC-2: Syntax (1) Parent-rated (2) Teacher-rated	CCC-2: Semantics (1) Parent-rated (2) Teacher-rated	CCC-2: Coherence (1) Parent-rated (2) Teacher-rated

Study ID	KOUIJZER2010			
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.38 (-1.26, 0.51; p = 0.40) (2) *Teacher-rated* SMD 0.75 (-0.16, 1.67; p = 0.11)	(1) *Parent-rated* SMD -0.54 (-1.44, 0.35; p = 0.23) (2) *Teacher-rated* SMD 0.20 (-0.68, 1.08; p = 0.65)	(1) *Parent-rated* SMD -0.89 (-1.82, 0.04; p = 0.06) (2) *Teacher-rated* SMD 1.12 (0.17, 2.08; p = 0.02)	(1) *Parent-rated* SMD -0.68 (-1.59, 0.23; p = 0.14) (2) *Teacher-rated* SMD 0.89 (-0.04, 1.82; p = 0.06)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Very low[1,2,3]		(1) Very low[1,2,3] (2) Very low[1,3,4]	Very low[1,2,3]
Number of studies/participants	K = 1; N = 20			
Forest plot	1.17.5; Appendix 13			

Note. [1]Downgraded for serious risk of bias – high risk of performance, response and detection bias as intervention administrators, participants and outcome assessors were non-blind. The risk of other bias due to potential conflict of interest is also high as neurofeedback equipment provided by manufacturer for trial.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as data cannot be extracted for 6-month follow-up.
[4]Downgraded due to serious imprecision as N <400.

There was no evidence for statistically significant effects of neurofeedback on parent- or teacher-rated speech production, syntax or coherence, or on parent-rated semantics as measured by the CCC-2. There was, however, a large and statistically significant negative treatment effect associated with neurofeedback on teacher-rated semantics (see Table 239). Narrative review of this effect showed that participants in the neurofeedback intervention group showed worsening (pre- to post-intervention) scores on the semantics subscale of the teacher-rated CCC-2, while the treatment as usual group showed an improvement over time.

8.3.7 Clinical evidence summary – effect of interventions on speech and language

There was limited low to very low quality evidence for positive treatment effects of an AAC intervention (PECS) on speech and language for children with autism. There was evidence for placebo/negative treatment effects on speech and language associated with auditory integration training and neurofeedback. In the case of auditory integration training, narrative review suggests improvement in both experimental and control groups but greater improvement in the attention-placebo condition. However, for neurofeedback, results reported suggest a worsening over time for the experimental group and an improvement over time for the treatment as usual group. Based on moderate to very low quality evidence it was not possible to reach a conclusion about arts-based interventions, behavioural interventions, educational interventions, parent training, social-communication

interventions, complementary interventions (acupuncture/ acupressure), hormones, medical procedures, nutritional interventions and sensory interventions.

8.3.8 Economic evidence – interventions aimed at speech and language

Systematic literature review and economic considerations

The systematic search of the literature identified one modelling study that estimated the overall cost-savings associated with enhanced versus standard speech and language therapy for children and young people with autism (Marsh et al., 2010). The study utilised efficacy data from GREEN2010, which is a trial that evaluated a social-communication intervention and is considered in Chapter 6. Therefore, the modelling study by Marsh and colleagues is also discussed in Chapter 6, in the respective economic section. Details on the methods used for the systematic review of the economic literature are described in Chapter 3; the full reference to the study and the evidence table with the study details are provided in Appendix 16. The completed methodology checklist is provided in Appendix 15. As discussed in Chapter 6, the study did not meet the set quality criteria for economic studies and therefore it was not considered further at guideline development.

According to the NHS reference costs for the financial year 2011-2012 (Department of Health, 2012) the national average unit cost per one-to-one contact with children's community speech therapy services was £89 (with £72 and £108 lower and upper quartiles, respectively). The unit cost of a community speech and language therapist was £17 per clinic visit and £47 per home visit in 2010 prices (Curtis, 2010) (more recent figures for community speech and language therapist national unit costs per clinic and home visit were not available).

8.3.9 From evidence to recommendations – interventions aimed at speech and language

Based on the review of the PECS data, the GDG decided that given the paucity of data and lack of blinded outcome assessment the evidence was not sufficient to warrant making a recommendation about the use of PECS in children and young people with autism. However, as the GDG agreed that the evidence was promising, the group proposed a research recommendation for further RCTs to be conducted to examine the effects of PECS on speech and language in children with autism. In reviewing the placebo/negative treatment effects associated with auditory integration training and neurofeedback, the GDG decided that these should not be recommended for the treatment of speech and language problems in children and young people with autism. Following stakeholder consultation, the GDG reconsidered the appropriateness of specifically recommending a referral to a speech and language therapist because such professionals are identified as key members

of the autism team as outlined in the 'Autism: Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum' guideline (NCCWCH, 2011). As NICE guidelines do not usually specify the health or social care professional who should be responsible for implementing recommendations, this has been omitted.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). Therefore, in the absence of evidence about moderators, the GDG did not make recommendations about subgroups of intervention features.

8.3.10 Recommendations

Clinical practice recommendations

8.3.10.1 Do not use neurofeedback to manage speech and language problems in children and young people with autism.

8.3.10.2 Do not use auditory integration training to manage speech and language problems in children and young people with autism.

Research recommendation

8.3.10.3 Is the Picture Exchange Communication System (PECS) effective in improving spontaneous requesting in non-verbal children with autism across a range of contexts that demonstrate generalisation of skills?

8.4 IQ, ACADEMIC SKILLS AND LEARNING

8.4.1 Introduction

Intellectual disability and academic skills

Intellectual disability (IQ<70) occurs in approximately 50% of young people with autism (Charman et al., 2011) and specific learning difficulties (literacy and numeracy and other academic skills) are common (Jones et al., 2009). However, profiles of skills and difficulties can be very variable and will require individual assessment. Although intellectual abilities and academic skills are sometimes assessed as part of the initial diagnostic or educational psychology assessment, routine monitoring of progress is rare in NHS clinical services. Skill is required in assessing IQ or intellectual ability in autism because of difficulties in social understanding and social interactions (including with the examiner); difficulties in understanding and processing verbal and non verbal language; problems in formulating and generating responses; and the ability to work a fixed time. This is also true for academic and attainment tests and caution is needed when interpreting the results of

formal assessments. Thus, it is helpful to gather information on ability and performance from more than one source (that is, both formal and informal assessments such as observation and analysis of school work).

Uneven profile of skills and abilities

Typically, people with autism show a very uneven profile of cognitive strengths and weaknesses and 'average' scores across different subdomains of a test can give a misleading impression of an individual's true level of ability. Wide discrepancies in verbal and non-verbal ability may also mean that a full scale IQ can often not be computed.

Different academic or subject areas pose a variety of challenges for pupils with autism (Guldberg, 2010). In the key areas of reading and writing, for example, children with autism typically have problems in understanding what they read (interpreting language literally and/or not getting the gist or moral of the story). Literature, arts and humanities can also present difficulties if children are asked to describe imaginary or hypothetical situations, or write about topics that upset them. Such problems are often compounded by motor difficulties that can affect all aspects of writing. Written work may be improved by focussing on situations that the children have actually experienced or enjoyed, and by providing access to computers and word processing or other relevant software. In maths, children who struggle with mental arithmetic may be able to solve complex problems as long as these are written down. In science and technology children with autism often have difficulties in working as part of a group; they can find the sensory properties of some materials aversive; coping with multiple tasks is difficult and they frequently have problems in explaining how they reached their conclusions.

PE and games are often the most difficult subjects for pupils with autism because of their difficulties with social interaction and understanding, clumsiness and co-ordination problems and difficulties in focussing on several aspects simultaneously. Many also find the sensory aspects anxiety provoking or uncomfortable (for example, being wet and cold, wearing different clothing or being exposed to the acoustics and lighting in the gym or swimming pool).

Current practice

Whatever the subject, many children with autism find working with their peers very challenging and need support to cope with the social demands of working in group activities. Lack of interest or motivation in school based topics is also a challenge. Techniques used are: incorporating aspects of the child or young person's special interest into the task; splitting work assignments into smaller, more manageable 'chunks'; offering opportunities for frequent feedback and reinforcement; providing explicit information (using visual or written cues) about how tasks should be worked through so

that pupils are clear about what is required at each stage rather than teaching about hypothetical issues as children with autism typically find it very difficult to generalise from theoretical to actual situations.

8.4.2 Studies considered – psychosocial interventions aimed at IQ and academic skills

Thirty-two papers from the search met the eligibility criteria for full-text retrieval. Of these, ten trials provided relevant clinical evidence and were included in the review. One of these studies examined the efficacy of psychosocial interventions on IQ or academic skills as a direct outcome (target of intervention), and nine provided data on IQ or academic skills as an indirect outcome. All studies were published in peer-reviewed journals between 2000 and 2012. In addition, 22 studies were excluded from the analysis. The most common reason for exclusion was that the paper was a systematic review with no new useable data. Further information about included and excluded studies can be found in Appendix 12d.

One of the behavioural intervention trials (ROGERS2012) examined effects on IQ as a direct outcome and two behavioural intervention trials (DAWSON2010, SMITH2000[79]) examined indirect effects on IQ and academic skills.

One educational intervention trial (STRAIN2011[80]) examined effects on IQ as an indirect outcome.

Four parent training trials (DREW2002, RICKARDS2007, TONGE2006, WELTERLIN2012[81]) examined indirect effects on IQ.

Finally, two social-communication intervention trials (CARTER2011, KASARI2006[82]) examined effects on IQ as an indirect outcome.

8.4.3 Clinical evidence – effect of psychosocial interventions on IQ and academic skills

Behavioural interventions for IQ and/or academic skills as a direct or indirect outcome

One of the included behavioural intervention trials (DAWSON2010) compared EIBI (ESDM) with treatment as usual, one of the behavioural intervention studies (ROGERS2012) compared EBI (P-ESDM) with treatment as usual and the other included trial (SMITH2000) compared EIBI with parent

[79] See Section 8.2.3 for direct outcomes from DAWSON2010 and SMITH2000.
[80] See Section 6.2.3 for direct outcomes from STRAIN2011.
[81] See Section 6.2.5 for direct outcomes from DREW2002, Section 8.2.3 for direct outcomes from RICKARDS2007, Section 9.2.2 for direct outcomes from TONGE2006 and Section 8.3.3 for direct outcomes from WELTERLIN2012.
[82] See Section 6.2.5 for direct outcomes from CARTER2011 and KASARI2006.

training (see Table 189). See Section 8.2.3 for further details about the interventions.

Evidence for the effectiveness of behavioural interventions on IQ and academic skills and the quality of the evidence is presented in Table 240. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 240: Evidence summary table for effects of behavioural interventions on IQ and academic skills as a direct or indirect outcome

	EIBI or EBI (ESDM or P-ESDM) versus treatment as usual	**EIBI versus parent training**	
Outcome	IQ	IQ	Academic skills
Outcome measure	(1) MSEL: Early-learning composite score or developmental quotient (2) MSEL: Verbal developmental quotient (3) MSEL: Non-verbal developmental quotient	Bayley Scales of Infant Development: Mental Development Index	Wechsler Individualized Achievement Test: total
Study ID	(1) DAWSON2010 ROGERS2012 (2)-(3) ROGERS2012	SMITH2000	
Effect size (CI; p value)	(1) Developmental quotient ESDM + P-ESDM SMD 0.25 (-0.08, 0.58; p = 0.13) ESDM SMD 0.59 (-0.01, 1.19; p = 0.05) P-ESDM SMD 0.11 (-0.29, 0.50; p = 0.60) (2) SMD 0.10 (-0.30, 0.50; p = 0.62) (3) SMD 0.08 (-0.31, 0.48; p = 0.68)	SMD 0.74 (-0.04, 1.51; p = 0.06)	SMD 0.84 (0.06, 1.62; p = 0.04)
Heterogeneity (chi²; p value; I^2)	(1) Test for subgroup differences: Chi² = 1.74, df = 1; p = 0.19; I^2 = 42.4% (2)-(3) Not applicable	Not applicable	
Quality of the evidence (GRADE)	(1) Very low[1,2,3] (2)-(3) Low[1,4]	Low[3]	Moderate[4]
Number of studies/participants	(1) K = 2; N = 143 (2)-(3) K = 1; N = 98	K = 1; N = 28	
Forest plot	1.18.1; Appendix 13		
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as			

intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported.
[2]Downgraded due to serious inconsistency as I^2 value indicates moderate heterogeneity.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded due to serious imprecision as N <400.

There was no evidence for a statistically significant effect of EIBI or EBI (relative to treatment as usual or parent training) on IQ as measured by the MSEL and the Bayley Scales of Infant Development (see Table 240). However, there was moderate quality single study evidence for a large and statistically significant effect of EIBI relative to parent training on academic skills as an indirect outcome as measured by the Wechsler Individualized Achievement Test (see Table 240).

Educational interventions for IQ as an indirect outcome

The one included educational intervention trial (STRAIN2011) compared direct training of the LEAP approach with a LEAP intervention manual-only control and examined effects on IQ as an indirect outcome (see Table 45). See Section 8.3.3 for further details of intervention.

Evidence for the effectiveness of LEAP on IQ and the quality of the evidence is presented in Table 241. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 241: Evidence summary table for effects of educational intervention on IQ as an indirect outcome

	LEAP training versus manual-only control
Outcome	IQ
Outcome measure	MSEL: Early-learning composite score
Study ID	STRAIN2011
Effect size (CI; p value)	SMD 0.87 (0.63, 1.12; p <0.00001)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 294
Forest plot	1.18.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported. [2]Downgraded due to serious imprecision as N <400.	

There was single study evidence for a large and statistically significant effect of LEAP training on IQ as measured by the MSEL (see Table 241). However, the quality of the evidence was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size, and IQ was an indirect outcome of the LEAP intervention.

Parent training for IQ as an indirect outcome

Three of the included parent training trials (DREW2002, TONGE2006, WELTERLIN2012) involved compared parent training with treatment as usual. The other included trial (RICKARDS2007) compared parent training and early intervention centre programme with early intervention centre programme only (see Table 242). See Section 8.2.3 for further details on the interventions in TONGE2006 and RICKARDS2007, and see Section 8.3.3 for further detail about the interventions in DREW2002 and WELTERLIN2012.

Table 242: Study information table for included trials of parent training for IQ

	Parent training versus treatment as usual	**Combined parent training and early intervention centre programme versus early intervention centre programme only**
No. trials (N)	3 (149)	1 (65)
Study IDs	(1) DREW2002 (2) TONGE2006 (3) WELTERLIN2012	RICKARDS2007
Study design	(1)-(3) RCT	RCT
% female	(1) 21 (2) 16 (3) 10	20
Mean age (years)	(1) 1.9 (2) 3.9 (3) 2.5	3.7
IQ	(1) Non-verbal IQ 77.1 (assessed using the D and E subscales of the Griffiths Scale of Infant Development; Griffiths, 1986) (2) 59.2 (assessed using the PEP-R – developmental quotient) (3) 55.4 (assessed using MSEL – developmental quotient)	60.4 (test not reported)
Dose/intensity (mg/hours)	(1) Planned intensity was 26 hours (3 hours/6 weeks, equating to 0.5 hours/week) (2) 25 hours (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions) (3) Planned intensity was 18 hours (1.5 hour/week)	Planned intensity for centre-based programme of 200 hours (5 hours/week). Actual number of sessions, rather than number of hours, was reported for the additional parent training intervention but number of hours was estimated and the estimated intensity for the additional parent training component was 43.5 hours, and total hours of intervention for the

		experimental group was 243.5 hours
Setting	(1) Home (2) Not reported (3) Home	Early intervention centre and home-based
Length of treatment (weeks)	(1) 52 (2) 20 (3) 12	40 (over 12-month period)
Continuation phase (length and inclusion criteria)	(1) 52 (2) 46 (including 6-month post-intervention follow-up) (3) 12	108 (including post-intervention assessment at 13 months and 12-month post-intervention follow-up assessment)

Evidence for the effectiveness of parent training on IQ and the quality of the evidence is presented in Table 243. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 243: Evidence summary table for effects of parent training on IQ as an indirect outcome

	Parent training versus treatment as usual	**Combined parent training and early intervention centre programme versus early intervention centre programme only**
Outcome	IQ	IQ
Outcome measure	Griffiths Scale of Mental Development: D and E scales (non-verbal IQ Non-Verbal Mental Age/age) or PEP-R – developmental quotient or MSEL – developmental quotient	Bayley Scales of Infant Development-Second Edition or WPPSI-R: (1) Post-intervention (mixed autism spectrum disorder and developmental disabilities sample) (2) Post-intervention (autism spectrum disorder only sample) (3) 12-month post-intervention follow-up (mixed autism spectrum disorder and developmental disabilities sample)
Study ID	(1) DREW2002 (2) TONGE2006 (3) WELTERLIN2012	RICKARDS2007
Effect size (CI; p value)	SMD 0.04 (-0.30, 0.38; p = 0.82)	(1) Post-intervention (mixed autism spectrum disorder and developmental disabilities sample) SMD 0.35 (-0.17, 0.86; p = 0.19) (2) Post-intervention (autism spectrum disorder only sample) SMD 0.43 (-0.21, 1.07; p = 0.19)

		(3) 12-month follow-up (mixed autism spectrum disorder and developmental disabilities sample) SMD 0.37 (-0.17, 0.91; p = 0.18)
Heterogeneity (chi²; p value; I²)	Chi² = 3.75, df = 2 (P = 0.15); *I²* = 47%	Not applicable
Quality of the evidence (GRADE)	Low[1,2]	(1) Very low[3,4] (2) Low[4] (3) Very low[3,4]
Number of studies/participants	K = 3; N = 147	(1) K = 1; N = 59 (2) K = 1; N = 39 (3) K = 1; N = 54
Forest plot	1.18.3; Appendix 13	
Note. [1]Downgraded due to serious inconsistency as the I2 value indicates moderate heterogeneity. [2]Downgraded due to serious imprecision as N <400. [3]Downgraded due to serious indirectness – population was indirect (as the sample included participants with developmental delay or language delay without autism). [4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for statistically significant effects of parent training (relative to treatment as usual or as an adjunct to early intervention centre programme) on IQ as an indirect outcome (see Table 243). Due to significant baseline group differences it was not possible to compare effects in the two active intervention arms for TONGE2006 and data from the two groups (PEBM and PEC) were combined to be entered into meta-analysis.

Social-communication interventions for IQ as an indirect outcome

One of the included social-communication intervention trials (CARTER2011) compared a caregiver-mediated social-communication intervention with treatment as usual, and the other included social-communication intervention study (KASARI2006) involved a comparison between joint attention training and EIBI and EIBI-only (see Table 244). See section 8.2.3 for further detail about the intervention in CARTER2011 and section 8.3.3 for further detail about the intervention in KASARI2006.

Table 244: Study information table for included trials of social-communication interventions for IQ

	Caregiver-mediated social-communication intervention versus treatment as usual	**Joint attention training and EIBI versus EIBI only**
No. trials (N)	1 (62)	1 (37)
Study IDs	CARTER2011	KASARI2006
Study design	RCT	RCT
% female	Not reported	19
Mean age (years)	1.8	3.6
IQ	Not reported	55.4 (assessed using the MSEL)

Dose/intensity (mg/hours)	Hours of intervention not reported (intervention consisted of 8 group parent-training sessions and 3 individualised parent–child sessions)	Combined joint attention training and EIBI: 194.3 (32 hours/week); EIBI only:180 hours (30 hours/week)
Setting	Clinic and home	Outpatient
Length of treatment (weeks)	15	5-6
Continuation phase (length and inclusion criteria)	39 (with post-intervention assessments at 22 weeks and follow-up assessments at 39 weeks)	52 (includes 6-month and 1-year post-intervention follow-ups)

Evidence for the effectiveness of social-communication interventions on IQ and the quality of the evidence is presented in Table 245. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 245: Evidence summary table for effects of social-communication interventions on IQ as an indirect outcome

	Caregiver-mediated social-communication intervention versus treatment as usual	**Joint attention training and EIBI versus EIBI only**
Outcome	IQ	IQ
Outcome measure	MSEL: Early-learning composite score	MSEL: Developmental quotient (at 12-month post-intervention follow-up)
Study ID	CARTER2011	KASARI2006
Effect size (CI; p value)	SMD -0.06 (-0.62, 0.50; p = 0.83)	SMD 0.54 (-0.13, 1.21; p = 0.12)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	Low[2]
Number of studies/participants	K = 1; N = 49	K = 1; N = 36
Forest plot	1.18.4; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as identity and blinding of outcome assessors is not reported.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

There was no evidence for statistically significant effects of a caregiver-mediated social-communication intervention or joint attention training (as an adjunct to EIBI) on IQ as an indirect outcome as measured by the MSEL (see Table 245).

8.4.4 Studies considered – pharmacological interventions aimed at IQ and academic skills

Three papers from the search met the eligibility criteria for full-text retrieval. Of these, one trial provided relevant clinical evidence and were included in the review. This study provided data on academic skills as an indirect outcome. In addition, two studies were excluded from the analysis. The reasons for exclusion were that the outcomes were outside the scope of this guideline or because the drug (fenfluramine) has been withdrawn from the market due to significant safety concerns. Further information about the excluded studies can be found in Appendix 12d.

The one included antipsychotic trial (RUPPRISPERIDONE2001[83]) examined indirect effects of risperidone on academic skills.

8.4.5 Clinical evidence – effect of pharmacological interventions on academic skills

Antipsychotics for academic skills as an indirect outcome

The one included antipsychotic trial (RUPPRISPERIDONE2001) compared risperidone with placebo (see Table 151).

Table 246: Study information table for included trial of antipsychotics for academic skills

	Risperidone versus placebo
No. trials (N)	1 (101)
Study IDs	RUPPRISPERIDONE2001
Study design	RCT
% female	19
Mean age (years)	8.8
IQ	Not reported
Dose/intensity (mg/hours)	Final dose of 1.8 mg/day of risperidone and 2.4 mg/day of placebo
Setting	Study was conducted across five university sites
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	8 (in the studies included in RUPPRISPERIDONE2002, an open-label 16-week extension is reported in Aman and colleagues [2005] and 95-week open-label follow-up phase in Anderson and colleagues [2007] but efficacy or safety data is not extractable for this follow-up)

Evidence for the effectiveness of risperidone on academic skills and the quality of the evidence is presented in Table 247. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

[83] See Chapter 7, Section 7.2.3, for direct outcomes from RUPPRISPERIDONE2001.

Table 247: Evidence summary table for effects of antipsychotics on academic skills as an indirect outcome

	Risperidone versus placebo
Outcome	Maths problem-solving
Outcome measure	Classroom Analogue Task: total number of maths problems correctly calculated
Study ID	RUPPRISPERIDONE2001
Effect size (CI; p value)	SMD -0.45 (-1.10, 0.19; p = 0.17)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 38
Forest plot	1.19.1; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of risperidone on academic skills as an indirect outcome as measured by the Classroom Analogue Task (see Table 247).

8.4.6 Studies considered – biomedical interventions aimed at IQ and academic skills

Six papers from the search met the eligibility criteria for full-text retrieval. Of these, five RCTs provided relevant clinical evidence and were included in the review. Two of these studies examined the efficacy of biomedical interventions on IQ or academic skills as a direct outcome (target of intervention), and three provided data on IQ or academic skills as an indirect outcome. All studies were published in peer-reviewed journals between 1996 and 2011. In addition, one study was excluded from the analysis. The reason for exclusion was that the sample size was less than ten participants per arm. Further information about both included and excluded studies can be found in Appendix 12d.

Two complementary therapy trials (WONG2010A, WONG2010B) examined effects on IQ as a direct outcome.

One hormone trial (MOLLOY2002[84]) examined effects on IQ as an indirect outcome.

One nutritional intervention trial (ADAMS2011[85]) examined indirect effects on IQ.

Finally, one sensory intervention trial (BETTISON1996[86]) examined effects on IQ as an indirect outcome.

[84] See Chapter 6, Section 6.4.3, for direct outcomes from MOLLOY2002.
[85] See Chapter 6, Section 6.4.3, for direct outcomes from ADAMS2011.
[86] See Section 8.5.6 for direct outcomes from BETTISON1996.

8.4.7 Clinical evidence – effect of biomedical interventions on IQ

Complementary therapies for IQ as a direct outcome

The two included complementary intervention trials (WONG2010A; WONG2010B) compared acupuncture/electro-acupuncture with sham acupuncture/electro-acupuncture (see Table 202). See Section 8.2.7 for further detail about the interventions.

Evidence for the effectiveness of acupuncture on IQ and the quality of the evidence is presented in Table 248. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 248: Evidence summary table for effects of complementary therapies on IQ as a direct outcome

	Acupuncture/electro-acupuncture versus sham acupuncture/electro-acupuncture
Outcome	IQ
Outcome measure	Griffiths Mental Development Scale/LIPS-R (change scores): (1) General Quotient/Full-scale IQ (2) Mental Age (months) (3) Locomotor (4) Personal-social (5) Hearing and speech (6) Eye and Hand Coordination (7) Performance (8) Practical Reasoning (9) Attention and Memory
Study ID	(1) WONG2010A WONG2010B (2)-(8) WONG2010A (9) WONG2010B
Effect size (CI; p value)	(1) *General quotient/full-scale IQ* SMD 0.23 (-0.15, 0.62; p = 0.24) (2) *Mental Age* SMD 0.43 (-0.13, 0.99; p = 0.13) (3) *Locomotor* SMD -0.20 (-0.76, 0.35; p = 0.48) (4) *Personal-social* SMD 0.53 (-0.03, 1.10; p = 0.06) (5) *Hearing and Speech* SMD 0.15 (-0.40, 0.71; p = 0.59) (6) *Eye and hand Coordination* SMD 0.12 (-0.44, 0.67; p = 0.67) (7) *Performance* SMD 0.41 (-0.15, 0.97; p = 0.16) (8) *Practical Reasoning* SMD 0.32 (-0.23, 0.88; p = 0.25) (9) *Attention and Memory* SMD -0.04 (-0.57, 0.49; p = 0.89)
Heterogeneity (chi²; p value; I²)	(1) Chi² = 0.31, df = 1; p = 0.58; *I²* = 0% (2)-(9) Not applicable
Quality of the evidence (GRADE)	(1) Very low[1,2] (2)-(8) Low[1] (9) Very low[1,2]
Number of studies/participants	(1) K = 2; N = 105 (2)-(8) K = 1; N = 50 (9) K = 1; N = 55
Forest plot	1.20.1; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of	

no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as trial protocol for WONG2010B states that follow-up measurements will be taken but these are not reported.

There was no evidence for statistically significant effects of acupuncture/electro-acupuncture on IQ as measured by the Griffiths Mental Development Scale or LIPS-R (see Table 248).

Hormones for IQ as an indirect outcome

The one included hormone trial (MOLLOY2002) compared secretin (synthetic human secretin) with placebo (see Table 249).

Table 249: Study information table for included trials of hormones for IQ

	Secretin versus placebo
No. trials (N)	1 (42)
Study IDs	MOLLOY2002
Study design	RCT (crossover)
% female	12
Mean age (years)	6.2
IQ	Not reported
Dose/intensity (mg/hours)	2 CU/kg
Setting	Not reported
Length of treatment (weeks)	Single dose
Continuation phase (length and inclusion criteria)	12 (including crossover period but data were extracted only for 6 week period corresponding to the end of the first phase)

Evidence for the effectiveness of secretin on IQ and the quality of the evidence is presented in Table 250. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 250: Evidence summary table for effects of hormones on IQ as an indirect outcome

	Secretin versus placebo
Outcome	IQ
Outcome measure	Merrill-Palmer Scale
Study ID	MOLLOY2002
Effect size (CI; p value)	SMD -0.31 (-0.92, 0.30; p = 0.32)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 42
Forest plot	1.20.2; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of secretin on IQ as an indirect outcome as measured by the Merrill-Palmer Scale (see Table 250).

Nutritional interventions for IQ as an indirect outcome

The one included nutritional intervention study (ADAMS2011) compared a multivitamin/mineral supplement with placebo (see Table 233). See section 8.3.5 for further detail about the intervention.

Evidence for the effectiveness of a multivitamin/mineral supplement on IQ and the quality of the evidence is presented in Table 251. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 251: Evidence summary table for effects of nutritional intervention on IQ as an indirect outcome

	Multivitamin/ mineral supplement versus placebo
Outcome	Cognition
Outcome measure	PGI-R: Cognition improvement
Study ID	ADAMS2011
Effect size (CI; p value)	SMD 0.32 (-0.06, 0.71; p = 0.10)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 104
Forest plot	1.20.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of a multivitamin/mineral supplement on cognition as an indirect outcome as measured by the PGI-R (see Table 251).

Sensory interventions for IQ as an indirect outcome

The one included sensory intervention trial (BETTISON1996) compared auditory integration training with an attention-placebo condition (see Table 100). See section 8.3.6 for further detail about intervention.

Evidence for the effectiveness of auditory integration training on IQ and the quality of the evidence is presented in Table 252. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 252: Evidence summary table for effects of sensory intervention on IQ as an indirect outcome

	Auditory integration training versus attention-placebo (structured listening)
Outcome	PIQ
Outcome measure	LIPS: total at: (1) 3-month post-intervention follow-up (2) 6-month post-intervention follow-up (3) 12-month post-intervention follow-up
Study ID	BETTISON1996
Effect size (CI; p value)	(1) *3-month follow-up* SMD -0.16 (-0.60, 0.28; p = 0.47) (2) *6-month follow-up* SMD -0.17 (-0.61, 0.26; p = 0.44) (3) *12-month follow-up* SMD -0.22 (-0.66, 0.22; p = 0.33)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 80
Forest plot	1.20.4; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of auditory integration training on PIQ as an indirect outcome as measured by the LIPS (see Table 252).

8.4.8 Clinical evidence summary – effect of interventions on IQ and academic skills

Based on low to very low quality evidence it is not possible to draw conclusions about the relative benefit of psychosocial interventions (behavioural interventions, parent training, and social-communication interventions) on IQ and academic skills as an indirect outcome. Low quality evidence from one relatively large trial suggests that an educational intervention (LEAP) may produce a large effect in terms of IQ (indirect outcome). Based on low to very low quality evidence it is not possible to draw conclusions about the relative benefit of pharmacological (antipsychotic drugs) or biomedical interventions (acupuncture, hormones, nutritional interventions, sensory interventions) on IQ and academic skills.

8.4.9 Economic evidence – interventions aimed at IQ and academic skills

Systematic literature review

No studies assessing the cost effectiveness of interventions aimed at IQ or academic skills in children and young people with autism were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

8.4.10 From evidence to recommendations – interventions aimed at IQ and academic skills

The GDG agreed that the results of the LEAP trial were promising; however, they would need to be replicated by at least one other study and with blinded outcome assessment. Therefore, considered together with the evidence for positive treatment effects on the target outcome of the intervention, a research recommendation was made for a comprehensive psychosocial intervention aimed at the core features of autism (the direct outcome for the LEAP intervention), see research recommendation 6.6.2.1. The GDG reached the decision that there was insufficient evidence on which to make a recommendation about the use of any of the reviewed interventions for IQ and academic skills in children and young people with autism.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

8.5 SENSORY SENSITIVITIES

8.5.1 Introduction

Sensory sensitivities associated with autism have most frequently been framed in terms of over or under sensitivity or poor sensory integration, both models reflecting theories about information processing and brain function current in the 1960s and 1970s. The evidence supporting these models has been called into question by recent developments in neuroscience, as has the efficacy of sensory therapies (American Academy of Pediatrics, 2012). Reviews of the literature suggest that sensory processing varies considerably between individuals with autism (Rogers & Ozonoff, 2005; Marco et al, 2011). Sensory sensitivities may be implicated in rigid behaviours and stereotypical and/or self-stimulatory behaviours such as spinning, hand flapping or rocking. Sensory difficulties can have a significant impact on the daily lives of children with autism, for example, extreme reactions to certain sights, sounds and textures, and their ability to adjust to new environments. Eating problems are also often associated with sensory problems.

Current practice

A wide range of sensory based interventions is used for individuals with autism (Williamson and Anzalone 1997; Baranek, 1998). These can include labour intensive interventions such as direct therapy aimed at changing the way the child or young person processes sensory information; indirect interventions such as using a 'safe space' for the child to retreat to when he/she can no longer tolerate the sensory information, or making small

changes in their surroundings. Sensory techniques and adaptations are employed by health practitioners such as occupational therapists, social care practitioners, parents and teachers. Some positive benefits from sensory-based interventions have been reported and it has been suggested that that therapists pair sensory-based interventions with functional tasks in order to affect performance on a daily basis. However, the effectiveness of this type of intervention still requires further research (Baranek, 2002; Mailloux & Roley, 2004).

Difficulties in processing sensory information can also limit the effectiveness of other interventions. Thus, environmental adaptations are often needed in order for children with autism to be able to focus their attention on the task presented to them. Parents and teachers may be advised to alter environments at home and within the classroom environment in order to elicit greater modulation of responses and a reduction in behavioural disturbance (Haack & Haldy, 1998).

Insistence on eating only certain brands, colours or types of food, or hyper-sensitivity to taste, smell or texture can result in a severely restricted diet and serious concerns about nutrition. A behavioural approach is usually taken in such circumstances but medical treatment may be required in extreme circumstances.

8.5.2 Studies considered – psychosocial interventions aimed at sensory sensitivities

Three papers from the search met the eligibility criteria for full-text retrieval. Two of these provided relevant clinical evidence and were included in the review, and both provided data on sensory sensitivities as an indirect outcome. The studies were published in peer-reviewed journals between 2009 and 2010. One study was excluded as there was no control group. See Appendix 12d for further information about the excluded study.

One animal-based trial (BASS2009[87]) examined effects on sensory sensitivities as an indirect outcome.

One educational intervention trial (WHALEN2010[88]) examined indirect effects on sensory sensitivities.

[87] See Chapter 6, Section 6.2.5, for direct outcomes from BASS2009.
[88] See Section 8.3.3 for direct outcomes from WHALEN2010.

8.5.3 Clinical evidence – effect of psychosocial interventions on sensory sensitivities

Animal-based interventions for sensory sensitivities as an indirect outcome

The animal-based intervention trial (BASS2009) compared horseback riding intervention with waitlist control in children with autism (see Table 32). Participants were trained in: mounting and dismounting (aimed at stimulating verbal communication, proprioception and vestibular processing); warm-up exercises; riding skills (aimed at stimulating sensory seeking, balance and coordination, and fine and gross motor skills); individualised and group games while on the horse, such as 'Simon says' and catch and throw (aimed at developing social and communication skills); and grooming activities. Throughout the intervention participants were verbally and physically reinforced (for instance, with high-fives and hugs).

Table 253: Study information table for included trial of animal-based intervention for sensory sensitivities

	Horseback riding versus waitlist control
No. trials (N)	1 (34)
Study IDs	BASS2009
Study design	RCT
% female	15
Mean age (years)	7.3
IQ	Not reported
Dose/intensity (mg/hours)	12 hours (1 hour/week)
Setting	Equestrian training centre
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of horseback riding on sensory sensitivities and the quality of the evidence is presented in Table 254. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 254: Evidence summary table for effects of animal-based intervention on sensory sensitivities as an indirect outcome

	Horseback riding versus waitlist control		
Outcome	Sensory problems	Sensory seeking	Sensory sensitivity
Outcome measure	Sensory Profile: total	Sensory Profile: Sensory seeking	Sensory Profile: Sensory sensitivity
Study ID	BASS2009		
Effect size (CI; p value)	SMD 0.45 (-0.23, 1.14; p = 0.20)	SMD 0.89 (0.17, 1.60; p = 0.01)	SMD 0.39 (-0.29, 1.08; p = 0.26)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence	Very low[1,2,3]	Very low[1,3,4]	Very low[1,2,3]

(GRADE)			
Number of studies/participants	K = 1; N = 34		
Forest plot	1.21.1; Appendix 13		
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [3]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as data not reported for selected subscales: low endurance/tone, oral sensory sensitivity, and poor registration subscales of the Sensory Profile scale. [4]Downgraded due to serious imprecision as N <400.			

There was single study evidence for a large and statistically significant effect of horseback riding on the sensory seeking subscale of the Sensory Profile, but non-significant effects for the total score and the sensory sensitivity subscale (see Table 254). The confidence in the significant effect estimate was very low due to risk of bias concerns (non-blind parent-rated outcome measure), small sample size and high risk of selective reporting bias (data not reported for all subscales of the Sensory Profile scale).

Educational interventions for sensory sensitivities as an indirect outcome

The one included educational intervention trial (WHALEN2010) compared combined computer-assisted educational intervention (TeachTown: Basics) and IBI day class programmes (Intensive Comprehensive Autism Programs) with IBI day class programmes only (see Table 45). See section 8.3.3 for further detail about the intervention.

Evidence for the effectiveness of the TeachTown intervention on sensory sensitivities and the quality of the evidence is presented in Table 255. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 255: Evidence summary table for effects of educational intervention on sensory sensitivities as an indirect outcome

	Combined TeachTown and IBI versus IBI-only
Outcome	Auditory processing
Outcome measure	Brigance Inventory of Child Development: Auditory processing: (1) Preschool (2) K-1
Study ID	WHALEN2010
Effect size (CI; p value)	(1)+(2) SMD 0.21 (-0.37, 0.79; p = 0.48) (1) *Preschool* SMD 0.13 (-0.69, 0.95; p = 0.76) (2) *Kindergarten and first grade* SMD 0.29 (-0.54, 1.11; p = 0.50)
Heterogeneity (chi²; p value; I²)	Test for subgroup differences: Chi² = 0.07,

	df = 1; p = 0.79, I^2 = 0%
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 46
Forest plot	1.21.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. Risk of detection bias is unclear/unknown as the identity and blinding of outcome assessors not reported. In addition, for the Brigance Inventory of Child Development scale there are no independent reliability and/or validity data reported. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of TeachTown (as an adjunct to IBI) on auditory processing as an indirect outcome, as measured by the Brigance Inventory of Child Development. There was also no evidence that the treatment effect was moderated by the age of the children (see Table 255).

8.5.4 Studies considered – pharmacological interventions aimed at sensory sensitivities

No pharmacological intervention studies that examined effects on sensory sensitivities (as a direct or indirect outcome) met the inclusion criteria for full-text retrieval.

8.5.5 Studies considered – biomedical interventions aimed at sensory sensitivities

Nine papers from the search met the eligibility criteria for full-text retrieval. Of these, four RCTs provided relevant clinical evidence and were included in the review. All four of these studies examined the efficacy of biomedical interventions on sensory sensitivities as a direct outcome (target of intervention). All studies were published in peer-reviewed journals between 1996 and 2011. In addition, five studies were excluded from the analysis. The reasons for exclusion were that less than 50% of the sample had a diagnosis of autism, the sample size was less than ten participants per arm, efficacy data could not be extracted, or the paper was a systematic review with no new useable data and any meta-analysis not appropriate to extract. Further information about both included and excluded studies can be found in Appendix 12d.

Two complementary therapy trials (SILVA2009, SILVA2011B) examined effects on sensory sensitivities as a direct outcome.

Two sensory intervention trials (BETTISON, FAZLIOGLU2008 [Fazlioğlu & Baran, 2008]) examined effect on sensory sensitivities as a direct outcome.

8.5.6 Clinical evidence – effect of biomedical interventions on sensory sensitivities

Complementary interventions for sensory sensitivities as a direct outcome

The two included complementary intervention trials (SILVA2009, SILVA2011B) compared Qigong massage training with waitlist control (see Table 256). Qigong massage is an intervention based in Chinese medicine. In SILVA2009, trained therapists administered qigong massage treatment to the child, and parents were trained in how to administer the massage for daily massage at home and in SILVA2011B the intervention was solely based on parent training of Qigong massage techniques.

Table 256: Study information table for included trials of complementary therapies for sensory sensitivities

	Qigong massage training versus waitlist
No. trials (N)	2 (112)
Study IDs	(1) SILVA2009 (2) SILVA2011B
Study design	(1)-(2) RCT
% female	(1) 20 (2) 30
Mean age (years)	(1) 5.0 (2) 4.8
IQ	(1)-(2) Not reported
Dose/intensity (mg/hours)	(1) Planned intensity: children were to be seen by the therapists 20 times and parents were required to give children daily massages. No information regarding the duration of the massages or actual intensity reported (2) 29.75 hours/119 sessions (1.75 hours/week; 7 sessions/week)
Setting	(1) Not reported (2) Home-based
Length of treatment (weeks)	(1) 22 (2) 17
Continuation phase (length and inclusion criteria)	(1) 44 (including 5-month post-intervention follow-up) (2) 17

Evidence for the effectiveness of Qigong massage on sensory sensitivities and the quality of the evidence is presented in Table 257. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 257: Evidence summary table for effects of complementary therapies on sensory sensitivities as a direct outcome

	Qigong massage training versus waitlist
Outcome	Sensory impairment

Outcome measure	(1) PDDBI: Sensory score (2) Sense and Self-Regulation Checklist: Sense score
Study ID	(1)-(2) SILVA2009 SILVA2011B
Effect size (CI; p value)	(1) *PDDBI* SMD -0.80 (-1.27, -0.34; p =0.0007) (2) *Sense and Self-Regulation Checklist* SMD -1.11 (-1.56, -0.65; p <0.00001)
Heterogeneity (chi²; p value; I^2)	(1) Chi² = 0.44, df = 1; p = 0.51; I^2 = 0% (2) Chi² = 0.55, df = 1; p = 0.46; I^2 = 0%
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	(1) K = 2; N = 79 (2) K = 2; N = 87
Forest plot	1.22.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of selection bias in SILVA2009 as although groups were assigned using a random number generator, there were caveats to the randomisation (five sets of siblings were co-assigned due to parental involvement in the treatment and different geographical areas were assigned separately to meet the 'therapist to participant requirements'). Groups were also not comparable at baseline for measures of parent rated social communication and autism composite and teacher rated sensory problems. There was also a high risk of performance and response bias as intervention administrators and participants were non-blind, and an unclear or high risk of detection bias due to unclear blinding or non-blind outcome assessment. [2]Downgraded due to serious imprecision as N <400.	

There was evidence from a meta-analysis with two studies for large and statistically significant effects of Qigong massage on sensory impairment as measured by the PDDBI and the Sense and Self-Regulation Checklist (see Table 257). However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (group allocation was not truly randomised and blinding of outcome assessment was either unclear or non-blind) and small sample size.

Sensory interventions for sensory sensitivities as a direct outcome

One of the included sensory intervention trials (BETTISON1996) compared auditory integration training with an attention-placebo condition, while the other included sensory intervention trials (FAZLIOGLU2008) involved a comparison between sensory integration therapy and treatment as usual (see Table 258). See section 8.3.6 for further detail about the intervention in BETTISON1996. In FAZLIOGLU2008, the sensory integration therapy was based on 'The Sensory Diet' (Chara et al., 2004). Participants were provided with a classroom programme of frequent and systematically applied somatosensory stimulation (brushing with a surgical brush and joint compression) followed by sensory-based activities designed to meet needs and integrated into the children's' daily routine. Targeted sensory behaviours included hearing, seeing, tasting, smelling, touching, balancing, moving (fine motor, gross motor, oral motor) and proprioception and intervention techniques included step-by-step activities, regular breaks (if children became over stimulated), prompt fading, modelling, extinction and reinforcement. Children learnt each skill to independence before moving on to the next skill.

Table 258: Study information table for included trials of sensory interventions for sensory sensitivities

	Auditory integration training versus attention-placebo (structured listening)	**Sensory integration therapy versus treatment as usual**
No. trials (N)	1 (80)	1 (30)
Study IDs	BETTISON1996	FAZLIOGLU2008
Study design	RCT	RCT
% female	18	20
Mean age (years)	Not reported	Not reported
IQ	PIQ 76 (as assessed using the LIPS)	Not reported (all participants described as 'low functioning')
Dose/intensity (mg/hours)	10 hours (7 hours/week)	Planned intensity of 18 hours (1.5 hour/week)
Setting	Educational	Educational (specialist)
Length of treatment (weeks)	1.4	12
Continuation phase (length and inclusion criteria)	52 (follow-up assessments at 1 month, 3 months, 6 months and 1 year)	12

Evidence for the effectiveness of sensory interventions on sensory sensitivities and the quality of the evidence is presented in Table 259. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 259: Evidence summary table for effects of sensory interventions on sensory sensitivities as a direct outcome

	Auditory integration training versus attention-placebo (structured listening)			**Sensory integration therapy versus treatment as usual**
Outcome	Sound sensitivity	Sound distress	Sensory self-stimulation	Sensory problems
Outcome measure	Sound Sensitivity Questionnaire: total at: (1) 1-month post-intervention follow-up (2) 3-month post-intervention follow-up (3) 6-month post-intervention follow-up	Sound Sensitivity Questionnaire: Sound distress at: (1) 1-month post-intervention follow-up (2) 3-month post-intervention follow-up (3) 6-month post-intervention	Sensory Problems checklist: total at: (1) 1-month post-intervention follow-up (2) 3-month post-intervention follow-up (3) 6-month post-intervention follow-up	Sensory Evaluation Form for Children with Autism: total

	(4) 12-month post-intervention follow-up	follow-up (4) 12-month post-intervention follow-up	(4) 12-month post-intervention follow-up	
Study ID	BETTISON1996			FAZLIOGLU2008
Effect size (CI; p value)	(1) *1-month follow-up* SMD -0.27 (-0.71, 0.17; p = 0.23) (2) *3-month follow-up* SMD -0.13 (-0.57, 0.31; p = 0.55) (3) *6-month follow-up* SMD 0.12 (-0.32, 0.56; p = 0.60) (4) *12-month follow-up* SMD 0.20 (-0.24, 0.64; p = 0.37)	(1) *1-month follow-up* SMD -0.02 (-0.46, 0.41; p = 0.91) (2) *3-month follow-up* SMD 0.00 (-0.44, 0.44; p = 1.00) (3) *6-month follow-up* SMD 0.43 (-0.01, 0.87; p = 0.06) (4) *12-month follow-up* SMD 0.20 (-0.24, 0.63; p = 0.38)	(1) *1-month follow-up* SMD 0.07 (-0.36, 0.51; p = 0.74) (2) *3-month follow-up* SMD 0.10 (-0.34, 0.54; p =0.66) (3) *6-month follow-up* SMD 0.05 (-0.39, 0.49; p = 0.82) (4) *12-month follow-up* SMD 0.22 (-0.22, 0.66; p = 0.32)	SMD -2.00 (-2.90, -1.11; p <0.0001)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Low[1]	(1)-(2) Moderate[2] (3)-(4) Low[1]	(1)-(2) Low[1] (3) Moderate[2] (4) Low[1]	Low[2,3]
Number of studies/participants	K = 1; N = 80			K = 1; N = 30
Forest plot	1.22.2; Appendix 13			

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and risk of detection bias is unclear/unknown as the identity and blinding of outcome assessor is not reported.

There was no evidence for a statistically significant effect of auditory integration training on sound sensitivity, distress or sensory self-stimulation at 1-month, 3-month, 6-month or 12-month post-intervention follow-up time points (see Table 259).

There was single study evidence for a large and statistically significant effect of sensory integration therapy on sensory problems as measured by a study-specific checklist (see Table 259). However, the quality of the evidence was downgraded to low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size.

8.5.7 Clinical evidence summary – effect of interventions on sensory sensitivities

There was low to very low quality evidence from small single studies for beneficial effects of horseback riding and sensory integration therapy, and

from a meta-analysis with two small studies for beneficial effects of massage, on sensory sensitivities.

8.5.8 Economic evidence – interventions aimed at sensory sensitivities

Systematic literature review

No studies assessing the cost effectiveness of interventions aimed at sensory sensitivities in children and young people with autism were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

8.5.9 From evidence to recommendations – interventions aimed at sensory sensitivities

The GDG concluded that there was insufficient evidence to recommend any of the interventions reviewed for sensory sensitivities in children and young people with autism. Nevertheless, the GDG felt that a research recommendation should be made about sensory integration therapy.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

8.5.10 Recommendations

Research recommendations

8.5.10.1 Does Sensory Integration Therapy reduce sensory sensitivities in children and young people with autism across a range of contexts?

8.6 MOTOR DIFFICULTIES

8.6.1 Introduction

It is estimated that around 50-73% of children with autism have significant motor delays (Berkeley et al., 2001; Manjiviona & Prior, 1995). Provost, Heimerl, and Lopez (2007) noted that at least 60% of young children with autism would meet criteria for early intervention from health professionals based on their motor difficulties alone. Motor problems reported in autism include clumsy gait, poor muscle tone, balance difficulties, poor motor control and manual dexterity and difficulties with praxis and planning of movements (Dziuk et al., 2007; Gidley et al., 2008; Jansiewicz et al., 2006). It has been hypothesised that these difficulties with motor control and praxis may

contribute to some of the classic features of autism such as using another individual's hand as a tool, a lack of or reduction in gestures and delay or difficulty with developing sequences of play (Wieder, 1996).

Current practice

Because of the impact that motor deficits may have on development it is recommended in the *Autism Diagnosis in Children and Young People* guideline (NICE, 2011) that an assessment of motor skills is completed as part of the diagnostic process. This may provide evidence for differential diagnoses, such as dyspraxia or developmental coordination disorder, as well as information needed to compile a detailed profile of the child's strengths and needs.

8.6.2 Studies considered – psychosocial interventions aimed at motor skills

Six papers from the search met the eligibility criteria for full-text retrieval. Of these, all six trials provided relevant clinical evidence and were included in the review. All six of these studies examined the efficacy of psychosocial interventions on motor skills as an indirect outcome of the intervention. All studies were published in peer-reviewed journals between 1998 and 2012. No studies were excluded from the analysis.

One animal-based intervention trial (BASS2009[89]) examined indirect effects on motor skills.

One behavioural intervention trial (DAWSON2010[90]) examined effects on motor skills as an indirect outcome.

One educational intervention trial (STRAIN2011[91]) examined effects on motor skills as an indirect outcome.

Two parent training studies (JOCELYN1998, TONGE2006[92]) examined indirect effects on motor skills.

Finally, one social-communication intervention trial (CARTER2011[93]) examined effects on motor skills as an indirect outcome.

[89] See Chapter 6, Section 6.2.5, for direct outcomes from BASS2009.
[90] See Section 8.2.3 for direct outcomes from DAWSON2010.
[91] See Chapter 6, Section 6.2.3, for direct outcomes from STRAIN2011
[92] See Section 6.2.3 and Section 9.2.2, respectively, for direct outcomes from JOCELYN1998 and TONGE2006.
[93] See Section 6.2.5 for direct outcomes from CARTER2011.

8.6.3 Clinical evidence – effect of psychosocial interventions on motor skills

Animal-based interventions for motor skills as an indirect outcome

The animal-based intervention trial (BASS2009) compared a horseback riding intervention with waitlist control in children with autism (see Table 32). See section 8.5.3 for further detail about the intervention.

Evidence for the effectiveness of horseback riding on motor skills and the quality of the evidence is presented in Table 260. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 260: Evidence summary table for effects of animal-based intervention on motor skills as an indirect outcome

	Horseback riding versus waitlist control
Outcome	Fine motor/perception
Outcome measure	Sensory Profile: Fine motor/perception
Study ID	BASS2009
Effect size (CI; p value)	SMD 0.22 (-0.45, 0.90; p = 0.52)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 34
Forest plot	1.23.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. There is also a high risk of detection bias as outcome measures are parent-rated and parents non-blind. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of horseback riding on motor skills as an indirect outcome, as measured by the fine motor/perception subscale of the Sensory Profile (see Table 260).

Behavioural interventions for motor skills as an indirect outcome

The one included behavioural intervention trial (DAWSON2010) compared EIBI (ESDM) with treatment as usual (see Table 189). See section 8.2.3 for further detail of intervention.

Evidence for the effectiveness of EIBI on motor skills and the quality of the evidence is presented in Table 261. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 261: Evidence summary table for effects of behavioural intervention on motor skills as an indirect outcome

	EIBI (ESDM) versus treatment as usual

Outcome	Fine motor skills	Motor skills
Outcome measure	MSEL: Fine motor	VABS: Motor skills
Study ID	DAWSON2010	
Effect size (CI; p value)	SMD 0.45 (-0.15, 1.04; p = 0.14)	SMD 0.78 (0.17, 1.39; p = 0.01)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	Low[2,3]
Number of studies/participants	K = 1; N = 45	
Forest plot	1.23.2; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind and risk of detection bias is unclear/unknown as although outcome assessors were blinded the outcome measure was based on interview with (non-blind) parent rather than direct observation. [3]Downgraded due to serious imprecision as N <400.		

There was single study evidence for a moderate and statistically significant effect of EIBI (ESDM) on motor skills as measured by the VABS (see Table 261). However, the quality of the evidence was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size. In addition, a non-significant effect was observed for the blinded outcome measure (MSEL) of fine motor skills (see Table 261).

Educational interventions for motor skills as an indirect outcome

The one included educational intervention trial (STRAIN2011) compared direct training of the LEAP approach with a LEAP intervention manual-only control (see Table 45). See section 8.3.3 for further detail about the intervention.

Evidence for the effectiveness of LEAP on motor skills and the quality of the evidence is presented in Table 262. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 262: Evidence summary table for effects of educational intervention on motor skills as an indirect outcome

	LEAP training versus manual-only control
Outcome	Fine motor skills
Outcome measure	MSEL: Fine motor age (months)
Study ID	STRAIN2011
Effect size (CI; p value)	SMD 0.69 (0.45, 0.93; p <0.00001)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 294
Forest plot	1.23.3; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind. In addition, risk of detection bias is unclear/unknown as identity and blinding of outcome assessors not reported. [2]Downgraded due to serious imprecision as N <400.	

There was single study evidence for a moderate and statistically significant effect of LEAP intervention on fine motor skills as an indirect outcome, as measured by the MSEL (see Table 262). However, the quality of the evidence was low due to risk of bias concerns (unclear blinding of outcome assessment) and small sample size.

Parent training for motor skills as an indirect outcome

One of the included parent training trials compared parent training with treatment as usual (TONGE2006) and the other (JOCELYN1998) compared parent and day care staff training with standard day care (see Table 263). See section 8.2.3 for further details about the interventions.

Table 263: Study information table for included trials of parent training for motor skills

	Parent training versus treatment as usual	Parent and day care staff training versus standard day care
No. trials (N)	1 (105)	1 (36)
Study IDs	TONGE2006	JOCELYN1998
Study design	RCT	RCT
% female	16	3
Mean age (years)	3.9	3.6
IQ	59.2 (assessed using the PEP-R – developmental quotient)	PIQ 63.1 (assessed using the LIPS; Leiter, 1948)
Dose/intensity (mg/hours)	25 hours (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions)	50 hours (3 hours/week of educational seminars for 5 weeks and 3 hours/week of on-site day-care staff consultation for 10 weeks, and three parent-staff review meetings at day care centre [estimated at 3 hours] and 2 in-home visits [estimated at 2 hours]; equating to 4 hours/week)
Setting	Not reported	Outpatient, educational (day care centre) and home-based
Length of treatment (weeks)	20	12
Continuation phase (length and inclusion criteria)	46 (including 6-month post-intervention follow-up)	12

Evidence for the effectiveness of parent training on motor skills and the quality of the evidence is presented in Table 264. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 264: Evidence summary table for effects of parent training on motor skills as an indirect outcome

	Parent training versus treatment as usual	Parent and day care staff training versus standard day care	
Outcome	Motor skills	Fine motor skills	Gross motor skills
Outcome measure	VABS: Motor skills	EIDP/PSDP: Perceptual/Fine motor (developmental age)	EIDP/PSDP: Gross motor (developmental age)
Study ID	TONGE2006	JOCELYN1998	
Effect size (CI; p value)	SMD 0.11 (-0.30, 0.52; p = 0.61)	SMD 0.01 (-0.66, 0.67; p = 0.98)	SMD -0.18 (-0.85, 0.48; p = 0.59)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2]	Low[2]	
Number of studies/participants	K = 1; N = 103	K = 1; N = 35	
Forest plot	1.23.4; Appendix 13		

Note. [1]Downgraded for serious risk of bias -High risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias is unclear/unknown as although the study included a blinded clinician outcome assessor this outcome measure was based on parental interview and simultaneous child observation and parents non-blind.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

There was no evidence for statistically significant effects of parent training or parent and day-care staff training on fine or gross motor skills as an indirect outcome, as measured by the VABS or EIDP/PSDP (see Table 264). Due to significant baseline group differences it was not possible to compare effects in the two active intervention arms for TONGE2006 and data from the two groups (PEBM and PEC) were combined to be entered into meta-analysis.

Social-communication interventions for motor skills as an indirect outcome

The one included social-communication intervention trial (CARTER2011) compared a caregiver-mediated social-communication intervention with treatment as usual (see Table 244). See section 8.2.3 for further detail about the intervention.

Evidence for the effectiveness of a caregiver-mediated social-communication intervention on motor skills and the quality of the evidence is presented in Table 265. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 265: Evidence summary table for effects of social-communication intervention on motor skills as an indirect outcome

	Caregiver-mediated social-communication intervention versus treatment as usual	
Outcome	Fine motor skills	Motor skills
Outcome measure	MSEL: Fine motor age (months)	VABS: Motor skills
Study ID	CARTER2011	
Effect size (CI; p value)	SMD 0.02 (-0.53, 0.58; p = 0.94)	SMD 0.19 (-0.44, 0.82; p = 0.56)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	Very low[2,3]
Number of studies/participants	K = 1; N = 50	K = 1; N = 39
Forest plot	1.23.5; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias unclear/unknown as identity and blinding of outcome assessors not reported.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and risk of detection bias unclear/unknown as outcome measure based on parent interview rather than direct behaviour observation and parents non-blind and involved in the intervention.

There was no evidence for a statistically significant effect of a caregiver-mediated social-communication intervention on motor skills as an indirect outcome, as measured by the MSEL or the VABS (see Table 265).

8.6.4 Studies considered – pharmacological interventions aimed at motor skills

No pharmacological intervention studies that examined effects on motor skills (as a direct or indirect outcome) met the inclusion criteria for full-text retrieval.

8.6.5 Studies considered – biomedical interventions aimed at motor skills

Four papers from the search met the eligibility criteria for full-text retrieval. Of these, three RCTs provided relevant clinical evidence and were included in the review. All three of these studies examined the efficacy of biomedical interventions on motor skills as an indirect outcome of the intervention. All studies were published in peer-reviewed journals between 1999 and 2010. In addition, one study was excluded from the analysis due to non-randomised group assignment. See Appendix 12d for further details about the excluded study.

One hormone trial (OWLEY1999[94]) examined indirect effects on motor skills.

[94] See Chapter 6, Section 6.4.5, for direct outcomes from OWLEY1999.

Two nutritional intervention trials (JOHNSON2010, KNIVSBERG2002[95]) examined effects on motor skills as an indirect outcome.

8.6.6 Clinical evidence – effect of biomedical interventions on motor skills

Hormones for motor skills as an indirect outcome

The one included hormone trial (OWLEY1999) compared secretin (porcine secretin) with placebo (see Table 266).

Table 266: Study information table for included trials of hormones for motor skills

	Secretin versus placebo
No. trials (N)	1 (56)
Study IDs	OWLEY1999
Study design	RCT (crossover)
% female	14
Mean age (years)	6.7
IQ	Non-verbal IQ 56.4 (assessed using DAS or MSEL)
Dose/intensity (mg/hours)	2 CU/kg
Setting	Not reported
Length of treatment (weeks)	Single dose
Continuation phase (length and inclusion criteria)	8 (including crossover period but data were extracted only for 4 week period corresponding to the end of the first phase)

Evidence for the effectiveness of secretin on motor skills and the quality of the evidence is presented in Table 267. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 267: Evidence summary table for effects of hormones on motor skills as an indirect outcome

	Secretin versus placebo
Outcome	Fine motor skills
Outcome measure	MSEL/DTVP-2: Fine motor age (months)
Study ID	OWLEY1999
Effect size (CI; p value)	SMD -0.04 (-0.57, 0.48; p = 0.87)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 56
Forest plot	1.24.1; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

[95] See Section 7.4.2 for direct outcomes from JOHNSON2010 and Section 6.4.3 for direct outcomes from KNIVSBERG2002.

There was no evidence for a statistically significant effect of secretin on fine motor skills as an indirect outcome, as measured by the MSEL or DTVP-2 (see Table 267).

Nutritional interventions for motor skills as an indirect outcome

One of the included nutritional intervention trials (JOHNSON2010) compared an omega-3 fatty acid supplement with a healthy-diet control comparator, and the other (KNIVSBERG2002) compared a gluten- and casein-free diet with treatment as usual (see Table 268). See section 8.2.7 for further details about the intervention in JOHNSON2010. In KNIVSBERG2002, a dietician visited parents and provided oral and written information about gluten- and casein-free diets. Parents were also able to contact the dietician by telephone during the trial period.

Table 268: Study information table for included trials of hormones for motor skills

	Omega-3 fatty acids versus healthy diet control	**Gluten-free and casein-free diet versus treatment as usual**
No. trials (N)	1 (23)	1 (20)
Study IDs	JOHNSON2010	KNIVSBERG2002
Study design	RCT	RCT
% female	Not reported	Not reported
Mean age (years)	3.4	7.4
IQ	Not reported	PIQ 82.8 (assessed using the LIPS)
Dose/intensity (mg/hours)	Planned intensity of 400 mg/day (in two daily doses)	Unknown (compliance not recorded)
Setting	Outpatient	Home
Length of treatment (weeks)	13	52
Continuation phase (length and inclusion criteria)	13	52

Evidence for the effectiveness of nutritional interventions on motor skills and the quality of the evidence is presented in Table 269. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 269: Evidence summary table for effects of nutritional interventions on motor skills as an indirect outcome

	Omega-3 fatty acids versus healthy diet control	Gluten-free and casein-free diet versus treatment as usual
Outcome	Fine motor skills	Motor impairment
Outcome measure	MSEL: Fine motor	Movement Assessment Battery for Children: Test of Motor Impairment
Study ID	JOHNSON2010	KNIVSBERG2002
Effect size (CI; p value)	SMD -0.03 (-0.86, 0.79; p = 0.93)	SMD -0.12 (-1.00, 0.76; p = 0.79)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2]	Very low[2,3]
Number of studies/participants	K = 1; N = 23	K = 1; N = 20
Forest plot	1.24.2; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind and unclear/unknown risk of detection bias as identity and blinding of outcome assessors not reported.

There was no evidence for a statistically significant effect of an omega-3 fatty acid supplement on fine motor skills as an indirect outcome, as measured by the MSEL (see Table 269).

There was also no evidence for a statistically significant effect of a gluten-free and casein-free diet on motor impairment as an indirect outcome, as measured by the Movement Assessment Battery for Children (see Table 269).

8.6.7 Clinical evidence summary – effect of interventions on motor skills

There was low quality evidence from a small study of EIBI on motor skills as an indirect outcome that suggested a moderate effect when compared to treatment as usual. There was also low quality evidence from a relatively large study (N = 294) for a moderate effect of LEAP intervention on motor skills as an indirect outcome.

8.6.8 Economic evidence –interventions aimed at motor skills

Systematic literature review

No studies assessing the cost effectiveness of interventions aimed at motor difficulties in children and young people with autism were identified by the systematic search of the economic literature undertaken for this guideline.

Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

8.6.9 From evidence to recommendations – interventions aimed at motor skills

The GDG agreed that the results of the LEAP trial were promising; however, they would need to be replicated by at least one other study and with blinded outcome assessment. Therefore, considered together with the evidence for positive treatment effects on the target outcome of the intervention, a research recommendation was made for a comprehensive psychosocial intervention aimed at the core features of autism (the direct outcome for the LEAP intervention), see research recommendation 6.6.2.1. The GDG reached the decision that there was insufficient evidence on which to make a recommendation about the use of any of the reviewed interventions for motor skills in children and young people with autism.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

8.7 COMMON COEXISTING MENTAL HEALTH PROBLEMS

8.7.1 Introduction

Children and young people with autism of all ages and levels of ability can develop mental health problems and rates of mental health problems are significantly higher in this group than in the general population or other high-risk groups of children (Green et al 2000; Leyfer et al 2006; de Bruin et al 2007; Simonoff et al 2008; Joshi et al., 2010). The *Autism Diagnosis in Children and Young People* guideline (NICE, 2011) identified the following most commonly reported mental health disorders in children and young people: ADHD 41%; anxiety 62%; ODD 7%; OCD 37%; and depression 13%. The UK population-based study by Simonoff et al (2008) of children aged 10 to 14 years, reported that at least 70% of children had one or more comorbid disorders and 41% had two or more.

There are a number of factors contributing to this increased risk. Children with autism are likely to have rigid and inflexible thinking styles, experience problems with social interaction, have difficulties making friends, experience difficulties managing in particular situations and environments, be subject to bullying and lack social awareness and understanding. Many individuals also find changes in their usual routines and everyday activities distressing. Other

features commonly associated with autism such as sensory sensitivities, sleep, feeding and gastrointestinal problems and medical problems such as epilepsy may also impact on the child's mental health, perhaps contributing to heightened levels of anxiety and other behavioural symptoms.

Current practice

The identification and management of a mental health disorder (s) in young people with autism can pose particular challenges because of their difficulties communicating their thoughts and feelings. Information gained from parents/carers and from other settings is especially important for the assessment and identification of co-morbid mental problems since the child's behaviour may be different in different social contexts. For all problems, but especially for emotional disorders, an attempt may be made to elicit personal experiences from the child/young person, using visual aids as appropriate. Although most clinicians in community child health services and other community settings are aware of the need to consider additional mental health problems in children and young people with autism not all professionals have had specific training in the identification of these problems. Indeed standardised diagnostic assessments for mental health disorders such as anxiety and ADHD have not been validated for use in autism. Further, the level of expertise amongst professionals in implementing treatment plans for the management of mental health disorders in children with autism and their families is limited (Madders 2010).

For the most complex presentations, for example a child or young person with severe mental health problems who is not responding to therapeutic interventions or with a possible regression or catatonia presentation, local community-based clinicians may refer to a tertiary (regional) specialist autism team for advice, consultation or a second opinion. In these situations, the regional team usually works in collaboration with local services by providing as appropriate further assessment, investigations and advice about or access to specialised therapeutic provision.

Research studies and policy guidance documents highlight the importance of professional expertise and continuity of care for young people with complex mental health problems, and the importance of early planning for healthcare transition from CAMHS to AMHS (Singh et al., 2010; HMSO, 2009; Department of Health, 2010; Watson et al 2011). However, there is limited research evidence on effective and efficient service models for the delivery of transition of mental health care.

8.7.2 Studies considered – psychosocial interventions aimed at coexisting mental health problems

Nine studies from the search met the eligibility criteria for full-text retrieval. Of these, four trials provided relevant clinical evidence and were included in the review. All four of these studies examined the efficacy of psychosocial

interventions on coexisting anxiety as a direct outcome of the intervention. All studies were published in peer-reviewed journals between 2005 and 2012. In addition, five studies were excluded from the analysis due to non-randomised group assignment or because the paper was a systematic review with no new useable data and any meta-analysis not appropriate to extract. See Appendix 12d for further details about the included and excluded studies.

Four cognitive-behavioural intervention trials (CHALFANT2007, DRAHOTA2011, REAVEN2012 [Reaven et al., 2012], SOFRONOFF2005 [Sofronoff et al., 2005]) examined direct effects on anxiety.

8.7.3 Clinical evidence – effect of psychosocial interventions on coexisting mental health problems

Cognitive-behavioural interventions for anxiety as a direct outcome

All of the included cognitive-behavioural intervention trials (CHALFANT2007, DRAHOTA2011, REAVEN2012, SOFRONOFF2005) compared CBT with treatment as usual (see Table 270). See Section 8.2.3 for further detail about the intervention in DRAHOTA2011.

In CHALFANT2007, the 'Cool Kids' programme (Lyneham et al., 2003) was adapted to meet the needs of children with autism and then applied to target components of anxiety. Topics included recognising the physical symptoms of anxiety, using coping skills such as 'self-talk', simple cognitive restructuring exercises and relapse prevention. Some sessions incorporated the families and involved planning weekly exposure tasks and parents were offered additional sessions and provided with a manual to support their child's learning. Autism-specific adaptations were made to the CBT programme including: extending the intervention over a longer period of time (6 months); using more visual aids and structured worksheets; devoting the most time to relaxation components (three treatment sessions and two booster sessions) and exposure (four and a half treatment sessions and all booster sessions) because they involve more concrete exercises and place less emphasis on the children's communication skills; simplifying the information included in the cognitive therapy component (one and a half treatment sessions and two booster sessions) and providing children with large lists of possible alternative responses to assist them when required to generate their own helpful and unhelpful thoughts.

In REAVEN2012, the intervention 'Facing Your Fears' involved multi-family group sessions that included large-group activities (children and parents together), small-group activities (children together; parents together), and dyadic work (parent/child pairs). CBT techniques were used throughout including emotion regulation, relaxation and graded exposure and children were taught strategies to cope with anxiety, while at the same time offering the opportunity for social skills development through group activities.

Parents attended sessions and the parent component of the intervention included psychoeducation (about anxiety symptoms, CBT strategies and how parenting style can impact upon the child's anxiety) and instruction in how to play a coaching role for their child. Autism-specific adaptations were made to the intervention including: consideration of the pacing of each session; use of a token reinforcement system to reward in-group behaviour; provision of visual structure and predictability of routine; use of multiple-choice worksheets and written examples of core concepts; inclusion of hands-on activities; focus on strengths and special interests; multiple opportunities for repetition and opportunity to practice new skills; the use of video to consolidate learning of concepts; and detailed break-down of the intervention for parents.

Finally, SOFRONOFF2005 was a three-armed trial that included two active intervention arms: child-only CBT and child and parent CBT. In the child-only group-based CBT intervention condition, techniques included group discussion, practice opportunities, the concept of an 'emotional tool box' and social stories and homework assignments. Using these CBT techniques, participants were encouraged to explore positive emotions, feelings of anxiety, and strategies for 'fixing the feeling' including constructive methods to release the energy, expending energy in another way, relaxation, thinking about how other people can help and methods to weigh-up the probability of fears being realised. In the child-only intervention, parents were debriefed on how their child participated and given an outline of the between-session work but otherwise were not involved in the sessions. Conversely, in the child and parent CBT intervention condition, parents were trained as 'co-therapists' and were encouraged to coach their child throughout the different stages of the programme, as well as support with the between-session work. For analysis, the two active intervention arms (child-only and child + parent) were compared and where there were no statistically significant differences data from the two groups were combined and entered into meta-analysis. Where there were significant differences between the two active intervention arms, the intervention condition that was most similar to the other studies in the meta-analysis was selected.

Table 270: Study information table for included trials of cognitive-behavioural interventions for anxiety

	CBT versus treatment as usual
No. trials (N)	4 (217)
Study IDs	(1) CHALFANT2007 (2) DRAHOTA2011 (3) REAVEN2012 (4) SOFRONOFF2005
Study design	(1)-(4) RCT
% female	(1) 26 (2) 33 (3) 4

	(4) 13
Mean age (years)	(1) 10.8 (2) 9.2 (3) 10.4 (4) 10.6
IQ	(1)-(2) Not reported (3) 104.6 (based on previous IQ test or Wechsler Abbreviated Scale of Intelligence) (4) 104.7 (assessed using Short form WISC-III)
Dose/intensity (mg/hours)	(1) Planned intensity of 24 hours (2 hours/week) (group sessions with therapist) (2) 24 hours (1.5 hours/week) (individual sessions) (3) 18 hours (1.5 hours/week) (group sessions) (4) Planned intensity of 12 hours (2 hours/week) (group sessions)
Setting	(1) Clinical (no further information reported) (2) Research setting (no further details reported) (3)-(4) Not reported
Length of treatment (weeks)	(1) 12 (2) 16 (3) 12-16 (4) 6
Continuation phase (length and inclusion criteria)	(1) 12 (2) 29 (including 3-month post-intervention follow-up, but outcome data is for post-intervention only as there is no follow-up data for the control group) (3) 50 weeks (including 16 weeks of intervention, 2 weeks for pre-intervention measures to be obtained and 2-6 weeks following the sessions for the post-intervention measures to be collected, there was also a 3-month and 6-month post-intervention follow-up but data could not be extracted) (4) 12 (including 6-week post-intervention follow-up)

Evidence for the effectiveness of cognitive-behavioural interventions on anxiety and the quality of the evidence is presented in Table 271 and Table 272. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 271: Evidence summary table for effects of cognitive-behavioural interventions on anxiety as a direct outcome

	CBT versus treatment as usual						
Outcome	Positive treatment response		Anxiety	Chronic anxiety	Social anxiety	Separation anxiety	Generalised anxiety
Outcome measure	Number of participants who no longer met DSM-IV criteria for a current primary anxiety disorder	Number of participants who were 'much improved/very improved' on CGI-I	(1) Self-rated (SCAS: total; MASC [child version]: total) (2) Parent-rated (SCAS-P: total; MASC [parent version]: total) (3) Clinician-rated (ADIS-C/P: Clinical Severity Rating [principal anxiety diagnosis])	Revised Children's Manifest Anxiety Scale: Chronic anxiety (trait)	ADIS-P: Social or SCAS-P: Social phobia	ADIS-P: Separation or SCAS-P: Separation Anxiety Disorder	ADIS-P: Generalized or SCAS-P: Generalized Anxiety Disorder
Study ID	(1) CHALFANT2007 (2) DRAHOTA2011	(1) DRAHOTA2011 (2) REAVEN2012	(1) CHALFANT2007 DRAHOTA2011 (2) CHALFANT2007 DRAHOTA2011 SOFRONOFF2005 (3) DRAHOTA2011 REAVEN2012	CHALFANT2007	(1) REAVEN2012 (2) SOFRONOFF2005		
Effect size (CI; p value)	RR 11.82 (3.14, 44.50; p = 0.0003)	RR 7.20 (2.74, 18.91; p <0.0001)	(1) *Self-rated* SMD -1.06 (-1.58, -0.55; p <0.0001) (2) *Parent-rated*	SMD -3.29 (-4.19, -2.38; p <0.00001)	SMD -0.20 (-0.59, 0.20; p = 0.34)	SMD -0.39 (-0.78, 0.01; p = 0.06)	SMD -0.66 (-1.10, -0.22; p = 0.003)

			SMD -0.99 (-1.39, -0.60; p <0.00001) (3) *Clinician-rated* SMD -1.19 (-1.70, -0.68; p <0.00001)				
Heterogeneity (chi²; p value; I²)	Chi² = 1.25, df = 1; p = 0.26; *I²* = 20%	Chi² = 0.18, df = 1; p = 0.67; *I²* = 0%	(1) Chi² = 24.92, df = 1; p <0.00001; *I²* = 96% (2) Chi² = 47.24, df = 2; p <0.00001; *I²* = 96% (3) Chi² = 11.26, df = 1; p = 0.0008; *I²* = 91%	Not applicable	Chi² = 1.54, df = 1; p = 0.21; *I²* = 35%	Chi² = 0.04, df = 1; p = 0.84; *I²* = 0%	Chi² = 1.61, df = 1; p = 0.20; *I²* = 38%
Quality of the evidence (GRADE)	Moderate[1]		(1)-(2) Very low[2,3,4] (3) Very low[3,4]	Low[2,4]	Very low[2,5]		Low[2,4]
Number of studies/participants	K = 2; N = 87	K = 2; N = 83	(1) K = 2; N = 83 (2) K = 3; N = 149 (3) K = 2; N = 79	K = 1; N = 47	K = 2; N = 109		K = 2; N = 87
Forest plot	1.25.1; Appendix 13						

Note. [1]Downgraded due to serious imprecision as number of events<300.
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as self- or parent-reported so outcome assessor non-blind.
[3]Downgraded due to very serious inconsistency – I² value indicates considerable to substantial heterogeneity.
[4]Downgraded due to serious imprecision as N <400.
[5]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 272: Evidence summary table for effects of cognitive-behavioural interventions on anxiety as a direct outcome *(continued)*

	CBT versus treatment as usual						
Outcome	Anxiety relating to a specific phobia	Panic	Fear of personal injury	OCD	Emotional symptoms	Self-directed negative thoughts	Outward-directed negative thoughts
Outcome measure	ADIS-P: Specific phobia	SCAS-P: Panic at: (1) Post-intervention (2) 6-week post-intervention follow-up	SCAS-P: Personal injury at: (1) Post-intervention (2) 6-week post-intervention follow-up	SCAS-P: OCD at: (1) Post-intervention (2) 6-week post-intervention follow-up	SDQ: Internalizing (1) Parent-rated (2) Teacher-rated	CATS: Internalizing	CATS: Hostile intent
Study ID	REAVEN2012	SOFRONOFF2005			CHALFANT2007		
Effect size (CI; p value)	SMD -0.99 (-1.63, -0.36; p = 0.002)	(1) SMD 0.15 (-0.37, 0.68; p = 0.57) (2) SMD -0.13 (-0.65, 0.40; p = 0.64)	(1) SMD 0.20 (-0.32, 0.73; p = 0.45) (2) SMD -0.31 (-0.84, 0.22; p = 0.25)	(1) SMD -0.33 (-0.86, 0.19; p = 0.22) (2) SMD -1.00 (-1.55, -0.45; p = 0.0004)	(1) SMD -4.29 (-5.37, -3.21; p <0.00001) (2) SMD -2.75 (-3.57, -1.93; p <0.00001)	SMD -4.61 (-5.75, -3.48; p <0.00001)	SMD -0.33 (-0.91, 0.26; p = 0.27)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Low[1,2]	Very low[3,4]		(1) Very low[3,4] (2) Low[2,3]	(1) Low[2,3] (2) Low[2,5]	Low[2,3]	Very low[3,4]
Number of studies/participants	K = 1; N = 43	K = 1; N = 66			K = 1; N = 47		
Forest plot	1.25.1; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and risk of detection bias was unclear/unknown as although outcome assessors were blind to treatment allocation the outcome measure was based on interview with parents who were involved in the intervention and not blind to treatment allocation.
[2]Downgraded due to serious imprecision as N <400.

[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as self- or parent-reported so outcome assessor non-blind.
[4]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[5]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and risk of detection bias unclear/unknown as teacher-reported and blinding of teachers not reported.

Meta-analysis with two studies revealed moderate quality evidence for a large and statistically significant positive treatment response of CBT on anxiety as measured by the number of participants who no longer met DSM-IV criteria for an anxiety disorder and by the number of participants who were rated as 'much improved/very improved' on the CGI-I. Participants who received CBT were nearly twelve times more likely to no longer meet DSM-IV criteria for an anxiety disorder, and over seven times more likely to show an improvement in anxiety symptoms, than participants receiving treatment as usual (see Table 271). There was no evidence to suggest heterogeneity of treatment effect, although this is difficult to detect with only two studies.

Meta-analysis with two to three studies also revealed evidence for large and statistically significant effects of CBT on continuous outcome measures of anxiety symptoms as measured by total scores on the self-rated or parent-rated SCAS or MASC and the clinician-rated ADIS-C/P and on the Generalized Anxiety Disorder subscale of the ADIS-P or SCAS-P (see Table 271). However, the confidence in these effect estimates was low to very low due to risk of bias concerns for the self- and parent-rated scales (non-blind outcome assessment), small sample size and inconsistency for the meta-analysis of the total anxiety symptoms scores (considerable to substantial heterogeneity). Note that for the total scores initial comparison of the two active intervention arms in SOFRONOFF2005 revealed no statistically significant differences between child-only and child and parent CBT (SMD 0.25 [-0.33, 0.83], Test for overall effect: $Z = 0.85$, $p = 0.40$), thus combined data was entered into meta-analysis. However, for the Generalized Anxiety Disorder subscale there was a statistically significant difference between the two active intervention arms in favour of the child and parent CBT (SMD 0.76 [0.16, 1.36]; Test for overall effect: $Z = 2.48$, $p = 0.01$). Therefore, data from the two groups could not be combined and data from the child and parent condition was entered into meta-analysis as the other study in the comparison (REAVEN2012) also involved a parent component to the CBT intervention.

There was also single study evidence for large and statistically significant effects of CBT on chronic anxiety as measured by the Revised Children's Manifest Anxiety Scale (see Table 271), on anxiety relating to a specific phobia as measured by the ADIS-P (see Table 272), for a delayed effect of CBT on OCD symptoms at 6-week post-intervention follow-up but not at post-intervention assessment, on emotional symptoms as measured by the parent- and teacher-rated SDQ, and on self-directed negative thoughts as measured by the CATS (see Table 272). However, the quality of this evidence was low due to risk of bias concerns (non-blind parent- or self-rated outcome measures) and small sample size.

Treatment effects were not universally statistically significant, with evidence from two studies for non-significant effects of CBT on the social anxiety and

separation subscales of the ADIS-P or SCAS-P (see Table 271). Note that initial comparison of the two active intervention arms in SOFRONOFF2005 revealed no statistically significant differences between child-only and child and parent CBT (Social anxiety subscale: SMD -0.10 [-0.68, 0.48], Test for overall effect: Z = 0.35, p = 0.73; Separation anxiety subscale SMD 0.42 [-0.17, 1.00], Test for overall effect: Z = 1.39, p = 0.16) so data from the two groups was combined and entered into meta-analysis. There was also evidence from a single study for non-significant effects of CBT (child-only and child and parent groups combined) on panic or fear of personal injury as measured by the SCAS-P, and from another study for non-significant effects of CBT on outward-directed negative thoughts as measured by the CATS (Table 272).

8.7.4 Studies considered – pharmacological interventions aimed at coexisting mental health problems

Four studies from the search met the eligibility criteria for full-text retrieval. Of these, one trial provided relevant clinical evidence and were included in the review and this study examined the efficacy of a pharmacological intervention on coexisting ADHD symptoms as a direct outcome of the intervention and was published in a peer-reviewed journal in 2012. In addition, three studies were excluded from the analysis due to high risk of carry-over given the crossover design, short duration of each phase and lack of any washout in between treatment phases or because the paper was a systematic review with no new useable data and any meta-analysis not appropriate to extract. See Appendix 12d for further details about the included and excluded studies.

One selective noradrenaline reuptake inhibitor (SNRI) trial (ELILILLY2009) examined direct effects on ADHD symptoms.

8.7.5 Clinical evidence – effect of pharmacological interventions on coexisting mental health problems

SNRIs for ADHD as a direct outcome

The SNRI trial (ELILILLY2009) compared atomoxetine with placebo in children with autism (see Table 74).

Table 273: Study information table for included trial of SNRIs for ADHD

	Atomoxetine versus placebo
No. trials (N)	1 (97)
Study IDs	ELILILLY2009
Study design	RCT
% female	14
Mean age (years)	9.9
IQ	92.9 (assessed using the WISC-III)
Dose/intensity (mg/hours)	Planned final dose of 1.2 mg/kg/day
Setting	Not reported

Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	28 weeks (8-week double-blind phase followed by 20-week open-label continuation phase; however, data only extracted for the double-blind phase as no control group data available for open-label continuation)

Evidence for the effectiveness of atomoxetine on ADHD symptoms and the quality of the evidence is presented in Table 274. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was moderate quality evidence for a small and statistically significant effect of atomoxetine on parent-rated ADHD symptoms as measured by the ADHD-RS based on DSM-IV (see Table 274). However, non-significant effects were observed on all teacher-rated subscales of the CTRS-R:S, on the parent-rated hyperactivity subscale of the ABC and on clinician-rated improvement in ADHD symptoms (CGI-ADHD-I). This study found evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo (see Chapter 10, Section 10.3.2, for adverse events associated with SNRIs).

Table 274: Evidence summary table for effects of SNRIs on ADHD symptoms as a direct outcome

	Atomoxetine versus placebo				
Outcome	Hyperactivity	ADHD symptoms	Inattention	Oppositional	Improvement in ADHD symptoms
Outcome measure	(1) Parent-rated (ABC: Hyperactivity and Non-compliance) (2) Teacher-rated (CTRS-R:S: Hyperactivity)	(1) Parent-rated (ADHD-RS: total) (2) Teacher-rated (CTRS-R:S: ADHD)	CTRS-R:S: Cognitive/Attention	CTRS-R:S: Oppositional	CGI-ADHD-I
Study ID	ELILILLY2009				
Effect size (CI; p value)	(1) *Parent-rated* SMD -0.19 (-0.61, 0.22; p = 0.36) (2) *Teacher-rated* SMD -0.12 (-0.59, 0.34; p = 0.60)	(1) *Parent-rated* SMD -0.48 (-0.90, -0.06; p = 0.02) (2) *Teacher-rated* SMD -0.15 (-0.61, 0.31; p = 0.53)	SMD 0.37 (-0.11, 0.84; p = 0.13)	SMD 0.10 (-0.36, 0.56; p = 0.67)	SMD -0.39 (-0.81, 0.03; p = 0.07)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	Low[1]	(1) Moderate[2] (2) Low[1]	Low[1]		
Number of studies/participants	(1) K = 1; N = 88 (2) K = 1; N = 72	(1) K = 1; N = 90 (2) K = 1; N = 72	K = 1; N = 70	K = 1; N = 72	K = 1; N = 89
Forest plot	1.26.1; Appendix 13				

Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[2]Downgraded due to serious imprecision as N <400.

8.7.6 Studies considered – biomedical interventions aimed at coexisting mental health problems

Four studies from the search met the eligibility criteria for full-text retrieval. All four trials provided relevant clinical evidence and were included in the review and these studies examined the efficacy of biomedical interventions on coexisting mental health problems as an indirect outcome. All of the studies were published in a peer-reviewed journal between 2009 and 2011.

Two nutritional intervention trials (JOHNSON2010, WHITELEY2010[96]) examined indirect effects on ADHD symptoms.

Two nutritional intervention trials (BENT2011, JOHNSON2010[97]) examined effects on anxiety as an indirect outcome.

Finally, one medical procedures trial (ADAMS2009A[98]) examined indirect effects on anxiety.

8.7.7 Clinical evidence – effect of biomedical interventions on coexisting mental health problems

Nutritional interventions for ADHD as an indirect outcome

One of the included nutritional intervention trials (JOHNSON2010) compared an omega-3 fatty acid supplement with healthy-diet control, and the other (WHITELEY2010) compared a gluten- and casein-free diet with treatment as usual (see Table 209). See section 8.2.7 for further detail about interventions.

Evidence for the effectiveness of nutritional interventions on ADHD symptoms and the quality of the evidence is presented in Table 275 and Table 276. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 275: Evidence summary table for effects of nutritional interventions (omega-3) on ADHD as an indirect outcome

	Omega-3 fatty acids versus healthy diet control
Outcome	ADHD
Outcome measure	CBCL/1.5-5: ADHD
Study ID	JOHNSON2010
Effect size (CI; p value)	SMD -0.30 (-1.13, 0.53; p = 0.48)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 23

[96] See Section 7.4.2 for direct outcomes from JOHNSON2010 and Section 6.4.5 for direct outcomes from WHITELEY2010.
[97] See Chapter 7, Section 7.4.2, for direct outcomes from BENT2011 and JOHNSON2010.
[98] See Chapter 6, Section 6.4.3, for direct outcomes from ADAMS2009A.

Forest plot	1.27.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of an omega-3 fatty acid supplement (relative to healthy diet control) on ADHD symptoms as an indirect outcome, as measured by the ADHD subscale of the CBCL/1.5-5 (see Table 275). There was also no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo by another trial (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

Table 276: Evidence summary table for effects of nutritional interventions (gluten- and casein-free diet) on ADHD as an indirect outcome

	Gluten- and casein-free diet versus treatment as usual	
Outcome	Inattention	Hyperactivity
Outcome measure	ADHD-RS: Inattention	ADHD-RS: Hyperactivity
Study ID	WHITELEY2010	
Effect size (CI; p value)	SMD -0.59 (-1.13, -0.05; p = 0.03)	SMD -0.50 (-1.04, 0.04; p = 0.07)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1,2]	Very low[1,3]
Number of studies/participants	K = 1; N = 55	
Forest plot	1.27.1; Appendix 13	
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators (parents) and participants were non-blind and high risk of detection bias as parent-reported and non-blind to treatment allocation and other potentially confounding factors. There was also a high risk of attrition bias as over twice as many dropouts in the experimental group relative to the controls (32% in experimental group and 15% in the control group). [2]Downgraded due to serious imprecision as N <400. [3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was single study evidence for a moderate and statistically significant effect of a gluten-free and casein-free diet on the inattention subscale of the ADHD-RS based on DSM-IV, but non-significant effects for the hyperactivity subscale (see Table 276). The confidence in the effect estimate for inattention was low due to risk of bias concerns (non-blind outcome assessment and higher drop-out in the experimental group) and small sample size. This study reported that no participants in either experimental or control groups experienced any adverse events during the trial.

Nutritional interventions for anxiety as an indirect outcome

Both of the included nutritional intervention trials examined effects of an omega-3 fatty acid supplement on anxiety as an indirect outcome, one study (BENT2011) examined effects relative to placebo and one trial (JOHNSON2010) used a healthy-diet control comparator (see Table 209). See section 8.2.7 for further detail about interventions.

Evidence for the effectiveness of nutritional interventions on anxiety and the quality of the evidence is presented in Table 277. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 277: Evidence summary table for effects of nutritional interventions (omega-3) on anxiety as an indirect outcome

	Omega-3 fatty acids versus placebo	**Omega-3 fatty acids versus healthy diet control**
Outcome	Internalizing	Anxiety
Outcome measure	BASC: Internalizing	CBCL/1.5-5 subscales: (1) Internalizing (2) Anxious/Depressed (3) Affective (4) Anxiety
Study ID	BENT2011	JOHNSON2010
Effect size (CI; p value)	SMD -0.48 (-1.30, 0.33; p = 0.24)	(1) SMD -0.17 (-0.99, 0.66; p = 0.69) (2) SMD -0.23 (-1.05, 0.60; p = 0.59) (3) SMD 0.07 (-0.76, 0.89; p = 0.87) (4) SMD -0.16 (-0.99, 0.66; p = 0.70)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	Very low[1,2]
Number of studies/participants	K = 1; N = 24	K = 1; N = 23
Forest plot	1.27.2; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded.		

There was no evidence for a statistically significant effect of omega-3 fatty acid supplements on anxiety as an indirect outcome, as measured by the BASC or the CBCL/1.5-5 (see Table 277). There was also no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared with placebo (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

Medical procedures for anxiety as an indirect outcome

The one included medical procedure trial (ADAMS2009A) compared long-term chelation (seven rounds of DMSA therapy) and short-term chelation (one round of DMSA therapy and six rounds of placebo) (see Table 92). See section 8.2.7 for further detail about intervention.

Evidence for the effectiveness of chelation on anxiety and the quality of the evidence is presented in Table 278. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 278: Evidence summary table for effects of medical procedures on anxiety as an indirect outcome

	Long-term chelation (seven rounds of DMSA therapy) versus short-term chelation (one round of DMSA therapy and six rounds of placebo)
Outcome	Specific fears
Outcome measure	PDDBI: Specific fears
Study ID	ADAMS2009A
Effect size (CI; p value)	SMD -0.11 (-0.75, 0.53; p = 0.74)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 40
Forest plot	1.27.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of chelation on anxiety as an indirect outcome, as measured by the specific fears subscale of the PDDBI (see Table 278). Data could not be extracted from this study for adverse events associated with chelation.

8.7.8 Clinical evidence summary – effect of interventions on coexisting mental health problems

There was no evidence for autism-specific modifications that might be made to the management of coexisting mental health problems, with the exception of anxiety. There was moderate quality evidence from meta-analyses with two studies for large effects of CBT on dichotomous measures of positive treatment response in terms of anxiety disorder diagnoses and symptom improvement on blinded outcome measures.

8.7.9 Economic evidence – interventions aimed at coexisting mental health problems

Systematic literature review

No studies assessing the cost effectiveness of coexisting mental health problems in children and young people with autism were identified by the

systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

Economic modelling

Introduction – objective of economic modelling and interventions assessed

The clinical evidence on interventions aiming at coexisting problems or disorders in children and young people with autism is limited and mostly inconclusive; the only intervention for which there is adequate evidence to indicate that it is clinically effective is CBT for the management of anxiety. Therefore, an economic model was developed to assess the cost effectiveness of CBT relative to wait list (that is, a 'do-nothing' option) for the management of anxiety in children and young people with autism. Wait list was chosen as the comparator in the economic analysis because it was also the comparator in all relevant RCTs included in the guideline systematic review.

Economic modelling methods

Model structure

A simple decision-tree was constructed in order to estimate the cost effectiveness of CBT versus wait list for the management of anxiety in children and young people with autism. According to the model structure, hypothetical cohorts of children and young people with autism and coexisting anxiety received either CBT for 12 weeks or were included in a wait list. At the end of the 12 weeks children and young people either remained anxious, or they recovered and no longer met criteria for an anxiety disorder. Children and young people that recovered could either relapse over the following 26 weeks, meeting again criteria for an anxiety disorder, or remain free from anxiety symptoms. Children and young people that were anxious at the end of the first 12 weeks (that is, at completion of treatment) were conservatively assumed to remain anxious over the next 26 weeks. The time horizon of the model was 38 weeks (12 weeks of treatment and 26 weeks of follow-up). The duration of treatment was consistent with the duration of treatment in the RCTs that provided clinical data for the economic analysis. A schematic diagram of the decision-tree is presented in Figure 4.

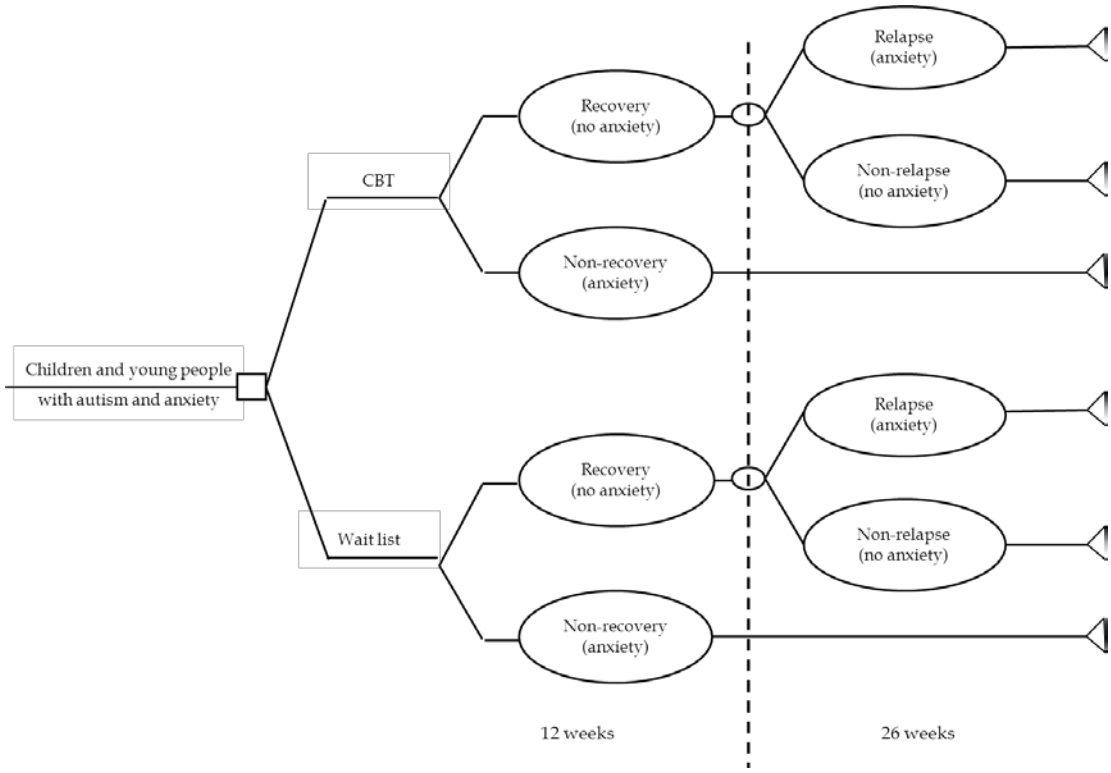
The economic analyses adopted the perspective of the NHS and personal social services, as recommended by NICE (NICE 2012, The Guidelines Manual). Costs consisted of intervention costs only, as no information on costs incurred by children and young people with autism due to coexisting anxiety were identified in the relevant literature. The measure of outcome was the quality adjusted life year (QALY).

Costs and outcomes considered in the analysis

The economic analyses adopted the perspective of the NHS and personal social services, as recommended by NICE (NICE 2012, The Guidelines

Manual). Costs consisted of intervention costs only, as no information on costs incurred by children and young people with autism due to coexisting anxiety were identified in the relevant literature. The measure of outcome was the quality adjusted life year (QALY).

Figure 4. Schematic diagram of the structure of the economic model evaluating CBT compared with waitlist for the management of anxiety in children and young people with autism



Clinical input parameters of the economic model

Clinical input parameters included the probability of not recovering from anxiety under waitlist at 12 weeks, the risk ratio of not recovering from anxiety of CBT versus wait list, and the 6-month (26-week) probability of relapse after recovering from anxiety.

Out of the 4 studies assessing CBT versus wait list for the management of anxiety in children and young people with autism that were included in the guideline systematic review (CHALFANT2007, DRAHOTA2011, REAVEN2012, SOFRONOFF2005), 2 studies (CHALFANT2007 and DRAHOTA2011) reported the rates of children and young people with autism that no longer met criteria for diagnosis of an anxiety disorder at treatment completion. Pooled weighted data from the wait list arms of these 2 trials were used to estimate the probability of not recovering from anxiety under

wait list at 12 weeks that was utilised in the model. The risk ratio of not recovering from anxiety of CBT versus wait list was derived from meta-analysis of data reported in the 2 studies.

The 6-month probability of relapse after recovering from anxiety for children and young people with autism was based on assumption, due to lack of relevant data in the literature. The same probability was conservatively applied in both arms of the economic model.

Utility data for estimation of QALYs

The systematic search of the literature identified one study reporting utility data for different levels of anxiety in children and young people with autism (Tilford et al., 2012). The study reported utility values for children with autism and no anxiety as well as children with autism and 3 different levels of anxiety, that is, mild, moderate and severe, based on HUI3 profiles. The economic model assumed that at the initiation of treatment the HRQoL of children and young people with autism and anxiety corresponded to the utility score of 'moderate anxiety'; children and young people with autism that no longer met diagnostic criteria for anxiety at treatment completion reached the utility score of 'no anxiety', while those who did not recover retained a utility score corresponding to 'moderate anxiety'. Children and young people who relapsed following recovery were assumed to return to the utility score of 'moderate anxiety'. All changes in utility from treatment initiation to treatment completion and from treatment completion to end of follow-up were assumed to occur linearly.

The findings of the systematic literature review of utility scores for children and young people with autism are reported in the economic modelling section in Chapter 7 (section 7.5).

Cost data

The intervention cost of CBT was calculated by combining relevant resource use (based on data reported in the four RCTs included in the guideline systematic review) with the respective national unit cost of CBT (Curtis, 2012). Table 279 presents the details of resource use (mode of delivery, number of sessions, duration of each session, number of children and therapists in group-delivered CBT) reported in each trial, and the respective total intervention costs, estimated using a unit cost of CBT of £113 per hour of face-to-face contact in 2012 prices (Curtis 2012). It can be seen that three of the trials included in the review assessed group-based CBT, and one trial assessed individual CBT. As reported above, the economic model utilised efficacy data from meta-analysis of CHALFANT2007 (group CBT) and DRAHOTA2011 (individual CBT), and therefore the economic analysis considered intervention costs associated with resource use reported in these two trials.

The intervention cost of wait list was zero. Costs incurred by anxiety symptoms were assumed to be zero due to lack of relevant data, but it is possible that the presence of anxiety in children and young people with autism incurs extra health and social care costs.

Table 280 presents the values of all input parameters utilised in the economic model. As the time horizon of the analysis was 38 weeks, no discounting was necessary.

Handling uncertainty

Model input parameters were utilised in a *probabilistic* analysis, as described in the economic modelling section of Chapter 7 (Section 7.5). The probability of not recovering from anxiety at completion of treatment (12 weeks) with wait list was assigned a beta distribution. Beta distributions were also assigned to utility values, using the method of moments. The risk ratio of not recovering from anxiety for CBT versus wait list was assigned a log-normal distribution. The estimation of distribution ranges was based on the guideline meta-analysis and available data in the published sources of evidence.

The intervention cost of CBT was not assigned a distribution. The cost of group CBT was deemed to be stable and not subject to uncertainty, irrespective of the child's or young person's compliance with therapy; this is because participants in a group are not replaced by another person when they occasionally miss one or more sessions or discontinue treatment. Therefore the same resources (in terms of healthcare professional time) are consumed and the full cost of therapy is incurred regardless of whether people attend the full course of treatment or a lower number of group sessions. Regarding the uncertainty around the intervention cost of individual CBT, this was examined in one-way sensitivity analysis, as described below.

Table 280 provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

Deterministic analysis, where data are analysed as point estimates using the mean value of each parameter, was also undertaken in order to explore alternative scenarios and assumptions in one-way sensitivity analysis. The following alternative scenarios were tested in one-way sensitivity analysis:

a. The intervention cost of individual CBT was reduced by 50%
b. The 6-month probability of relapse for CBT and wait list was assumed to be zero and 0.50, respectively.

Results are presented as the ICER of CBT versus wait list, expressing the additional cost per QALY gained associated with provision of CBT in children and young people with autism and coexisting anxiety. In addition, the probability of CBT being cost-effective at the NICE cost effectiveness

threshold of £20,000-£30,000/QALY (NICE 2008, social value judgments) is reported.

Table 279: Resource use data reported in RCTs assessing CBT for the management of anxiety in children and young people with autism and respective intervention costs

Study ID	*Mode of delivery*	*Number of sessions*	*Duration of each session (minutes)*	*Number of children per group*	*Number of therapists per group*	*Total cost per child (2012 prices)**
CHALFANT2007	Group	12	120	7	1	£387
REAVEN2012	Group	12	90	4	1	£509
SOFRONOFF2005	Group	6	120	3	2	£904
DRAHOTA2011	individual	16	90	1	1	£2,712
*based on a national unit cost of CBT equalling £113 per hour of face-to-face contact (Curtis 2012)						

Table 280: Input parameters utilised in the economic model of CBT versus wait list for the management of anxiety in children and young people with autism

Input parameter	*Deterministic value*	*Probabilistic distribution*	*Source of data – comments*
Clinical input parameters		**Beta distribution**	Pooled weighed rate for wait list, guideline meta-analysis
Probability of not recovering from anxiety at end of treatment – wait list	0.952	α= 40, β= 2	
		Log-normal distribution	Guideline meta-analysis
Risk ratio of not recovering from anxiety, CBT versus wait list	0.40	95% CIs: 0.23 to 0.68	
	0.20	**Beta distribution**	Assumption
Probability of relapse at 6 months' follow up		α= 20, β= 80	
Utility scores		**Beta distribution**	Tilford et al., 2012; based on method of moments. Utility score for 'no anxiety' not allowed to fall below that for 'moderate anxiety'
No anxiety	0.72	α= 21, β= 8	
Moderate anxiety	0.65	α= 30, β= 16	
Cost data		**No distributions assigned**	Based on resource use reported in RCTs included in the guideline systematic review (see Table 185) and the unit cost of CBT (Curtis 2012)
Group-based CBT intervention cost	£387		
Individual CBT intervention cost	£2,712		
Wait list intervention cost	£0		

Validation of the economic model

The economic model (including the conceptual model and the excel spreadsheet) was developed by the guideline health economist and checked by a second modeller not working on the guideline. The model was tested for logical consistency by setting input parameters to null and extreme values and examining whether results changed in the expected direction. The results were discussed with the GDG for their plausibility.

Results

Over the 38 weeks of the analysis, provision of CBT resulted in 2.79 additional QALYs per 100 children and young people with autism and coexisting anxiety, compared with waitlist. Individual CBT was dominated by group CBT, as it provided the same benefit at a higher cost. The ICER of group CBT versus wait list was £13,910/QALY, which is well below the NICE lower cost-effectiveness threshold of £20,000/QALY. However, the ICER of individual CBT versus wait list was £97,367/QALY. Full results are presented in Table 281.

Table 281: Results of probabilistic economic analysis of CBT for the management of anxiety in children and young people with autism – mean costs and QALYs for 100 children and young people with autism receiving treatment

Intervention	*Mean total cost*	*Mean total QALYs*	*ICER versus wait list*
Group CBT	£38,743	50.36	£13,910/QALY
Individual CBT	£271,200	50.36	£97,367/QALY
Wait list	£0	47.57	N/A

The probability of group CBT being cost-effective relative to wait list at the NICE lower (£20,000/QALY) and upper (£30,000/QALY) cost effectiveness threshold was 0.53 and 0.62, respectively. The probability of individual CBT being cost-effective relative to wait list at the two NICE thresholds (lower and upper) was 0 and 0.03, respectively.

According to the deterministic analysis, the ICERs of group CBT and individual CBT versus wait list were £17,131/QALY and £119,918/QALY, respectively. One-way sensitivity analysis showed that if the intervention cost of individual CBT was reduced by 50%, its ICER versus wait list would fall at £59,959/QALY. If the 6-month probability of relapse was zero for CBT and 0.50 for wait list, then the ICER for group CBT and individual CBT would reach £15,477/QALY and £108,341/QALY, respectively.

Discussion of findings – limitations of the analysis

The results of the economic model indicate that group CBT is likely to be a cost-effective intervention for the management of anxiety in children and young people

with autism; individual CBT, on the other hand, does not appear to be a cost-effective treatment option. The model assumed the same efficacy for both group and individual CBT, using the results of the guideline meta-analysis. It must be noted that the individual study data did not show any potential advantage for individual CBT over group-CBT in terms of clinical effectiveness (risk ratio of non-recovery versus wait list, CHALFANT2007 – group CBT: 0.30 [95% CI 0.17 to 0.53]; DRAHOTA2011 – individual CBT: 0.52 [95% CI 0.31 to 0.87]). This means that individual CBT is dominated by group CBT, as it provides the same benefit at an extra cost, and should not be considered further in incremental analysis. However, the ICER of individual CBT versus wait list was estimated because there may be instances where group CBT is not available or not appropriate for some sub-populations, and individual CBT may be the only treatment option to offer.

The economic analysis utilised dichotomous clinical data from 2 RCTs (out of the 4 included in the respective guideline systematic review) that reported rates of children no longer meeting diagnostic criteria for an anxiety disorder following treatment. The total number of participants in the 2 trials was small (N = 87). No long-term appropriate follow-up data were available to populate the economic model, and therefore the 6-month probability of relapse following recovery from anxiety was based on an assumption. However, 3 of the RCTs included in the guideline systematic review (DRAHOTA2011, REAVEN2012, SOFRONOFF2005) reported that the treatment effect was retained or further improved over 6 weeks to 6 months post-treatment which is consistent with the model structure and the assumption that only a part of children and young people that recovered from anxiety post-treatment relapsed after 6 months.

Estimation of QALYs was based on utility data derived from HUI3 responses of parents of children with autism in the US; utility scores for HUI3 have been elicited from members of the Canadian general population and therefore they are not directly applicable to the UK context. More importantly, HUI3 has not been designed for use in children, and the GDG judged that it is not directly relevant to children and young people with autism (as some items are not related to autism symptoms) and not adequately sensitive to capture small changes in the HRQoL of this population. Ideally an alternative utility measure should be used for the estimation of QALYs, but at the moment no such measure designed specifically for children and young people with autism is available.

The economic model assumed that the presence of coexisting anxiety in children and young people with autism bears no extra costs, due to lack of any relevant data. However, this may not be the case; if the presence of anxiety does incur extra costs to health, social and, possibly, educational services, then part of (or all) the intervention cost of CBT could be offset, meaning that the cost effectiveness of CBT may be higher than that estimated by the guideline economic analysis. It is also likely that the presence of anxiety in this population incurs extra intangible as well as informal care costs to the family, which have not been taken into account in the economic analysis.

Overall conclusion from economic modelling

Taking into account the results and limitations of the analysis, it appears that group-CBT is likely to be a cost-effective intervention for the management of anxiety in children and young people with autism, but this is not likely for individual CBT.

8.7.10 From evidence to recommendations – interventions aimed at coexisting mental health problems

In the absence of evidence of how coexisting mental health disorders (including ADHD, OCD, post-traumatic stress disorder, depression and conduct disorder) should be treated differently in autism, the GDG agreed that management should be in line with existing NICE guidance. There was, however, evidence for clinical efficacy of CBT programmes with autism-specific modifications on coexisting anxiety for children with autism. There was evidence for a positive treatment response to CBT in terms of no longer meeting diagnostic criteria for the anxiety disorder and/or showing global improvement in anxiety symptoms. Economic analysis suggested that group-based CBT is likely to be a cost-effective intervention for the management of anxiety in children and young people with autism, whereas, individual CBT is probably not cost-effective. However, the GDG were concerned that for some individuals with autism participating in a group-based intervention would be difficult or impossible, therefore, the GDG agreed that it was important that for these children or young people individual-based CBT could be considered. The GDG recognised that CBT may not be appropriate for individuals with coexisting learning disabilities given that the intervention dictates a certain level of cognitive functioning and verbal ability to enable participation.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

8.7.11 Recommendations – interventions aimed at coexisting mental health problems

Clinical practice recommendations

8.7.11.1 Offer psychosocial and pharmacological interventions for the management of coexisting mental health or medical problems in children and young people with autism in line with NICE guidance for children and young people, including:

- Attention deficit hyperactivity disorder (ADHD) (NICE clinical guideline 72)
- Conduct disorders in children and young people (NICE clinical guideline 158)
- Constipation in children and young people (NICE clinical guideline 99)

- Depression in children and young people (NICE clinical guideline 28)
- Epilepsy (NICE clinical guideline 137)
- Obsessive-compulsive disorder (OCD) and body dysmorphic disorder (BDD) (NICE clinical guideline 31)
- Post-traumatic stress disorder (PTSD) (NICE clinical guideline 26).

8.7.11.2 Consider the following for children and young people with autism and anxiety who have the verbal and cognitive ability to engage in a cognitive behavioural therapy (CBT) intervention:

- group CBT adjusted to the needs of children and young people with autism
- individual CBT for children and young people who find group-based activities difficult.

8.7.11.3 Consider adapting the method of delivery of CBT for children and young people with autism and anxiety to include:

- emotion recognition training
- greater use of written and visual information and structured worksheets
- a more cognitively concrete and structured approach
- simplified cognitive activities, for example, multiple-choice worksheets
- involving a parent or carer to support the implementation of the intervention, for example, involving them in therapy sessions
- maintaining attention by offering regular breaks
- incorporating the child or young person's special interests into therapy if possible.

Research recommendations

8.7.11.4 What is the comparative clinical and cost effectiveness of pharmacological and psychosocial interventions for anxiety disorders in children and young people with autism?

8.8 COMMON MEDICAL AND FUNCTIONAL PROBLEMS

8.8.1 Introduction

Conditions that may be associated with neurological injury or dysfunction and autism or autistic-like features, for example:

- Epilepsy and epileptic encephalopathy
- Neurometabolic disorders such as phenylketonuria, mitochondrial disorders
- Tuberous sclerosis
- Muscular dystrophy

- Neurofibromatosis
- Hydrocephalus
- Cerebral Palsy
- Foetal alcohol spectrum disorder
- Teratogens such as valproate in pregnancy
- Prematurity
- Vision impairment

Certain genetic conditions may be associated with autism.

- Chromosome disorders
- Commonly recognised genetic abnormalities including Fragile X
- Less commonly recognised or uncertain genetic features including micro duplications deletions or copy number variants such as may be detected with array comparative genomic hybridisation (CGH).

The above medical disorders also constitute risk factors for autism. Diagnosis of coexisting medical disorders is to be found in the *Autism Diagnosis in Children and Young People* guideline (NICE, 2011). Management of any coexisting medical conditions such as epilepsy follows expected treatment pathways but may be made more complex by the presence of autism. Diagnosis and management of epilepsy is covered by *The Epilepsies* NICE guideline (NICE, 2012b). Epilepsy commonly coexists with autism and is especially associated with intellectual disability and reduced verbal skills (Bolton et al, 2011). Early onset epilepsy constitutes a particular risk for autism.

Functional problems and disorders associated with autism

The majority of individuals with autism experience functional problems at some time. These may be chronic, episodic or recurrent and have a significant impact on the individual's health, activity and social participation and an impact on their family and others with caring responsibilities. Functional problems include:

- feeding problems including restricted diets and PICA
- constipation, altered bowel habit, faecal incontinence or encopresis
- sleep disturbances

Functional difficulties and clinical practice

Feeding difficulties, restricted diets, adherence to sameness in appearance, taste, smell and texture are common in autism. Huge distress is caused to families by eating problems and occasionally nutrition is severely compromised. There is variable access to specialist services for children with feeding problems. Common approaches usually involve treatment strategies that combine psychosocial interventions along with dietary advice and support.

Problems with sleep, including difficulties with sleep onset, frequent waking and overall sleep duration, are reported in between 40 to 86% of children with autism.

One recent population-based cohort study of sleep problems in children aged 7-9 years and 11-13 years (Sivertsen, 2012) found that the prevalence of 'chronic insomnia' in children identified as having 'autism spectrum problems' was more than ten times greater than in controls; sleep problems were also more persistent over time. In a longitudinal study, children with autism (aged from 30 months to 11 years) were found to sleep for 15 to 45 minutes less each day when compared with contemporary controls (Humphreys et al., 2010). A significant difference (mostly in night time sleep) was apparent from 30 months, and continued through to early adolescence. A further study (of children aged 4 and 10 years) found that more than half of the families of children with autism (57.6%) voiced sleep concerns, including long sleep latencies, frequent night wakings, sleep terrors, and early risings. Only 12.5% families of typically-developing controls reported sleep concerns (Souders, 2009). Malow (2006), using objective actigraphy measurements, also found that children with autism took longer to fall asleep, were more active and had the longest duration of a wake episode compared with typically-developing controls.

Treatment advice commonly follows the behavioural principles applied to all children with sleep disturbances, that is, appropriate sleeping environment and good sleep hygiene. In those whose difficulties persist, medical treatment using melatonin is often considered and used in combination with these strategies. It is accepted that the effectiveness of this treatment can be variable and should be reviewed for each individual.

Increased rates of gastrointestinal symptoms (from 22 to 70%) are reported in autism. This variability in estimates may depend on the sample; the age, definition and number of symptoms; the method of investigation employed and whether symptoms are current or life-time. The gastro- intestinal symptoms most commonly reported are diarrhoea, constipation, and abdominal discomfort or pain. Some children with autism have particularly persistent symptoms and are over represented in, for example, clinics for constipation (Pang & Croaker, 2011) Gastrointestinal symptoms tend to be more marked in younger children with poorer expressive language and greater social impairment (Gorrindo et al., 2012). No evidence has been found for an enterocolitis specific to autism (Buie et al., 2010a). Usual investigation and treatment of gastrointestinal symptoms is recommended (Buie et al., 2010b).

8.8.2 Studies considered – psychosocial and pharmacological interventions aimed at coexisting medical or functional problems

Nine studies from the search met the eligibility criteria for full-text retrieval. Of these, three trials provided relevant clinical evidence and were included in the review, two of these studies examined the efficacy of psychosocial and/or pharmacological interventions on coexisting sleep problems as a direct outcome (target of the intervention), and one study examined effects on sleep problems as an indirect outcome. All studies were published in peer-reviewed journals between 2009 and 2012. In addition, six studies were excluded from the analysis. The most

common reason for exclusion was that the paper was a systematic review with no new useable data and any meta-analysis not appropriate to extract. See Appendix 12d for further details about the included and excluded studies.

One four-armed trial (CORTESI2012 [Cortesi et al., 2012]) compared CBT, melatonin, and COMB to placebo and examined direct effects on sleep problems. Another trial (GRINGRAS2012 [Gringras et al., 2012]) also compared melatonin to placebo and examined effects on sleep problems as a direct outcome.

Finally, one SNRI trial (ELILILLY2009) examined effects on sleep problems as an indirect outcome.

8.8.3 Clinical evidence – effect of psychosocial and pharmacological interventions on coexisting medical or functional problems

Cognitive-behavioural intervention for sleep problems as a direct outcome

The one included trial (CORTESI2012) that involved a cognitive-behavioural intervention arm (amongst two other active intervention arms) compared CBT with placebo (see Table 282). The CBT intervention comprised cognitive, behavioural and educational components and was delivered to families, with the focus of reducing insomnia in children. The cognitive component focused on addressing maladaptive beliefs/attitudes about sleep, while the behavioural and educational components included instructions around managing the child's sleep and methods of implementing healthy sleep behaviours to replace poor habits. Instructions included monitoring length and frequency of naps, encouraging children to remain in their own bed the whole night and engaging in fun pre-bedtime activities before the child was required to go to sleep. Following completion of the initial CBT course, maintenance sessions continued for the duration of the study to continue to consolidate treatment strategies.

Table 282: Study information table for included trial of CBT for sleep problems

	CBT versus placebo
No. trials (N)	1 (80)
Study IDs	CORTESI2012
Study design	RCT
% female	16.5
Mean age (years)	6.7
IQ	Not reported
Dose/intensity (mg/hours)	CBT: Families received four, weekly CBT sessions of 50 minutes. A total of 3.3 hours. (Following the four sessions, families were also offered twice-monthly, 'individually tailored' sessions, but duration on these sessions was not reported). Placebo: Participants received 3 mg of the placebo formulation, once a day in the evening for 12 weeks.

Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for the effectiveness of CBT on sleep problems and the quality of the evidence is presented in Table 283. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 283: Evidence summary table for effects of CBT on sleep problems as a direct outcome

	CBT versus placebo			
Outcome	Sleep problems	Positive sleep behaviour	Sleep problems	Positive treatment response
Outcome measure	Actigraph: (1) Sleep onset latency (2) Wake after sleep onset (3) Nap time (4) Bedtime	Actigraph: (1) Total sleep time (2) Sleep efficiency	CSHQ: (1) Total score (2) Bedtime resistance (3) Sleep onset delay (4) Sleep anxiety (5) Night-wakings (6) Sleep duration (7) Parasomnias (8) Sleep-disordered breathing (9) Daytime sleepiness	(1) Sleep onset latency: Number of participants who showed sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on actigraph data (2) Sleep efficiency: Number of participants who showed ≥85% for sleep efficiency based on actigraph data
Study ID	CORTESI2012			
Effect size (CI; p value)	(1) SMD -0.68 (-1.18, -0.18; p = 0.008) (2) SMD -0.24 (-0.73, 0.24; p = 0.33) (3) SMD -0.81 (-1.32, -0.30; p = 0.002) (4) SMD -0.89 (-1.40, -0.38; p = 0.0006)	(1) SMD 0.62 (0.12, 1.12; p = 0.01) (2) SMD 1.98 (1.38, 2.58; p <0.00001)	(1) SMD -1.01 (-1.53, -0.50; p = 0.0001) (2) SMD -1.18 (-1.71, -0.65; p <0.0001) (3) SMD -0.94 (-1.45, -0.42; p = 0.0003) (4) SMD -0.43 (-0.92, 0.06; p = 0.09) (5) SMD -0.84 (-1.34, -0.33; p = 0.001) (6) SMD 0.23 (-0.26, 0.71; p = 0.36)	(1) RR 6.79 (0.36, 126.50; p = 0.20) (2) RR 6.79 (0.36, 126.50; p = 0.20)

			(7) SMD 0.34 (-0.15, 0.83; p = 0.18) (8) SMD 0.00 (-0.49, 0.49; p = 1.00) (9) SMD -0.50 (-1.00, -0.01; p = 0.05)	
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	(1) Moderate[1] (2) Low[2] (3)-(4) Moderate[1]	Moderate[1]	(1)-(3) Low[1,3] (4) Very low[2,3] (5) Low[1,3] (6)-(7) Very low[2,3] (8)-(9) Low[1,3]	Low[4]
Number of studies/participants	K = 1; N = 65			
Forest plot	1.28.1; Appendix 13			

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as parent-completed and parents non-blind and involved in the intervention.
[4]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

There was single study moderate quality evidence for large and statistically significant effects of CBT (relative to placebo pill) on nap time, bedtime, and sleep efficiency, and moderate and statistically significant effects on sleep onset latency and total sleep time as measured by actigraph. The only non-significant subscale for continuous actigraph data was for wake after sleep onset. However, dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency were also non-significant (see Table 283).

There was also single study evidence for large and statistically effects of CBT (relative to placebo pill) on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, and night-wakings), and for a moderate and statistically significant effect on the daytime sleepiness subscale of the CSHQ. However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size. Non-significant effects were observed for the sleep anxiety, sleep duration, parasomnias, and sleep-disordered breathing subscales of the CSHQ (see Table 283).

Melatonin for sleep problems as a direct outcome

Two of the included trials (CORTESI2012, GRINGRAS2012) compared melatonin with placebo. However, the data from the two studies could not be combined in meta-analysis due to differences in population (in the GRINGRAS2012 trial participants were treatment resistant to a psychosocial sleep hygiene programme

[used as a run-in] but this was not the case for CORTESI2012 where a psychosocial intervention was included as an active intervention arm). There were also differences in the melatonin formulation across the two trials (controlled release in CORTESI2012 and immediate release in GRINGRAS2012). Note that in the published trial report for GRINGRAS2012 a mixed autism and developmental disabilities sample was included. However, as this sample did not meet the review inclusion criteria of >50% of the population having a diagnosis of autism, autism-only disaggregated unpublished data was requested and supplied by the author (see Table 284). Unfortunately, due to the subsequently smaller size of the sample actigraph data could not be extracted from GRINGRAS2012 as there were less than ten participants per arm.

CORTESI2012 also included a comparison of melatonin and CBT (see Table 284). See above for details of the CBT intervention.

Table 284: Study information table for included trials of melatonin for sleep problems

	Melatonin versus placebo		**Melatonin versus CBT**
No. trials (N)	1 (80)	1 (63)	1 (80)
Study IDs	CORTESI2012	GRINGRAS2012	CORTESI2012
Study design	RCT	RCT	RCT
% female	17	29	17.5
Mean age (years)	6.6	8.7	7.0
IQ	Not reported	Not reported	Not reported
Dose/intensity (mg/hours)	3 mg/day of melatonin or placebo. Formulation included 1 mg fast-release and 2 mg slow-release melatonin	Planned intensity of initial dose of 0.5 mg at randomisation, increased every week for four weeks (if necessary) in three dose increments: 2 mg, 6 mg to a maximum of 12 mg. Formulation was immediate-release	Melatonin: 3 mg/day. Formulation included 1 mg fast-release and 2 mg slow-release melatonin CBT: Families received four, weekly CBT sessions of 50 minutes. A total of 3.3 hours. (Following the four sessions, families were also offered twice-monthly, 'individually tailored' sessions, but duration on these sessions was not reported).
Setting	Outpatient	Outpatient	Outpatient
Length of treatment (weeks)	12	12	12
Continuation phase (length and inclusion criteria)	12	12	12

Evidence for the effectiveness of melatonin on sleep problems and the quality of the evidence is presented in Table 285 and Table 286. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was single study moderate quality evidence from CORTESI2012 for large and statistically significant effects of melatonin (relative to placebo) on sleep onset latency, wake after sleep onset, bedtime, total sleep time, and sleep efficiency, and a moderate and statistically significant effect on nap time, as measured by actigraph. There was also evidence for large and statistically significant effects of melatonin on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received melatonin being over 25 times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving placebo, and participants receiving melatonin were over 31 times more likely to show at least 85% for sleep efficiency than participants who received placebo (see Table 285).

There was also moderate quality evidence from CORTESI2012 for large and statistically effects of melatonin (relative to placebo) on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, night-wakings, and sleep duration), and for a moderate and statistically significant effect on the daytime sleepiness subscale of the CSHQ. Non-significant effects were observed for the sleep anxiety, parasomnias, and sleep-disordered breathing subscales of the CSHQ (see Table 285).

Finally, there was moderate quality data from GRINGRAS2012 for a large and statistically significant effect of melatonin (relative to placebo) on sleep onset latency as measured by sleep diary. However, effects on total sleep time were non-significant (see Table 285).

Table 285: Evidence summary table for effects of melatonin (versus placebo) on sleep problems as a direct outcome

	Melatonin versus placebo					
Outcome	Sleep problems	Positive sleep behaviour	Sleep problems	Sleep onset latency	Total sleep time	Positive treatment response
Outcome measure	Actigraph: (1) Sleep onset latency (2) Wake after sleep onset (3) Nap time (4) Bedtime	Actigraph: (1) Total sleep time (2) Sleep efficiency	CSHQ: (1) Total score (2) Bedtime resistance (3) Sleep onset delay (4) Sleep anxiety (5) Night-wakings (6) Sleep duration (7) Parasomnias (8) Sleep-disordered breathing (9) Daytime sleepiness	Sleep diary: Sleep onset latency	Sleep diary: total sleep time	(1) Sleep onset latency: Number of participants who showed sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on actigraph data (2) Sleep efficiency: Number of participants who showed ≥85% for sleep efficiency based on actigraph data
Study ID	CORTESI2012			GRINGRAS2012		CORTESI2012
Effect size (CI; p value)	(1) *Sleep onset latency* SMD -1.23 (-1.75, -0.70; p <0.00001) (2) *Wake after sleep onset* SMD -0.82 (-1.32, -0.31; p = 0.001) (3) *Nap time* SMD -0.57 (-1.06, -0.08; p = 0.02) (4) *Bedtime* SMD	(1) *Total sleep time* SMD 1.45 (0.90, 1.99; p <0.00001) (2) *Sleep efficiency* SMD 2.47 (1.82, 3.12; p <0.00001)	(1) *Total score* SMD -1.81 (-2.39, -1.23; p <0.00001) (2) *Bedtime resistance* SMD -1.72 (-2.29, -1.15; p <0.00001) (3) *Sleep onset delay* SMD -1.58 (-2.14, -1.03; p <0.00001) (4) *Sleep anxiety* SMD -0.37 (-0.86,	SMD -0.76 (-1.35, -0.18; p = 0.01)	SMD 0.15 (-0.43, 0.72; p = 0.62)	(1) *Sleep onset latency* RR 25.46 (1.58, 411.30; p = 0.02) (2) *Sleep efficiency* RR 31.11 (1.94, 498.04; p = 0.02)

	-1.08 (-1.60, -0.56; p <0.0001)		0.12; p = 0.14) (5) *Night-wakings* SMD -2.88 (-3.58, -2.18; p <0.00001) (6) *Sleep duration* SMD -1.39 (-1.93, -0.85; p <0.00001) (7) *Parasomnias* SMD 0.11 (-0.37, 0.60; p = 0.65) (8) *Sleep-disordered breathing* SMD -0.11 (-0.59, 0.38; p = 0.66) (9) *Daytime sleepiness* SMD -0.72 (-1.21, -0.22; p = 0.005)			
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Moderate[1]		(1)-(3) Moderate[1] (4) Low[2] (5)-(6) Moderate[1] (7)-(8) Low[2] (9) Moderate[1]	Moderate[1]	Low[2]	Moderate[3]
Number of studies/participants	K = 1; N = 66			K = 1; N = 49	K = 1; N = 47	K = 1; N = 66
Forest plot	1.28.2; Appendix 13					
Note. [1]Downgraded due to serious imprecision as N <400. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5). [3]Downgraded due to serious imprecision as number of events <300.						

Table 286: Evidence summary table for effects of melatonin (relative to CBT) on sleep problems as a direct outcome

	Melatonin versus CBT			
Outcome	Sleep problems	Positive sleep behaviour	Sleep problems	Positive treatment response
Outcome measure	Actigraph: (1) Sleep onset latency (2) Wake after sleep onset (3) Nap time (4) Bedtime	Actigraph: (1) Total sleep time (2) Sleep efficiency	CSHQ: (1) Total score (2) Bedtime resistance (3) Sleep onset delay (4) Sleep anxiety (5) Night-wakings (6) Sleep duration (7) Parasomnias (8) Sleep-disordered breathing (9) Daytime sleepiness	(1) Sleep onset latency: Number of participants who showed sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on actigraph data (2) Sleep efficiency: Number of participants who showed ≥85% for sleep efficiency based on actigraph data
Study ID	CORTESI2012			
Effect size (CI; p value)	(1) *Sleep onset latency* SMD -0.54 (-1.03, -0.05; p = 0.03) (2) *Wake after sleep onset* SMD -0.73 (-1.22, -0.23; p = 0.004) (3) *Nap time* SMD 0.16 (-0.32, 0.64; p = 0.51) (4) *Bedtime* SMD -0.23 (-0.71, 0.25; p = 0.34)	(1) *Total sleep time* SMD 0.76 (0.26, 1.26; p = 0.003) (2) *Sleep efficiency* SMD 0.89 (0.39, 1.40; p = 0.0005)	(1) *Total score* SMD -0.94 (-1.45, -0.44; p = 0.0003) (2) *Bedtime resistance* SMD -0.50 (-0.99, -0.01; p = 0.04) (3) *Sleep onset delay* SMD -0.65 (-1.14, -0.15; p = 0.01) (4) *Sleep anxiety* SMD 0.02 (-0.46, 0.50; p = 0.92) (5) *Night-wakings* SMD -1.86 (-2.44, -1.28; p <0.00001) (6) *Sleep duration* SMD -1.74 (-2.31, -1.18; p <0.00001) (7) *Parasomnias* SMD -0.23 (-0.71, 0.25; p = 0.35) (8) *Sleep-disordered breathing* SMD -0.11 (-0.59, 0.37; p = 0.65)	(1) *Sleep onset latency* RR 4.21 (1.32, 13.42; p = 0.02) (2) *Sleep efficiency* RR 5.18 (1.66, 16.13; p = 0.005)

			(9) *Daytime sleepiness* SMD -0.26 (-0.74, 0.22; p = 0.29)	
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	(1)-(2) Moderate[1] (3)-(4) Low[2]	Moderate[1]	(1)-(6) Low[1,3] (7)-(9) Very low[2,3]	Moderate[4]
Number of studies/participants	K = 1; N = 67			
Forest plot	1.28.2; Appendix 13			

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as parent-completed and parents non-blind and involved in the intervention.
[4]Downgraded due to serious imprecision as number of events <300.

There was single study moderate quality evidence for a large and statistically significant effect of melatonin (relative to CBT), in favour of melatonin, on sleep efficiency, and moderate and statistically significant effects on sleep onset latency, wake after sleep onset, and total sleep time. The only non-significant subscales for continuous actigraph data were for nap time and bedtime. There was also evidence for large and statistically significant effects of melatonin on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received melatonin being over four times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving CBT, and participants receiving melatonin were over five times more likely to show at least 85% for sleep efficiency than participants who received CBT (see Table 286).

There was also single study evidence for large and statistically effects of melatonin (relative to CBT), in favour of melatonin, on the total score for the CSHQ and on CSHQ subscales (night-wakings, sleep duration), and for a moderate and statistically significant effects on the bed resistance and sleep onset delay subscales of the CSHQ. However, the confidence in these effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size. Non-significant effects were observed for the sleep anxiety, parasomnias, sleep-disordered breathing, and daytime sleepiness subscales of the CSHQ (see Table 286).

In CORTESI2012, the paper narratively reports that no adverse events were reported or observed and none of the participants dropped out because of side effects and in GRINGRAS2012 treatment emergent signs and symptoms were reported and analysed and there was no evidence for statistically significant harms associated with melatonin (see Chapter 10, Section 10.3.2, for adverse events associated with melatonin).

Combined cognitive-behavioural intervention and melatonin for sleep problems as a direct outcome

The one included trial (CORTESI2012) that involved a combined cognitive-behavioural and melatonin intervention arm included comparisons between COMB and placebo, COMB and CBT-only, and COMB and melatonin-only (see Table 287). See above for further detail about interventions.

Table 287: Study information table for included trials of combined CBT and melatonin for sleep problems

	COMB versus placebo	**COMB versus CBT-only**	**COMB versus melatonin-only**
No. trials (N)	1 (80)		
Study IDs	CORTESI2012		
Study design	RCT		
% female	18	18.5	19
Mean age (years)	6.4	6.8	6.6
IQ	Not reported		
Dose/intensity (mg/hours)	CBT: Families received four, weekly CBT sessions of 50 minutes. A total of 3.3 hours. (Following the four sessions, families were also offered twice-monthly, 'individually tailored' sessions, but duration on these sessions was not reported) Melatonin: 3 mg/day. Formulation included 1 mg fast-release and 2 mg slow-release melatonin Placebo: 3 mg/day		
Setting	Outpatient		
Length of treatment (weeks)	12		
Continuation phase (length and inclusion criteria)	12		

Evidence for the effectiveness of COMB on sleep problems and the quality of the evidence is presented in Table 288, Table 289 and Table 290. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 288: Evidence summary table for effects of combined CBT and melatonin (relative to placebo) on sleep problems as a direct outcome

	COMB versus placebo			
Outcome	Sleep problems	Positive sleep behaviour	Sleep problems	Positive treatment response
Outcome measure	Actigraph: (1) Sleep onset latency (2) Wake after sleep onset (3) Nap time (4) Bedtime	Actigraph: (1) Total sleep time (2) Sleep efficiency	CSHQ: (1) Total score (2) Bedtime resistance (3) Sleep onset delay (4) Sleep anxiety (5) Night-wakings (6) Sleep duration	(1) Sleep onset latency: Number of participants who showed sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on

			(7) Parasomnias (8) Sleep-disordered breathing (9) Daytime sleepiness	actigraph data (2) Sleep efficiency: Number of participants who showed ≥85% for sleep efficiency based on actigraph data
Study ID	CORTESI2012			
Effect size (CI; p value)	(1) *Sleep onset latency* SMD -1.86 (-2.44, -1.29; p <0.00001) (2) *Wake after sleep onset* SMD -1.29 (-1.82, -0.76; p <0.00001) (3) *Nap time* SMD -0.95 (-1.45, -0.44; p = 0.0003) (4) *Bedtime* SMD -1.32 (-1.85, -0.79; p <0.00001)	(1) *Total sleep time* SMD 2.33 (1.70, 2.96; p <0.00001) (2) *Sleep efficiency* SMD 2.80 (2.12, 3.49; p <0.00001)	(1) *Total score* SMD -4.44 (-5.35, -3.53; p <0.00001) (2) *Bedtime resistance* SMD -3.34 (-4.09, -2.58; p <0.00001) (3) *Sleep onset delay* SMD -2.21 (-2.82, -1.59; p <0.00001) (4) *Sleep anxiety* SMD -1.74 (-2.30, -1.17; p <0.00001) (5) *Night-wakings* SMD -3.96 (-4.80, -3.12; p <0.00001) (6) *Sleep duration* SMD -1.73 (-2.29, -1.16; p <0.00001) (7) *Parasomnias* SMD -0.16 (-0.64, 0.32; p = 0.51) (8) *Sleep-disordered breathing* SMD 0.03 (-0.45, 0.51; p = 0.91) (9) *Daytime sleepiness* SMD -1.15 (-1.67, -0.63; p <0.0001)	(1) *Sleep onset latency* RR 55.92 (3.56, 878.39; p = 0.004) (2) *Sleep efficiency* RR 41.25 (2.60, 653.27; p = 0.008)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Moderate[1]		(1)-(6) Low[1,2] (7)-(8) Very low[2,3] (9) Low[1,2]	Moderate[4]
Number of studies/participants	K = 1; N = 67			
Forest plot	1.28.3; Appendix 13			

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as parent-completed and parents non-blind and involved in the intervention.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and

measure of appreciable benefit or harm (SMD -0.5/0.5).
[4]Downgraded due to serious imprecision as number of events <300.

Table 289: Evidence summary table for effects of combined CBT and melatonin (relative to CBT-only) on sleep problems as a direct outcome

	COMB versus CBT-only			
Outcome	Sleep problems	Positive sleep behaviour	Sleep problems	Positive treatment response
Outcome measure	Actigraph: (1) Sleep onset latency (2) Wake after sleep onset (3) Nap time (4) Bedtime	Actigraph: (1) Total sleep time (2) Sleep efficiency	CSHQ: (1) Total score (2) Bedtime resistance (3) Sleep onset delay (4) Sleep anxiety (5) Night-wakings (6) Sleep duration (7) Parasomnias (8) Sleep-disordered breathing (9) Daytime sleepiness	(1) Sleep onset latency: Number of participants who showed sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on actigraph data (2) Sleep efficiency: Number of participants who showed ≥85% for sleep efficiency based on actigraph data
Study ID	CORTESI2012			
Effect size (CI; p value)	(1) *Sleep onset latency* SMD -1.15 (-1.67, -0.64; p <0.0001) (2) *Wake after sleep onset* SMD -1.40 (-1.94, -0.87; p <0.00001) (3) *Nap time* SMD -0.13 (-0.61, 0.35; p = 0.59) (4) *Bedtime* SMD -0.47 (-0.95, 0.01; p = 0.06)	(1) *Total sleep time* SMD 1.46 (0.93, 2.00; p <0.00001) (2) *Sleep efficiency* SMD 1.33 (0.81, 1.86; p <0.00001)	(1) *Total score* SMD -3.10 (-3.81, -2.38; p <0.00001) (2) *Bedtime resistance* SMD -1.70 (-2.26, -1.14; p <0.00001) (3) *Sleep onset delay* SMD -1.23 (-1.75, -0.71; p <0.00001) (4) *Sleep anxiety* SMD -1.55 (-2.10, -1.01; p <0.00001) (5) *Night-wakings* SMD -2.66 (-3.32, -2.00; p <0.00001) (6) *Sleep duration* SMD -2.09 (-2.68, -1.49; p <0.00001) (7) *Parasomnias* SMD -0.48 (-0.96, 0.00; p = 0.05) (8) *Sleep-*	(1) *Sleep onset latency* RR 9.43 (3.18, 27.97; p <0.0001) (2) *Sleep efficiency* RR 6.91 (2.28, 20.95; p = 0.0006)

			disordered breathing SMD 0.03 (-0.45, 0.50; p = 0.91) (9) *Daytime sleepiness* SMD -0.61 (-1.09, -0.12; p = 0.01)	
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	(1)-(2) Moderate[1] (3)-(4) Low[2]	Moderate[1]	Low[1,3]	Moderate[4]
Number of studies/participants	K = 1; N = 68			
Forest plot	1.28.3; Appendix 13			

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as parent-completed and parents non-blind and involved in the intervention.
[4]Downgraded due to serious imprecision as number of events <300.

Table 290: Evidence summary table for effects of combined CBT and melatonin (relative to melatonin-only) on sleep problems as a direct outcome

	COMB versus melatonin-only			
Outcome	Sleep problems	Positive sleep behaviour	Sleep problems	Positive treatment response
Outcome measure	Actigraph: (1) Sleep onset latency (2) Wake after sleep onset (3) Nap time (4) Bedtime	Actigraph: (1) Total sleep time (2) Sleep efficiency	CSHQ: (1) Total score (2) Bedtime resistance (3) Sleep onset delay (4) Sleep anxiety (5) Night-wakings (6) Sleep duration (7) Parasomnias (8) Sleep-disordered breathing (9) Daytime sleepiness	(1) Sleep onset latency: Number of participants who showed sleep onset latency <30 minutes or reduction of sleep onset latency ≥50% based on actigraph data (2) Sleep efficiency: Number of participants who showed ≥85% for sleep efficiency based on actigraph data
Study ID	CORTESI2012			
Effect size (CI; p value)	(1) *Sleep onset latency* SMD -0.59 (-1.07, -0.11; p = 0.02) (2) *Wake after sleep*	(1) *Total sleep time* SMD 0.61 (0.13, 1.10; p = 0.01) (2) *Sleep efficiency*	(1) *Total score* SMD -1.42 (-1.95, -0.89; p <0.00001) (2) *Bedtime resistance* SMD -	(1) *Sleep onset latency* RR 2.24 (1.43, 3.51; p = 0.0004) (2) *Sleep efficiency*

	onset SMD -0.68 (-1.17, -0.19; p =0.006) (3) *Nap time* SMD -0.27 (-0.75, 0.20; p = 0.26) (4) *Bedtime* SMD -0.22 (-0.69, 0.25; p = 0.36)	SMD 0.42 (-0.06, 0.90; p = 0.08)	1.10 (-1.61, -0.59; p <0.0001) (3) *Sleep onset delay* SMD -0.57 (-1.06, -0.09; p = 0.02) (4) *Sleep anxiety* SMD -1.33 (-1.85, -0.80; p <0.00001) (5) *Night-wakings* SMD -0.60 (-1.08, -0.12; p = 0.01) (6) *Sleep duration* SMD -0.44 (-0.92, 0.03; p = 0.07) (7) *Parasomnias* SMD -0.27 (-0.74, 0.21; p = 0.27) (8) *Sleep-disordered breathing* SMD 0.09 (-0.38, 0.56; p = 0.70) (9) *Daytime sleepiness* SMD -0.27 (-0.74, 0.21; p = 0.27)	RR 1.34 (0.86, 2.07; p = 0.20)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	(1)-(2) Moderate[1] (3)-(4) Low[2]	(1) Moderate[1] (2) Low[2]	(1)-(5) Low[1,3] (6)-(9) Very low[2,3]	(1) Moderate[4] (2) Low[5]
Number of studies/participants	K = 1; N = 69			
Forest plot	1.28.3; Appendix 13			

Note. [1]Downgraded due to serious imprecision as N <400.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind, and high risk of detection bias as parent-completed and parents non-blind and involved in the intervention.
[4]Downgraded due to serious imprecision as number of events <300.
[5]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

There was moderate quality evidence for large and statistically significant effects of COMB, relative to placebo and in favour of COMB, on all continuous actigraph outcome measures for sleep. There was also evidence for large and statistically significant effects of COMB on dichotomous measures based on the actigraph data of positive treatment response for sleep onset latency and sleep efficiency, with participants who received COMB being nearly 56 times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving placebo, and participants receiving COMB were over 41 times more likely to show at least 85% for sleep efficiency than participants

who received placebo. There was also evidence for large and statistically effects of COMB (relative to placebo), in favour of COMB, on the total score for the CSHQ and on CSHQ subscales (bed resistance, sleep onset delay, sleep anxiety, night-wakings, sleep duration, and daytime sleepiness). The only non-significant effects observed were for the parasomnias and sleep-disordered breathing subscales of the CSHQ (see Table 288). However, it is important to note that for the CSHQ data, unlike the actigraph data, the confidence in effect estimates was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size.

There was also evidence for benefits of COMB over CBT-only on sleep onset latency, wake after sleep onset, total sleep time, and sleep efficiency as measured by continuous actigraph data and evidence for large and statistically significant effects of COMB relative to CBT-only on dichotomous measures based on the actigraph data. Participants who received COMB were over nine times more likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving CBT-only, and participants receiving COMB were nearly seven times more likely to show at least 85% for sleep efficiency than participants who received CBT-only. In addition, there was evidence for benefits of COMB relative to CBT-only on all but one subscale (sleep-disordered breathing) of the parent-completed CSHQ (see Table 289).

Finally, there was also evidence for benefits of COMB over melatonin-only on sleep onset latency, wake after sleep onset, and total sleep time as measured by continuous actigraph data and evidence for a large and statistically significant effect of COMB relative to melatonin-only on a dichotomous measure based on the actigraph data, with participants who received COMB being more than twice as likely to show sleep onset latency of less than 30 minutes or reduction of sleep onset latency by at least 50% than participants receiving melatonin-only. There was also evidence for benefits of COMB relative to melatonin-only on the total sleep problems score as measured by the CSHQ and on CSHQ subscales of bed resistance, sleep onset delay, sleep anxiety, and night-wakings (see Table 290).

SNRIs for sleep problems as an indirect outcome

The one included SNRI trial (ELILILLY2009) compared atomoxetine with placebo in children with autism (see Table 74).

Evidence for the effectiveness of atomoxetine and the quality of the evidence is presented in Table 291. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 291: Evidence summary table for effects of SNRIs on sleep problems as an indirect outcome

	Atomoxetine versus placebo		
Outcome	Time to fall asleep	Total hours of sleep	Sleep problems
Outcome measure	Sleep Measure Scale (study-specific)		Sleep Measure Scale (study-specific)

			subscales: (1) Difficulty falling asleep (2) Quality of sleep (3) Functional outcome during the day
Study ID	ELILILLY2009		
Effect size (CI; p value)	SMD -0.29 (-0.70, 0.13; p = 0.18)	SMD -0.13 (-0.55, 0.29; p = 0.54)	(1) *Difficulty falling asleep* SMD 0.17 (-0.24, 0.59; p = 0.42) (2) *Quality of sleep* SMD -0.23 (-0.65, 0.18; p = 0.27) (3) *Functional outcome during the day* SMD -0.18 (-0.60, 0.24; p = 0.40)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Low[1]		
Number of studies/participants	K = 1; N = 89		
Forest plot	1.28.4; Appendix 13		
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).			

There was no evidence for statistically significant effects of atomoxetine on sleep problems as an indirect outcome, as measured by a study-specific Sleep Measure Scale (see Table 291). This study did, however, find evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo (see Chapter 10, Section 10.3.2, for adverse events associated with SNRIs).

8.8.4 Studies considered – biomedical interventions aimed at coexisting medical or functional problems

Six studies from the search met the eligibility criteria for full-text retrieval. Of these, four trials provided relevant clinical evidence and were included in the review, one of these studies examined the efficacy of a biomedical intervention on coexisting sleep problems as an indirect outcome, one study examined the efficacy of a biomedical intervention on both coexisting sleep problems and gastrointestinal symptoms as indirect outcomes, one study examined the efficacy of a biomedical intervention on gastrointestinal symptoms as a direct outcome (target of the intervention), and one study examined effects on gastrointestinal symptoms as an indirect outcome. All studies were published in peer-reviewed journals between 2000 and 2011. In addition, two studies were excluded from the analysis. The reasons

for exclusion were that data could not be extracted as the sample size was less than ten participants per arm due to crossover and multisite design, or because attrition was greater than 50% of the sample randomised and because much of this drop-out occurred either during the baseline period or in equal numbers by group before the end of the first crossover trial period analysis of the dichotomous measure of drop-out was not considered informative. See Appendix 12d for further details about the included and excluded studies.

Two nutritional intervention trials (ADAMS2011, JOHNSON2010[99]) examined effects on sleep problems as an indirect outcome.

One hormones trial (DUNNGEIER2000[100]) examined effects on gastrointestinal symptoms as an indirect outcome.

Finally, one nutritional intervention trial (HANDEN2009) examined effects on gastrointestinal symptoms as a direct outcome, and one nutritional intervention study (ADAMS2011[101]) examined indirect effects on gastrointestinal symptoms.

8.8.5 Clinical evidence – effect of biomedical interventions – on coexisting medical or functional problems

Nutritional interventions for sleep problems as an indirect outcome

One of the included nutritional intervention trials (JOHNSON2010) examined effects of an omega-3 fatty acid supplement relative to a healthy-diet control comparator. The other included nutritional intervention study (ADAMS2011) compared a multivitamin/mineral supplement with placebo (see Table 233). See Section 8.3.6 for further detail about the intervention in ADAMS2011 and see Section 8.2.7 for further detail about the intervention in JOHNSON2010.

Evidence for the effectiveness of nutritional intervention and the quality of the evidence is presented in Table 292 and Table 293. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 292: Evidence summary table for effects of nutritional interventions (multivitamin) on sleep problems as an indirect outcome

	Multivitamin/mineral supplement versus placebo
Outcome	Sleep improvement
Outcome measure	PGI-R: Sleep improvement
Study ID	ADAMS2011
Effect size (CI; p value)	SMD 0.18 (-0.20, 0.57; p = 0.36)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 104

[99] See Section 6.4.3 and Section 7.4.2, respectively, for direct outcomes from ADAMS2011 and JOHNSON2010.
[100] See Chapter 6, Section 6.4.3, for direct outcomes from DUNNGEIER2000.
[101] See Section 6.4.3 for direct outcomes from ADAMS2011.

Forest plot	1.29.1; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of a multivitamin and mineral supplement on sleep improvement as an indirect outcome, as measured by the PGI-R (see Table 292). There was also no evidence for statistically significant harms associated with a multivitamin/mineral supplement (see Chapter 10, Section 10.4.2, for adverse events associated with a multivitamin/mineral supplement).

Table 293: Evidence summary table for effects of nutritional interventions (omega-3) on sleep problems as an indirect outcome

Comparison	**Omega-3 fatty acids versus healthy diet control**
Outcome	Sleep problems
Outcome measure	CBCL/1.5-5: Sleep problems
Study ID	JOHNSON2010
Effect size (CI; p value)	SMD 1.11 (0.21, 2.00; p = 0.02)
Heterogeneity (chi^2; p value; I^2)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 23
Forest plot	1.29.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the outcome assessor for this outcome measure was not blinded. [2]Downgraded due to serious imprecision as N <400.	

There was statistically significant evidence for a negative treatment effect with omega-3 fatty acids on sleep problems. Narrative review of this effect showed that the omega-3 group worsened from pre- to post-intervention, while the healthy diet control group showed some improvement. Data could not be extracted from this study for adverse events. However, there was no statistically significant evidence for harms associated with an omega-3 fatty acid supplement when compared against placebo by another trial (see Chapter 10, Section 10.4.2, for adverse events associated with omega-3 fatty acids).

Hormones for gastrointestinal symptoms as an indirect outcome

The one included hormone trial (DUNNGEIER2000) involved a comparison between secretin (porcine secretin) and placebo (see Table 294).

Table 294: Study information table for included trials of hormones for gastrointestinal symptoms

	Secretin versus placebo
No. trials (N)	1 (95)
Study IDs	DUNNGEIER2000
Study design	RCT
% female	7
Mean age (years)	5.1
IQ	Not reported

Dose/intensity (mg/hours)	2 CU/kg (up to 75 CU)
Setting	Not reported
Length of treatment (weeks)	Single dose
Continuation phase (length and inclusion criteria)	3

Evidence for the effectiveness of secretin and the quality of the evidence is presented in Table 295. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 295: Evidence summary table for effects of hormones on gastrointestinal symptoms as an indirect outcome

	Secretin versus placebo
Outcome	Number of gastrointestinal problems
Outcome measure	Gastrointestinal symptoms questionnaire: total (change score)
Study ID	DUNNGEIER2000
Effect size (CI; p value)	SMD -0.18 (-0.59, 0.22; p = 0.37)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 95
Forest plot	1.29.2; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of secretin on the number of gastrointestinal problems as an indirect outcome, as measured by a study-specific gastrointestinal symptoms questionnaire (see Table 295). Data could not be extracted for adverse events associated with secretin.

Nutritional interventions for gastrointestinal symptoms as a direct or indirect outcome

One of the included nutritional intervention trials (HANDEN2009) compared oral human immunoglobulin with placebo, and examined effects on gastrointestinal symptoms as a direct outcome. The other included nutritional intervention trial (ADAMS2011) compared a multivitamin/mineral supplement with placebo (see Table 296). HANDEN2009 was a four-armed trial and included three active intervention arms (low dose [140 mg/day], moderate dose [420 mg/day] or high dose [840 mg/day]). Initial analysis compared high dose and low dose groups; however, as no statistically significant differences were found on the gastrointestinal symptoms outcome the groups were combined (across dosages) and compared with placebo. See section 8.3.6 for further detail about the intervention in ADAMS2011.

Table 296: Study information table for included trials of nutritional interventions for gastrointestinal symptoms

	Immunoglobulin versus placebo	Multivitamin/ mineral supplement versus placebo
No. trials (N)	1 (125)	1 (141)
Study IDs	HANDEN2009	ADAMS2011
Study design	RCT	RCT
% female	14	11
Mean age (years)	7.3	10.8
IQ	Not reported	Not reported
Dose/intensity (mg/hours)	Planned intensity of 140 mg/day, 420 mg/day or 840 mg/day for low, moderate and high dose arms respectively	One dose a day at lunchtime (formulation of vitamin/ mineral supplement based on 60 lb which was adjusted up or down according to body weight up to a maximum of 100 lb: 1000 IU vitamin A; 600 mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70 mg mixed tocopherols; 20 mg B1, 20 mg B2, 15 mg niacin and 10 mg niacinamide B3; 15 mg B5; 40 mg B6; 500 mcg B12; 100 mcg folic acid; 550 mcg folinic acid; 150 mcg biotin; 250 mcg choline; 100 mcg inositol; 3.6 mg mixed carotenoids; 50 mg coenzyme Q10; 50 mg N-acetylcysteine; 100 mg calcium; 70 mcg chromium; 100 mcg iodine; 500 mcg lithium; 100 mg magnesium; 3 mg manganese; 150 mcg molybdenum; 50 mg potassium; 22 mcg selenium; 500 mg sulphur; 12 mg zinc)
Setting	Not reported	Outpatient
Length of treatment (weeks)	12	13
Continuation phase (length and inclusion criteria)	12	13

Evidence for the effectiveness of nutritional interventions and the quality of the evidence is presented in Table 297 and Table 298. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 297: Evidence summary table for effects of nutritional interventions (immunoglobulin) on gastrointestinal symptoms as a direct outcome

	Immunoglobulin versus placebo
Outcome	Positive treatment response
Outcome measure	Number of participants who scored 'moderately or substantially improved' on at least two of last four assessments or 'somewhat improved' for all of last four assessments of the Modified Global Improvement Scale for

	gastrointestinal symptoms
Study ID	HANDEN2009
Effect size (CI; p value)	RR 0.73 (0.45, 1.18; p = 0.20)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 125
Forest plot	1.29.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [2]Downgraded due to strongly suspected publication bias – high risk of selective reporting bias as continuous data could not be extracted for the Modified Global Improvement Scale.	

There was no evidence for a statistically significant effect of immunoglobulin (dosages combined) on gastrointestinal symptoms as measured by the number of participants who showed a positive treatment response, defined as 'moderately or substantially improved' on at least two of last four assessments or 'somewhat improved' for all of last four assessments of the Modified Global Improvement Scale for gastrointestinal symptoms (see Table 297). This study also examined potential subgroup differences in the treatment response for gastrointestinal symptoms but found no evidence that the treatment effect was moderated by either predominant bowel pattern (diarrhoea, constipation, or alternating) or age (2-11 years or 12-17 years). There was also no statistically significant evidence for harms associated with immunoglobulin (see Chapter 10, Section 10.4.2, for adverse events associated with immunoglobulin).

Table 298: Evidence summary table for effects of nutritional interventions (multivitamin) on gastrointestinal symptoms as an indirect outcome

	Multivitamin/ mineral supplement versus placebo
Outcome	Gastrointestinal symptom improvement
Outcome measure	PGI-R: gastrointestinal improvement
Study ID	ADAMS2011
Effect size (CI; p value)	SMD 0.30 (-0.09, 0.68; p = 0.13)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1]
Number of studies/participants	K = 1; N = 104
Forest plot	1.29.3; Appendix 13
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was no evidence for a statistically significant effect of a multivitamin/mineral supplement on gastrointestinal symptom improvement as an indirect outcome, as measured by the PGI-R (see Table 298). There was also no evidence for statistically significant harms associated with a multivitamin/mineral supplement (see Chapter 9, Section 10.4.2, for adverse events associated with a multivitamin/mineral supplement).

8.8.6 Clinical evidence summary – effect of interventions on coexisting medical or functional problems

There was moderate quality evidence for positive treatment effects of CBT, melatonin, and COMB on sleep problems in children with autism. However, analysis was confined to single-study data as even in the case of melatonin where there were only two included trials, differences in the population and melatonin formulation meant that meta-analysis was not possible. There was single-study evidence for negative treatment effects of an omega-3 fatty acid supplement on sleep problems in children with autism, with narrative review of the effect suggesting that the omega-3 group worsened from pre- to post-intervention, while the healthy diet control group showed some improvement. Finally, there was no evidence for significant benefits or harms associated with biomedical interventions aimed at gastrointestinal symptoms.

8.8.7 Economic evidence – interventions aimed at coexisting medical or functional problems

Systematic literature review

No studies assessing the cost effectiveness of interventions aimed at common medical and functional problems in children and young people with autism were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

8.8.8 From evidence to recommendations – interventions aimed at coexisting medical or functional problems

The GDG agreed that the evidence for CBT, melatonin and COMB was promising, but would require replication by further RCTs before they could consider recommending any of these treatments. The expert opinion of the GDG was that the CBT described in the evidence section closely resembled what is usually included in a sleep hygiene intervention. In view of the negative treatment effect associated with omega-3 fatty acids, and on the basis of expert opinion, the GDG decided that a recommendation not to use this treatment for sleep problems in children and young people with autism was warranted.

Given that sleep can be a significant problem for children and young people with autism and their families or carers, following stakeholder consultation the GDG decided to construct a pathway to manage sleep problems. The consensus opinion was that the first step should be a full assessment of any sleep problem to determine its precise nature and any factors that might be contributing to it, such as the sleep environment, comorbidities and current medication. Following the assessment, the GDG judged that parents and carers should be supported to develop a sleep plan to encourage the child or young person to develop positive sleep habits, and use a diary to record sleeping patterns and bedtimes. Although no evidence for a specific pharmacological intervention was found, the GDG accepted that there would be times when behavioural interventions would be ineffective and the child or young

person's negative sleep behaviours would persist and have a detrimental impact on them and their family or carers. The GDG took the view that pharmacological interventions should not be considered until that point had been reached and should only be used following consultation with a specialist paediatrician or psychiatrist who has expertise in the management of autism or paediatric sleep medicine, and in conjunction with behavioural interventions. The GDG also wished to emphasise that any medication to aid sleep should be regularly reviewed to ensure that that its benefits continue to outweigh the side effects and risks in children and young people with autism. Finally, loud snoring, choking or witnessed apnoeas should prompt referral to a sleep expert to exclude diagnosis of obstructive sleep apnoea.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

8.8.9 Recommendations – interventions aimed at coexisting medical or functional problems

Clinical practice recommendations

8.8.9.1 If a child or young person with autism develops a sleep problem offer an assessment that identifies:

- what the sleep problem is (for example, delay in falling asleep, frequent waking, unusual behaviours, breathing problems or sleepiness during the day)
- day and night sleep patterns, and any change to those patterns
- whether bedtime is regular
- what the sleep environment is like for example:
  - the level of background noise
  - use of a blackout blind
  - a television or computer in the bedroom
  - whether the child shares the room with someone
- presence of comorbidities especially those that feature hyperactivity or other behavioural problems
- levels of activity and exercise during the day
- possible physical illness or discomfort (for example, reflux, ear or tooth ache, constipation or eczema)
- effects of any medication
- any other individual factors thought to enhance or disturb sleep, such as emotional relationships or problems at school
- the impact of sleep and behavioural problems on parents or carers and other family members.

8.8.9.2 If the child or young person with autism snores loudly, chokes or appears to stop breathing while sleeping, refer to a specialist to check for obstructive sleep apnoea.

8.8.9.3 Develop a sleep plan (this will often be a specific sleep behavioural intervention) with the parents or carers to help address the identified sleep problems and to establish a regular night-time sleep pattern. Ask the parents or carers to record the child or young person's sleep and wakefulness throughout the day and night over a 2-week period. Use this information to modify the sleep plan if necessary and review the plan regularly until a regular sleep pattern is established.

8.8.9.4 Do not use a pharmacological intervention to aid sleep unless:

- sleep problems persist despite following the sleep plan
- sleep problems are having a negative impact on the child or young person and their family or carers.

If a pharmacological intervention is used to aid sleep it should:

- only be used following consultation with a specialist paediatrician or psychiatrist with expertise in the management of autism or paediatric sleep medicine
- be used in conjunction with non-pharmacological interventions
- be regularly reviewed to evaluate the ongoing need for a pharmacological intervention and to ensure that the benefits continue to outweigh the side effects and risks.

8.8.9.5 If the sleep problems continue to impact on the child or young person or their parents or carers, consider:

- referral to a paediatric sleep specialist, and
- short breaks and other respite care for one night or more. Short breaks may need to be repeated regularly to ensure that parents or carers are adequately supported. Agree the frequency of breaks with them and record this in the care plan.

8.8.9.6 Do not use omega-3 fatty acids to manage sleep problems in children and young people with autism.

Research recommendations

8.8.9.7 Is a sleep hygiene intervention or melatonin clinically and cost effective in the management of sleep onset, night waking and reduced total sleep in children (aged 4–10 years) with autism?

9 INTERVENTIONS AIMED AT IMPROVING THE IMPACT ON THE FAMILY

9.1 INTRODUCTION

The wide range of difficulties, including developmental delays, marked social and communication problems and emotional and behavioural disturbances, associated with autism not only have a major impact on the children themselves, but also on family life. High levels of stress among parents of children with autism have been well documented in many studies over the years (see Osborne et al., 2008 for a review). Parental stress is greater, and mental health poorer, than in families of children with other developmental disorders (for example Down syndrome or Fragile X; Abbeduto, et al., 2004) or chronic life-threatening conditions such as cystic fibrosis (Bouma & Schweitzer, 1990). Quality of life is relatively impaired (Mugno et al., 2007), rates of medical disorders in families are high (Brimacombe et al., 2007) and the financial costs of raising a child with autism are considerable (Knapp et al., 2007). There is also an interaction between levels of parental stress and the severity of problems shown by their children, with stress being higher in parents (particularly mothers) of children with more severe behavioural problems. In turn, emotional stress in parents can result in more maladaptive behaviours in their children (Greenberg et al., 2006) and can also reduce the effectiveness of intervention programmes (Osborne et al., 2008).

Nevertheless, many studies have also a shown that family stress can be modified by a number of different variables; improved 'self-efficacy', the development of effective coping mechanisms and access to appropriate support have been identified as particularly important moderating factors (Benson & Karlof, 2009; Dunn et al., 2001; Hastings & Brown, 2002). Moreover, it has long been recognised that directly involving parents in interventions as 'co-therapists' is much more likely to result in generalisation and maintenance of treatment effects than interventions that are predominantly clinic based (Howlin & Rutter, 1987; Lovaas, 1987; Schopler et al., 1982). Thus, over recent years, there has been an increase in studies with a focus on increasing parental competence and providing parents with the strategies and knowledge required to manage their child's difficult behaviours more effectively and to enhance communication, social and other developmental skills.

Models of working with parents vary widely: some involve individual work with parents (for example, Drew et al., 2002); others are group based (for example, Tonge et al., 2006); still others use a combination of individual and group-based intervention (for example, Sofronoff et al., 2004); and some (for example, Neef, 1995) have used parent peers to help parents learn new strategies. In most of these studies, parents are helped to develop more effective management skills, although in some (for example, Aman et al., 2009) behavioural interventions are combined with

pharmacological treatments. Treatment goals and outcome measures also vary. The majority of programmes that work with parents focus on reducing children's 'challenging' behaviours or the severity of autism symptoms and/or improving developmental and adaptive skills. However, others have also included measures of parental stress (for example, Drew et al., 2002; Jocelyn et al., 1998; Welterlin et al., 2012) and for some the main outcome measure has focused specifically on parental mental health (Tonge et al., 2006).

Current practice

Unfortunately, although research indicates the potential value of interventions that focus on improving the impact of autism on families, for the majority of parents, access to evidence-based or specialised help is very limited. Few parents receive more than a few sessions of advice or group-based psychoeducational training (which is rarely evaluated and has a very limited evidence base) from CAMHS or paediatric services after the diagnosis of their child's autism.

9.1.1 Review protocol – interventions aimed at improving the impact of autism on the family

The review protocol, including the review questions, information about the databases searched and the eligibility criteria used for this section of the guideline, can be found in Table 7 (further information about the search strategy can be found in Appendix 7).

Table 299: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s)	**RQ 7.1**: For children and young people with autism, what are the benefits of psychosocial, pharmacological or biomedical interventions for improving the impact on the family* when compared with alternative management strategies? *Subgroup analyses will examine and compare treatment effects on the impact for the family when the interventions are specifically aimed at improving the impact on the family (direct outcomes) and when the primary target of the intervention was another outcome but effects on the family are examined (indirect outcomes) on coexisting problems or disorders are examined (indirect outcomes).
Sub-question(s)	**RQ 7.1.1:** For children and young people with autism, and their families and carers, is the engagement with or effectiveness of interventions aimed at improving the impact on the family different for: • looked-after children? • immigrant groups? • children with regression in skills? **RQ 7.1.2**: For children and young people with autism is the effectiveness of interventions aimed at improving the impact on the family moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and

	behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)? **RQ 7.1.3**: For children and young people with autism is the effectiveness of interventions aimed at improving the impact on the family mediated by: • the intensity of the intervention? • the duration of the intervention? • the length of follow-up? • programme components?
Objectives	To evaluate the clinical and cost effectiveness of interventions aimed at improving the impact on the family for children and young people with autism.
Criteria for considering studies for the review	
Population	Children and young people (from birth until their 19th birthday) with autism, (across the full range of intellectual ability) and their families and carers. If some, but not all, of a study's participants are eligible for our review, we will ask the study authors for disaggregated data. If we are unable to obtain the appropriate disaggregated data, then we will include a study if the majority (at least 51%) of its participants are eligible for our review. If we are unable to determine the exact percent of a study's participants who are eligible, then we will include the study if its participants are eligible on average (for example, the mean participant age is less than 19 years). Consideration will be given to the particular management and support needs of: • looked-after children • immigrant groups • children with regression in skills Excluded groups include: • adults (19 years and older).
Intervention	Psychosocial, biomedical or pharmacological interventions which are aimed at improving the impact of autism on the family as a direct or indirect outcome
Comparison	No treatment or treatment as usual (includes placebo and waitlist control up until receiving intervention), other active interventions
Critical outcomes	• Parental mental health • Parental stress
Time points	Some studies may measure outcomes at multiple time points. We will run the following analyses: • Post-intervention (end of treatment) • Longest follow-up
Study design	• RCTs • Systematic reviews Non-English language papers will be excluded, as will books, dissertation

	abstracts, trade magazines, policy and guidance, and non-empirical research.
Include unpublished data?	Yes but only where: • the evidence was accompanied by a trial report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	No limit
Minimum sample size	• N ≥ 10 per arm (ITT) Exclude studies with >50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
Study setting	• Primary, secondary and tertiary health and social care. This guideline will also be relevant to other health and social care settings (including forensic services and youth justice settings) although they are not explicitly covered. • The guideline will also address interventions relevant to early years services and educational settings.
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, HTA, IBSS, MEDLINE, PreMEDLINE, PsycEXTRA, PsycINFO, Social Policy and Practice, Sociological Abstracts, SSA, SSCI
Date searched	Systematic reviews: 1995 up to January 2013 RCTs: inception of database up to January 2013
Searching other resources	Hand-reference searching and citation searches of included studies, hand-searching of the 'Research Autism' website, and searching the ISRCTN and ClinicalTrials.gov website using the term 'autism'
The review strategy	• The initial aim is to conduct a meta-analysis evaluating the clinical effectiveness of the interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. Consider subgroup meta-analyses that takes into account the effectiveness of interventions as moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)?

9.1.2 Outcomes

A large number of outcome measures for impact on the family were reported. Those that reported sufficient data to be extractable and were not excluded (see Appendix 12e) are in Table 21.

Table 300: Outcome measures for impact on the family extracted from studies of interventions aimed at improving the impact of autism on the family

Category	Sub-category	Scale
Impact on the family	Family quality of life	• Beach Family Quality of Life Questionnaire (Summers et al., 2005) – Total score, and Family Interaction, Parenting, Emotional Wellbeing, Physical Wellbeing, and Disability Support subscales • McMaster Family Assessment Device (Epstein et al., 1983) – Total score • Parent-Child Interaction Questionnaire (Wood, 2006) – Parent Intrusiveness subscale
	Parental coping skills	• Parent Perception Questionnaire (study-specific; Roberts et al., 2011) – Total score, and Confidence, Coping, Knowledge, Understanding, Family Issues, and Planning subscales
	Parental mental health	• General Health Questionnaire, 28 items (GHQ-28; Goldberg & Williams, 1988) – Total score, and Somatic Symptoms, Anxiety and Insomnia, Social Dysfunction, and Severe Depression subscales
	Parental stress	• Autism Parenting Stress Index (Silva & Schalock, 2012b) – Total score • Nijmeegse Ouderlijke Stress Index (Brock et al., 1990) – Total score • Parenting Stress Index (PSI; Abidin, 1986) – Total score • PSI (3rd edition; PSI-3), Short form (Abidin, 1995) – Total score, and Defensive Responding, Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child subscales • Parenting Stress Thermometer (study-specific; Tonge et al., 2006) – Total score • Stress-Arousal Checklist (MacKay et al., 1978) – Mothers' Stress, Mothers' Arousal, Fathers' Stress and Fathers' Arousal subscales

9.2 PSYCHOSOCIAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

9.2.1 Studies considered

Fifteen studies from the search met the eligibility criteria for full-text retrieval. Of these, six trials provided relevant clinical evidence and were included in the review. One of these studies examined the efficacy of a psychosocial intervention on improving the impact of autism on the family as a direct outcome (target of intervention), and five provided data on improving the impact of autism on the family as an indirect outcome. All studies were published in peer-reviewed journals between 1998 and 2012. In addition, nine studies were excluded from the analysis. The most common reasons for exclusion were non-randomised group allocation or sample size less than ten participants per arm. Further information about both included and excluded studies can be found in Appendix 12e.

One behavioural intervention study examined effects on the family as an indirect outcome (ROBERTS2011[102]).

One cognitive-behavioural intervention study examined effects on the family as an indirect outcome (DRAHOTA2011[103]).

One parent training intervention trial examined effects on the family as a direct outcome (TONGE2006), and three parent training trials (DREW2002, JOCEYLN1998, WELTERLIN2012[104]) examined effects on the family as an indirect outcome.

9.2.2 Clinical evidence

Behavioural interventions for improving the impact of autism on the family as an indirect outcome

The one included behavioural intervention trial (ROBERTS2011) compared a home-based EBI programme and a centre-based EBI programme (see Table 189). In this trial, the 'Building Blocks' programme was delivered in a home-based EBI condition (Autism Association of NSW, 2004a) or a centre-based EBI condition (Autism Association of NSW, 2004b). For the experimental group (home-based EBI) the EBI intervention was individualised and delivered in the home to both the child and their parent/s. Intervention targets included behaviour management, functional communication skills, social development, attending and play skills, sensory processing issues, self-care skills, motor skills and academic skills and the intervention administrator trained parents to work effectively with their child using techniques including direct modelling of skills and constructive feedback to parents.

[102] See Chapter 8, Section 8.2.3, for direct outcomes from ROBERTS2011.
[103] See Chapter 8, Section 8.3.3, for direct outcomes from DRAHOTA2011.
[104] See Sections 6.2.3 and 6.2.5, respectively, for direct outcomes from DREW2002 and JOCELYN1998; see Section 8.3.3 for direct outcomes from WELTERLIN2012.

In the control group (centre-based EBI) the EBI intervention involved group-based playgroup sessions for the children and concurrent group-based parent support and training groups. The playgroup programme was run according to a condensed preschool programme manual which aimed to prepare children for integration into regular preschool settings by focusing on the development of social play skills, functional communication skills and participation in small group activities. The parent training and support groups were also run according to a manual and intended to provide parents with an opportunity to meet with other parents and professionals and to discuss a range of set topics (prioritised according to interest and need) including positive behaviour support, communication, self-care issues, school options, specialist services and sensory issues.

Table 301: Study information table for included trials of behavioural interventions for improving the impact of autism on the family

	Home-based EBI versus centre-based EBI
No. trials (N)	1 (67)
Study IDs	ROBERTS2011
Study design	RCT
% female	Not reported
Mean age (years)	3.5
IQ	61.8 (assessed using the GMDS)
Dose/intensity (mg/hours)	Planned intensity of 40 hours (2 hours/fortnightly) for the home-based intervention and 80 hours (2 hours/weekly) for the centre-based intervention
Setting	Home-based versus centre-based
Length of treatment (weeks)	40
Continuation phase (length and inclusion criteria)	40

Evidence for the effectiveness of a behavioural intervention on improving the impact of autism on the family and the quality of the evidence is presented in Table 302. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was no evidence for a statistically significant effect of home-based EBI (relative to centre-based EBI) on family quality of life, parental coping skills or parental stress as indirect outcomes (see Table 302).

Table 302: Evidence summary table for effects of behavioural intervention on improving the impact of autism on the family as an indirect outcome

	Home-based EBI versus centre-based EBI		
Outcome	Family quality of life	Parental coping skills	Parental stress
Outcome measure	Beach Family Quality of Life Questionnaire: (1) Total score (2) Family interaction (3) Parenting (4) Emotional wellbeing (5) Physical wellbeing (6) Disability support	Parent Perception Questionnaire: (1) Total score (2) Confidence (3) Coping (4) Knowledge (5) Understanding (6) Family issues (7) Planning	PSI-3 (Short form): (1) Total score (2) Defensive responding (3) Parental distress (4) Parent–child dysfunctional interaction (5) Difficult child
Study ID	ROBERTS2011		
Effect size (CI; p value)	(1) *Total score* SMD 0.16 (-0.43, 0.76; p = 0.59) (2) *Family interaction* SMD 0.14 (-0.45, 0.73; p = 0.65) (3) *Parenting* SMD 0.00 (-0.59, 0.59; p = 1.00) (4) *Emotional wellbeing* SMD 0.22 (-0.38, 0.81; p = 0.48) (5) *Physical wellbeing* SMD 0.00 (-0.59, 0.59; p = 1.00) (6) *Disability support* SMD 0.10 (-0.49, 0.69; p = 0.73)	(1) *Total score* SMD -0.15 (-0.73, 0.43; p = 0.61) (2) *Confidence* SMD 0.00 (-0.58, 0.58; p = 1.00) (3) *Coping* SMD 0.33 (-0.25, 0.91; p = 0.27) (4) *Knowledge* SMD -0.52 (-1.11, 0.07; p = 0.08) (5) *Understanding* SMD -0.26 (-0.84, 0.32; p = 0.38) (6) *Family issues* SMD 0.23 (-0.35, 0.81; p = 0.44) (7) *Planning* SMD -0.09 (-0.67, 0.49; p = 0.76)	(1) *Total score* SMD -0.26 (-0.89, 0.36; p = 0.41) (2) *Defensive responding* SMD -0.21 (-0.83, 0.42; p = 0.52) (3) *Parental distress* SMD -0.22 (-0.84, 0.40; p = 0.49) (4) *Parent–child dysfunctional interaction* SMD -0.15 (-0.77, 0.47; p = 0.64) (5) *Difficult child* SMD -0.35 (-0.98, 0.27; p = 0.27)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2]		
Number of studies/participants	K = 1; N = 44	K = 1; N = 46	K = 1; N = 40
Forest plot	1.30.1; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and unclear/unknown risk of detection bias as although the outcome assessors were blinded, this outcome measure was based on interview with parent and parents were non-blind and were part of the intervention.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Cognitive-behavioural interventions for improving the impact of autism on the family as an indirect outcome

The one included cognitive-behavioural intervention trial (DRAHOTA2011) examined indirect effects of CBT that was targeted at anxiety on improving the impact of autism on the family (see Table 192). The CBT was manualised and based on the 'Building Confidence' CBT programme (Wood & McLeod, 2008) modified for use with children with autism (Wood et al., 2007). The intervention included coping skills training (for instance, affect recognition, cognitive restructuring and the principle of exposure) followed by in vivo practice of the skills. The intervention also included a parent training component where parents were taught to support in vivo exposures and use positive reinforcement and communication skills to encourage their children's independence and autonomy. Autism-specific adaptations included the addition of some new modules aimed at social skills training for children with autism. For instance, additional intervention components included social coaching provided at school, home or in public immediately before the child attempted to join a social activity, reinforcement for positive social skills and a mentoring system at school. Other adaptations included an additional module which focused on building independence in self-care skills. In addition to adding new modules, autism-specific adaptations were also made to general teaching approaches, for example, children's special interests were used as examples and rewards in teaching.

Table 303: Study information table for included trial of cognitive-behavioural interventions for improving the impact of autism on the family

	CBT versus waitlist
No. trials (N)	1 (40)
Study IDs	DRAHOTA2011
Study design	RCT
% female	33
Mean age (years)	9.2
IQ	Not reported
Dose/intensity (mg/hours)	24 (1.5 hours/week)
Setting	Research setting (no further details reported)
Length of treatment (weeks)	16
Continuation phase (length and inclusion criteria)	29 (6-week intervention followed by 3-month follow-up; however, outcome data are for post-treatment only as there are no follow-up data for the control group)

Evidence for the effectiveness of CBT on improving the impact of autism on the family and the quality of the evidence is presented in Table 304. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 304: Evidence summary table for effects of cognitive-behavioural intervention on improving the impact of autism on the family as an indirect outcome

	CBT versus waitlist
Outcome	Parent intrusiveness/Child independence
Outcome measure	Parent-Child Interaction Questionnaire: Parent intrusiveness
Study ID	DRAHOTA2011
Effect size (CI; p value)	SMD -0.68 (-1.32, -0.04; p = 0.04)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 40
Forest plot	1.30.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors were non-blind parents. [2]Downgraded due to serious imprecision as N <400.	

There was single study evidence for a moderate and statistically significant effect of CBT on parent intrusiveness/child independence as an indirect outcome, as measured by the Parent-Child Interaction Questionnaire (see Table 304). However, the quality of the evidence was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size.

Parent training for improving the impact of autism on the family as a direct or indirect outcome

Three of the included parent training trials compared parent training with treatment as usual; one (TONGE2006) examined effects on the family as a direct outcome and two (DREW2002, WELTERLIN2012) examined indirect effects on the family. The other included parent training trial (JOCELYN1998) compared parent and day care staff training with standard day care and examined effects on the family as an indirect outcome (see Table 222).

TONGE2006 examined effects of the 'Preschoolers with Autism' programme (Brereton & Tonge, 2005) and included two active intervention arms, the PEBM training intervention and the PEC intervention. In both cases, intervention consisted of small group parent training sessions and individual family sessions. Group sessions (for both PEBM and PEC) included: education about autism; features of communication, social, play, and behavioural impairments; principles of managing behaviour and change; teaching new skills; improving social interaction and communication; services available; managing parental stress, grief and mental health problems; and sibling, family and community responses to autism. The key 'active' ingredient which differed between PEBM and PEC intervention arms was that in the PEBM individual family sessions the parents were provided with workbooks, modelling, videos, rehearsal (with child when present), homework tasks and feedback, while for the PEC intervention, although the educational material in the manual was the same, no skills training or homework tasks were set for the

individual sessions and the emphasis was on non-directive interactive discussion and counselling. Initially the two active intervention arms (PEBM and PEC) were compared and as there were no significant differences between them the data from the two groups were combined and compared against treatment as usual.

In DREW2002 the parent training intervention emphasised the development of JA and joint action routines, and included advice about behaviour management. Speech and language therapists described developmental principles to parents and then monitored and provided feedback on implementation. Parents were instructed on how to teach JA behaviours such as pointing and gaze switching, including the use of visual supports for spoken language and techniques were implemented in allocated times for activities (for instance, joint play times) but also integrated into everyday routines, such as mealtimes, dressing and bedtimes. Instruction in behaviour management techniques followed a similar structure and included instruction in the principles of reinforcement, interrupting unwanted behaviours and encouraging alternative behaviours through joint action routines.

In WELTERLIN2012 the home TEACCH programme incorporated parent training in how to teach specific cognitive, fine motor and language skills to their child. The intervention began with the clinician teaching the child the specific skills and modelling appropriate prompting behaviour and teaching environment set-up for the parents. Parents were also provided with education about autism and intervention strategies and assigned written homework and requested to practice applying new skills in between intervention sessions. From week eight onwards, parents took over the active teaching of their child and the clinician provided coaching and feedback.

Finally, in JOCELYN1998 the intervention was delivered through hospital-based educational seminars (covering an introduction to autism, behaviour analysis techniques, interventions aimed at communication, techniques to improve social interaction and engage the child in play, and problem solving); on-site consultations to day care centres (conducted in parallel with seminars to facilitate practical application of techniques); and psychoeducational and supportive work with the family (including review meetings at the day care centre with the parents and home visits to parents where written information about autism was provided, parents were given the opportunity to discuss concerns and questions, expectations and goals for the child were discussed and videotapes of the child at day care were reviewed to share intervention strategies and techniques).

Table 305: Study information table for included trials of parent training for improving the impact of autism on the family

	Parent training versus treatment as usual	Parent and day care staff training versus standard day care
No. trials (N)	3 (149)	1 (36)
Study IDs	(1) DREW2002 (2) TONGE2006 (3) WELTERLIN2012	JOCELYN1998
Study design	(1)-(3) RCT	RCT
% female	(1) 21 (2) 16 (3) 10	3
Mean age (years)	(1) 1.9 (2) 3.9 (3) 2.5	3.6
IQ	(1) Non-verbal IQ 77.1 (assessed using the D and E subscales of the Griffiths Scale of Infant Development; Griffiths, 1986) (2) 59.2 (assessed using the PEP-R – developmental quotient) (3) 55.4 (assessed using MSEL – developmental quotient)	PIQ 63.1 (assessed using the LIPS; Leiter, 1948)
Dose/intensity (mg/hours)	(1) Planned intensity was 26 hours (3 hours/6 weeks, equating to 0.5 hours/week) (2) 25 hours (alternate 1.5 hour/week group sessions and 1 hour/week individual family sessions) (3) Planned intensity was 18 hours (1.5 hour/week)	50 hours (3 hours/week of educational seminars for 5 weeks and 3 hours/week of on-site day care staff consultation for 10 weeks, and three parent-staff review meetings at day care centre [estimated at 3 hours] and 2 in-home visits [estimated at 2 hours]; equating to 4 hours/week)
Setting	(1) Home (2) Not reported (3) Home	Outpatient, educational (day care centre) and home-based
Length of treatment (weeks)	(1) 52 (2) 20 (3) 12	12
Continuation phase (length and inclusion criteria)	(1) 52 (2) 46 (including 6-month post-intervention follow-up) (3) 12	12

Evidence for the effectiveness of parent training on improving the impact of autism on the family and the quality of the evidence is presented in Table 306 and Table 307. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 306: Evidence summary table for effects of parent training on improving the impact of autism on the family as a direct or indirect outcome

	Parent training versus treatment as usual						
Outcome	Parental stress (direct or indirect outcome)	Parental mental health	Parental somatic symptoms	Parental anxiety and insomnia	Parental social dysfunction	Parental severe depression	General family function
Outcome measure	(1) Parenting Stress Thermometer: total (direct outcome) (2) PSI/PSI-3: total (indirect outcome)	GHQ-28: total score at: (1) Post-intervention (2) 6-month post-intervention follow-up	GHQ-28: Somatic symptoms at: (1) Post-intervention (2) 6-month post-intervention follow-up	GHQ-28: Anxiety and insomnia at: (1) Post-intervention (2) 6-month post-intervention follow-up	GHQ-28: Social dysfunction at: (1) Post-intervention (2) 6-month post-intervention follow-up	GHQ-28: Severe depression at: (1) Post-intervention (2) 6-month post-intervention follow-up	McMaster Family Assessment Device: total at: (1) Post-intervention (2) 6-month post-intervention follow-up
Study ID	(1) TONGE2006 (2) DREW2002 WELTERLIN2012	TONGE2006					
Effect size (CI; p value)	(1) SMD -0.42 (-0.84, -0.01; p = 0.04) (2) SMD -0.30 (-0.93, 0.32; p = 0.35) (1)+(2) SMD -0.39 (-0.73, -0.04; p = 0.03)	(1) SMD -0.26 (-0.67, 0.15; p = 0.21) (2) SMD -0.45 (-0.86, -0.03; p = 0.03)	(1) SMD -0.19 (-0.60, 0.22; p = 0.37) (2) SMD -0.22 (-0.63, 0.19; p = 0.29)	(1) SMD -0.16 (-0.57, 0.25; p = 0.44) (2) SMD -0.54 (-0.95, -0.12; p = 0.01)	(1) SMD -0.65 (-1.07, -0.23; p = 0.002) (2) SMD -0.37 (-0.78, 0.04; p = 0.08)	(1) SMD 0.09 (-0.32, 0.49; p = 0.68) (2) SMD -0.14 (-0.55, 0.27; p = 0.50)	(1) SMD -0.31 (-0.72, 0.10; p = 0.13) (2) SMD -0.14 (-0.55, 0.27; p = 0.50)
Heterogeneity (chi²; p value; I²)	Chi² = 0.15, df = 2; p = 0.93; I² = 0%	Not applicable					
Quality of the evidence (GRADE)	Low[1,2]	(1) Very low[1,3] (2) Low[1,2]	Very low[1,3]	(1) Very low[1,3] (2) Low[1,2]	(1) Low[1,2] (2) Very low[1,3]		Very low[1,3]
Number of studies/participants	K = 3; N = 143	K = 1; N = 103					
Forest plot	1.30.3; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants non-blind and high risk of detection bias as parent-completed and parents involved in intervention and not blinded
[2]Downgraded due to serious imprecision as N <400
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)

Table 307: Evidence summary table for effects of parent training (parent and day care staff training) on improving the impact of autism on the family as an indirect outcome

	Parent and day care staff training versus standard day care
Outcome	Parental stress
Outcome measure	Stress-Arousal Checklist subscales: (1) Mothers' Stress (2) Mothers' Arousal (3) Fathers' Stress (4) Fathers' Arousal
Study ID	JOCELYN1998
Effect size (CI; p value)	(1) *Mothers' Stress* SMD -0.06 (-0.73, 0.61; p = 0.86) (2) *Mothers' Arousal* SMD 0.18 (-0.48, 0.85; p = 0.59) (3) *Fathers' Stress* SMD 0.14 (-0.53, 0.80; p = 0.69) (4) *Fathers' Arousal* SMD 0.51 (-0.16, 1.19; p = 0.14)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Very low[1,2]
Number of studies/participants	K = 1; N = 35
Forest plot	1.30.3; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as the reliability and validity of this outcome measure is unclear and parent-completed and parents involved in the intervention so non-blind. [2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).	

There was evidence from a meta-analysis with three studies for a small and statistically significant effect of parent training on parental stress, as measured by the Parenting Stress Thermometer (a visual analogue scale) or the PSI (see Table 306). However, the quality of the evidence was downgraded to low due to risk of bias concerns (non-blind parent-rated outcome measure) and small sample size.

There was also single study evidence for statistically significant effects of parent training on parental mental health; however, effects were mixed. For instance, a delayed effect (significant at 6-month post-intervention follow-up but not at post-intervention) was observed for parental mental health as measured by the total score on the GHQ-28 and the GHQ-28 Anxiety and Insomnia subscale. While a transient effect (significant at post-intervention but not at 6-month post-intervention follow-up) was observed for the GHQ-28 Social Dysfunction subscale (see Table 306). The quality of this evidence was also low due to non-blind parent-rated outcome assessment and small sample sizes. Non-significant effects were observed for the GHQ-28 Somatic Symptoms and Severe Depression subscales, and for general family function as measured by the McMaster Family Assessment Device (see Table 306).

There was no evidence for a statistically significant effect of parent and day care staff training (relative to standard day care) on maternal or paternal stress as an indirect outcome, as measured by the Stress-Arousal Checklist (see Table 307).

9.3 PHARMACOLOGICAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

9.3.1 Studies considered

One study from the search met the eligibility criteria for full-text retrieval and this trial provided relevant clinical evidence and were included in the review. The study examined the efficacy of a pharmacological intervention on improving the impact of autism on the family as an indirect outcome. The study was published in a peer-reviewed journal in 2012. No studies were excluded from the analysis.

One selective noradrenaline reuptake inhibitor (SNRI) trial (ELILILLY2009[105]) examined effects on the family as an indirect outcome.

9.3.2 Clinical evidence

SNRIs for improving the impact of autism on the family as an indirect outcome

The SNRI trial (ELILILLY2009) compared atomoxetine with placebo in children with autism (see Table 74).

Table 308: Study information table for included trial of SNRIs for improving the impact of autism on the family

	Atomoxetine versus placebo
No. trials (N)	1 (97)
Study IDs	ELILILLY2009
Study design	RCT
% female	14
Mean age (years)	9.9
IQ	92.9 (assessed using the WISC-III)
Dose/intensity (mg/hours)	Planned final dose of 1.2 mg/kg/day
Setting	Not reported
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	28 weeks (8-week double-blind phase followed by 20-week open-label continuation phase; however, data were only extracted for the double-blind phase as no control group data were available for open-label continuation)

Evidence for the effectiveness of atomoxetine on improving the impact of autism on the family and the quality of the evidence is presented in Table 309. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

[105] See Chapter 8, Section 8.7.5, for direct outcomes from ELILILLY2009.

Table 309: Evidence summary table for effects of SNRIs on improving the impact of autism on the family as an indirect outcome

	Atomoxetine versus placebo	
Outcome	Parental mental health	Parental stress
Outcome measure	GHQ-28: total	Nijmeegse Ouderlijke Stress Index: total
Study ID	ELILILLY2009	
Effect size (CI; p value)	SMD -0.24 (-0.66, 0.18; p = 0.26)	SMD -0.24 (-0.69, 0.21; p = 0.30)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Low[1]	
Number of studies/participants	K = 1; N = 89	K = 1; N = 77
Forest plot	1.31.1; Appendix 13	
Note. [1]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).		

There was no evidence for a statistically significant effect of atomoxetine on parental mental health or parental stress as an indirect outcome, as measured by the GHQ-28 or the Nijmeegse Ouderlijke Stress Index (see Table 309). There was, however, evidence for statistically significant harms associated with atomoxetine, with participants who received atomoxetine being over three and a half times more likely to experience nausea during the trial and over four times more likely to experience decreased appetite than participants receiving placebo (see Chapter 10, section 10.3.2, for adverse events associated with SNRIs).

9.4 BIOMEDICAL INTERVENTIONS AIMED AT IMPROVING THE IMPACT OF AUTISM ON THE FAMILY

9.4.1 Studies considered

One study from the search met the eligibility criteria for full-text retrieval and this trial provided relevant clinical evidence and were included in the review. The study examined the efficacy of a biomedical intervention on improving the impact of autism on the family as an indirect outcome. The study was published in a peer-reviewed journal in 2011. No studies were excluded from the analysis.

One complementary intervention trial (SILVA2011B[106]) examined effects on the family as an indirect outcome.

9.4.2 Clinical evidence

Complementary therapies for improving the impact of autism on the family as an indirect outcome

The one included complementary therapy trial (SILVA2011B) compared Qigong massage training with waitlist control (see Table 256). Qigong massage is an

[106] See Chapter 8, Section 8.5.6, for direct outcomes from SILVA2011B).

intervention based in Chinese medicine and parents were trained in how to administer the massage for daily massage at home.

Table 310: Study information table for included trial of complementary therapies for improving the impact of autism on the family

	Qigong massage training versus waitlist
No. trials (N)	1 (47)
Study IDs	SILVA2011B
Study design	RCT
% female	30
Mean age (years)	4.8
IQ	Not reported
Dose/intensity (mg/hours)	29.75 hours/119 sessions (1.75 hours/week; 7 sessions/week)
Setting	Home-based
Length of treatment (weeks)	17
Continuation phase (length and inclusion criteria)	17

Evidence for the effectiveness of Qigong massage training on improving the impact of autism on the family and the quality of the evidence is presented in Table 311. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 311: Evidence summary table for effects of complementary therapies on improving the impact of autism on the family as an indirect outcome

	Qigong massage training versus waitlist
Outcome	Parental stress
Outcome measure	Autism Parenting Stress Index: total
Study ID	SILVA2011B
Effect size (CI; p value)	SMD -0.78 (-1.42, -0.14; p = 0.02)
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Low[1,2]
Number of studies/participants	K = 1; N = 41
Forest plot	1.32.1; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of performance and response bias as intervention administrators and participants were non-blind, and high risk of detection bias as outcome assessors were parents who were delivering the intervention and the outcome measure was created for this study so reliability and validity is unknown. [2]Downgraded due to serious imprecision as N <400.	

There was single study evidence for a moderate and statistically significant effect of Qigong massage training on parental stress as an indirect outcome, as measured by the Autism Parenting Stress Index (see Table 311). However, the quality of the evidence was low due to risk of bias concerns (non-blind parent-rated outcome measure and parents involved in intervention) and small sample size.

9.5 CLINICAL EVIDENCE SUMMARY

There was only one meta-analysis possible for effects on the family, and this comparison (with three studies) provided evidence for a small and statistically significant effect of parent training on parental stress. However, improving the impact of autism on the family was only a direct outcome (target of the intervention) in one study, and the quality of the evidence was low.

9.6 ECONOMIC EVIDENCE

Systematic literature review

No studies assessing the cost effectiveness of interventions aimed at improving the impact on the family of a child or young person with autism were identified by the systematic search of the economic literature undertaken for this guideline. Details on the methods used for the systematic search of the economic literature are described in Chapter 3.

9.7 FROM EVIDENCE TO RECOMMENDATIONS

Based on the limited and low quality evidence for interventions aimed at improving the impact of autism on the family, the GDG concluded that there was insufficient evidence to make a recommendation about the use of psychosocial, pharmacological or biomedical interventions for improving parental mental health, parental stress or quality of life for families or carers of children and young people with autism.

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

10 ADVERSE EVENTS ASSOCIATED WITH INTERVENTIONS

10.1INTRODUCTION

Adverse events are unwanted and unintended occurrences during a course of treatment. A full evaluation of any intervention should not only test its effectiveness but its unwanted effects and harms if any as well as its cost. Adverse events can vary both in their frequency (from very common to exceedingly rare) and severity (from mild to severe). They may also be physical symptoms or signs (such as sleep disturbance or high blood pressure) or psychological experiences (such as irritability or anxiety).

It is often difficult to be certain whether an intervention *causes* an adverse event or whether the adverse event is occurring coincidentally. The most robust tests of causality are those made during RCTs of interventions compared with placebo when adverse effects are measured in a standardised way in both treatment arms and the trial is powered sufficient to detect potential adverse effects. If a particular occurrence is statistically more common in the active intervention, it is likely an adverse event. However, the failure to identify adverse events does not mean they did not occur. Rare and/or unexpected events may not be detected in clinical trials (either because they did not occur or they were not measured or the trial was not big enough to detect them). Therefore, their identification can depend on 'post-trial' reports made by clinicians implementing the intervention. In such situations, findings are often more difficult to interpret, because the base-rate for the untoward occurrence in the population receiving the intervention is often unknown and there is, by definition, unlikely to be a test for causal effect in such reports.

Current practice

In general, adverse events have been better measured in interventions involving physical treatments such as medication or supplements than in trials of psychosocial, behavioural or educational interventions because of standardised procedures for pharmacovigilance. However, even in pharmaceutical trials, there is no standardised approach to the detection and measurement of potential adverse effects and research indicates that the more carefully and extensively adverse events are investigated, the more frequently they will be identified (Greenhill, et al., 2003). The use of passive and general enquiry rather than specific elicitation may reduce the number of events identified. Almost all the systematic identification of adverse events occurs during the trial intervention, which may be of relatively short duration. In some interventions, treatment may continue for a substantial period after the formal evaluation ends and hence adverse events that emerge only after a longer period of time or with longer duration of intervention are less likely to be identified. The sample size for most clinical trials is selected to provide statistical power for the primary outcome of the intervention rather than for the identification of multiple

and/or rare adverse events, which means they may be analysed in aggregate rather than individually.

The failure to record adverse events in interventions employing psychosocial, behavioural and educational methods partly reflects an assumption by researchers that such interventions may not cause adverse events at all (Barlow, 2010); but logically, if an intervention is powerful enough to have wanted effects it is also potentially powerful enough to cause unwanted effects.

In general, severity or otherwise of adverse effects is evaluated by clinician (rather than patient/service user) ratings and this is a limitation to the current methodology. Adverse effects constitute one reason for drop-out from treatment, but because they are not the only cause, it is difficult to use this as a proxy for the patient/service user view of the acceptability of adverse effects. A related and significant concern is the difficulty in detecting adverse effects experienced by children and young people with the communication difficulties present in many people with autism. In many of the studies where adverse effects are recorded, the primary informant is a parent/caregiver rather than the child or young person whose perspective and experience may be different from that reported by others.

Given these limitations, the following review of adverse events should be considered as limited in both its identification of possible short- and longer-term adverse effects, and also their causal relationship to the intervention. The relative absence of reported adverse effects' association with non-pharmacological (and supplement) interventions should not be considered as good evidence that such interventions are either safer or more acceptable than other approaches as this may reflect only measurement differences.

10.1.1 Review protocol – adverse events associated with interventions

The review protocol, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Table 7 (further information about the search strategy can be found in Appendix 7).

Table 312: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s)	**RQ 9.1**: For children and young people with autism, what are the potential harms associated with psychosocial, pharmacological or biomedical interventions?
Objectives	To evaluate the potential harms associated with psychosocial, pharmacological and biomedical interventions for children and young people with autism.
Criteria for considering studies for the review	
Population	Children and young people (from birth until their 19th birthday) with autism, (across the full range of intellectual ability) and their families and carers. If some, but not all, of a study's participants are eligible for our review, we will ask the study authors for disaggregated data. If we are unable to obtain the appropriate disaggregated data, then we will include a study if the majority (at least 51%) of its participants are eligible for our review. If we are unable to determine the exact percent of a study's participants who are eligible, then we will include the study if its participants are eligible on average (for example, the mean participant age is less than 19 years). Consideration will be given to the particular management and support needs of: • Looked-after children • immigrant groups • children with regression in skills Excluded groups include: • adults (19 years and older).
Intervention	Any psychosocial, pharmacological or biomedical intervention for children and young people with autism
Comparison	No treatment or treatment-as-usual (includes placebo and waitlist control up until receiving intervention), other active interventions
Critical outcomes	• Any adverse event (dichotomous measure of number of participants expediting any adverse event during the treatment period) • Discontinuation due to adverse events • Weight gain • Prolactin concentration • Extrapyramidal symptoms • Metabolic measures • Blood pressure
Time points	Some studies may measure outcomes at multiple time points. We will run the following analyses: • Post-intervention (end of treatment) • Longest follow-up
Study design	• RCTs • Systematic reviews Non-English language papers will be excluded, as will books, dissertation abstracts, trade magazines, policy and guidance, and non-empirical research.
Include unpublished data?	Yes but only where:

	• the evidence was accompanied by a trial report containing sufficient detail to properly assess the quality of the data • the evidence was submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG should not accept evidence submitted as commercial in confidence. However, the GDG should recognise that unpublished evidence submitted by investigators, might later be retracted by those investigators if the inclusion of such data would jeopardise publication of their research.
Restriction by date?	No limit
Minimum sample size	• N ≥ 10 per arm (ITT) Exclude studies with >50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data).
Study setting	• Primary, secondary and tertiary health and social care. This guideline will also be relevant to other health and social care settings (including forensic services and youth justice settings) although they are not explicitly covered. • The guideline will also address interventions relevant to early years services and educational settings.
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, HTA, IBSS, MEDLINE, PreMEDLINE, PsycEXTRA, PsycINFO, Social Policy and Practice, Sociological Abstracts, SSA, SSCI
Date searched	Systematic reviews: 1995 up to January 2013 RCTs: inception of database up to January 2013
Searching other resources	Hand-reference searching and citation searches of included studies, hand-searching of the 'Research Autism' website, and searching the ISRCTN and ClinicalTrials.gov website using the term 'autism'
The review strategy	• The initial aim is to conduct a meta-analysis evaluating the clinical effectiveness of the interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. Consider subgroup meta-analyses that takes into account the effectiveness of interventions as moderated by: • the nature and severity of the condition? • the presence of coexisting conditions (including, mental and behaviour, neurodevelopmental, medical or genetic, and functional, problems and disorders)? • age? • gender? • the presence of sensory differences? • IQ? • language level? • family/carer contextual factors (for example, socioeconomic status, parental education, parental mental health, sibling with special education needs)?

10.1.2 Outcomes

A large number of outcome measures for adverse events were reported, those that reported sufficient data to be extractable and were not excluded (see Appendix 12f) are in Table 21.

Table 313: Outcome measures for impact on the family extracted from studies of interventions aimed at improving the impact of autism on the family

Category	Sub-category	Scale
Adverse events	Any adverse event	Number of participants experiencing any adverse event during the trial, measured using: • Checklist derived from the Physicians' Desk Reference (PDR, 1997; study-specific, Hellings et al., 2005) • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) • Study-specific daily treatment logbooks (Rossignol et al., 2009) • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) • Study-specific outcome measure (Shea et al., 2004) • Study-specific report (Bent et al., 2011; King et al., 2001; Marcus et al., 2009; Owen et al., 2009) • Study-specific side effect checklist (Campbell et al., 1993) Number of participants experiencing more than one adverse event during the trial, measured using: • Physical examination (study-specific; Hollander et al., 2010) Number of participants experiencing any serious adverse event, measured using: • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) Discontinuation due to adverse event
	Neuropsychiatric symptoms	• Dosage Record and Treatment Emergent Symptom Scale (DOTES; Guy, 1976) – Excitement/agitation, Depressed affect, and Akathisia subscales • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Aggression, Akathisia, Agitation, and Depression subscales • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) – Increased energy level, Anger or irritability, Aggression or hostility, Headache or migraine, Restlessness or difficulty settling down, Disinhibited, impulsive or intrusive behaviour, Silliness, Anxiety, Mood lability, Increased speech, Decreased attention and concentration, Hyperactivity, and

		Stereotypy subscales • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Aggression subscale • Study-specific outcome measure (Shea et al., 2004) – Apathy, and Anorexia subscales • Study-specific report of adverse event (Bent et al., 2011; Gringras et al., 2012; Handen et al., 2009; King et al., 2001; Marcus et al., 2009; Owen et al., 2009) – Psychiatric disorders total, and Antisocial behaviour, Aggression, Akathisia, Mood swings, Increased excitability, Self-stimulatory behaviour, Hyperactivity, and Increased activity subscales • Study-specific side effect checklist (Akhondzadeh et al., 2004, 2008; Campbell et al., 1993; Hasanzadeh et al., 2012; Rupp, 2002) – Aggressiveness, Irritability, Hyperactivity, Anxiety, Nervousness, Restlessness, Temper tantrums, Stereotypies, Decreased verbal production (transient), and Self-injurious behaviour subscales
	Gastrointestinal symptoms	• DOTES – Any gastrointestinal symptom, and Constipation, Nausea/vomiting, and Diarrhoea subscales • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Abdominal discomfort, Abdominal pain upper, Constipation, Nausea, Vomiting, and Diarrhoea subscales • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Diarrhoea or loose stools, Abdominal discomfort, and Vomiting or nausea subscales • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Abdominal pain, Abdominal pain (upper), Diarrhoea, Nausea, and Vomiting subscales • Study-specific outcome measure (Shea et al., 2004) – Abdominal pain, Vomiting, and Constipation subscales • Study-specific report of adverse event (Bent et al., 2011; Gringras et al., 2012; Handen et al., 2009; Marcus et al., 2009; Owen et al., 2009) – Gastrointestinal disorders total, and gastrointestinal symptoms, Abdominal pain upper, Nausea, Vomiting, Diarrhoea, and Gastroenteritis viral subscales • Study-specific side effect checklist (Akhondzadeh et al., 2004, 2008; Campbell et al., 1993; Hasanzadeh et al., 2012; Rupp, 2002) – Stomach ache, Abdominal pain, Constipation, Diarrhoea, Nausea, and Vomiting subscales
	Sleep disturbance	• Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011)

		– Hypersomnia, and Insomnia subscales • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Any insomnia, Initial insomnia or difficulty falling asleep, and Midcycle or other insomnia subscales • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Early morning awakening, and Initial insomnia subscales • Study-specific outcome measure (Shea et al., 2004) – Insomnia, and Sleep problems subscales • Study-specific report of adverse event (King et al., 2001; Marcus et al., 2009; Owen et al., 2009) – Insomnia, and Hypersomnia subscales • Study-specific side effect checklist (Rupp, 2002) – Insomnia
	Infections and infestations	• Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Cold, flu or other systemic infection subscale • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Influenza subscale • Study-specific outcome measure (Shea et al., 2004) – Fever, and Influenza-like symptoms subscales • Study-specific report of adverse event (Handen et al., 2009) – Infections and infestations total
	Metabolic measures	• DOTES – increased appetite and decreased appetite subscales • Laboratory assessment: Fasting glucose (mg/dL); Fasting glucose (≥115 mg/dL); Fasting triglycerides (≥120 mg/dL for females or 160 mg/dL for males); Insulin Resistance (homeostatic model assessment – insulin resistance [HOMA-IR]) • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Increased appetite subscale • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Increased appetite, and Decreased appetite subscales • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Decreased appetite subscale • Study-specific outcome measure (Shea et al., 2004) – Increased appetite • Study-specific report of adverse event (Handen et al., 2009; Marcus et al., 2009; Owen et al., 2009) – Metabolism and nutritional disorders total, and Increased appetite, and Decreased appetite subscales • Study-specific side effect checklist (Akhondzadeh et al., 2004, 2008; Campbell et al., 1993; Hasanzadeh et al., 2012; Rupp, 2002) – Increased appetite subscale, Mild increased

		appetite and Moderate increased appetite subscales, and Decreased appetite subscale
	Weight gain	• Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Weight increased subscale • Study-specific outcome measure (Shea et al., 2004) – Weight increase subscale • Study-specific report of adverse event (Marcus et al., 2009) – Weight increased subscale • Weight assessment: Weight gain (in kg or lb); Clinically relevant weight gain (≥7%); BMI change (kg/m-squared)
	Skin and subcutaneous tissue disorders	• Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Rash subscale • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Rash, and Other skin or subcutaneous tissue disorder subscales • Study-specific report of adverse event (Bent et al., 2011; Gringras et al., 2012; Handen et al., 2009; Marcus et al., 2009) – Skin and subcutaneous tissue disorders total, and Rash subscale • Study-specific side effect checklist (Rupp, 2002) – Skin irritation subscale
	General symptoms	• DOTES -Dizziness, Increased salivation, and Sweating subscales • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Pyrexia, Thirst, Fatigue, Sedation, Somnolence, and Headache subscales • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Fatigue subscale • Simpson-Angus Scale (Simpson & Angus, 1970) – Drooling subscale • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Dizziness, Headache, Fatigue, and Pyrexia subscales • Study-specific outcome measure (Shea et al., 2004) – Somnolence, Fatigue, Saliva increased, and Headache subscales • Study-specific report of adverse event (Gringras et al., 2012; Handen et al., 2009; Marcus et al., 2009; Owen et al., 2009) – General disorders and administration site conditions total, and Dizziness, Drooling, Salivary hypersecretion, Thirst, Sedation, Somnolence, Fatigue, Lethargy, Headache, Hung-over feeling, Pyrexia, Hypothermia, and Other adverse event subscales • Study-specific side effect checklist (Akhondzadeh et al., 2004, 2008; Campbell et al., 1993; Hasanzadeh et al., 2012; Rupp, 2002) – Dizziness, Headache, Trouble swallowing, Stiffness, Fatigue, Drowsiness, Slight sleepiness,

		Falling asleep, Day time drowsiness, Morning drowsiness, Slow movement, Dry mouth, Increased thirst, and Sore throat subscales
	Immune system	• Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Allergies subscale • Study-specific report of adverse event (Handen et al., 2009) – Immune system disorders total
	Nervous system disorders	• Study-specific report of adverse event (Handen et al., 2009) – Nervous system disorders total
	Respiratory, thoracic and mediastinal symptoms	• DOTES – Nasal congestion subscale • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Nasopharyngitis, Nosebleed, Cough, and Upper respiratory tract infection subscales • Safety Monitoring Uniform Report Form (Greenhill et al., 2004) –Cough subscale • Study-specific outcome measure (Shea et al., 2004) – Upper respiratory tract infection, Rhinitis, and Coughing subscales • Study-specific report of adverse event (Bent et al., 2011; Gringras et al., 2012; Handen et al., 2009; Marcus et al., 2009; Owen et al., 2009) – Respiratory, thoracic and mediastinal disorders total, and Breathlessness, Upper respiratory tract infection, Cough, Nasal congestion, Nose bleed, Rhinorrhea, and Nasopharyngitis subscales • Study-specific side effect checklist (Rupp, 2002) – Nasal congestion, and Upper respiratory tract infection subscales
	Ear and labyrinth disorders	• Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Ear infection subscale • Study-specific report of adverse event (Handen et al., 2009) – Ear and labyrinth disorders total • Study-specific side effect checklist (Rupp, 2002) – Earache subscale
	Eye disorders	• Study-specific report of adverse event (Handen et al., 2009) – Eye disorders total
	Prolactin concentration	• Prolactin concentration (in ng/ml) • Laboratory assessment: Number of participants with clinically relevant prolactin levels (greater than the upper limit of normal)
	Motor measures	• Abnormal Involuntary Movements Scale (AIMS; Guy, 1976) – Total score • DOTES – Increased motor activity, and Tremor subscales • Extrapyramidal Symptoms Rating Scale (Chouinard et al., 1980) – Total score and Section I (dystonia, parkinsonism and dyskinesia) • Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Psychomotor hyperactivity subscale • Simpson-Angus Scale – Tremor subscale • Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) –

		Psychomotor hyperactivity subscale • Study-specific outcome measure (Shea et al., 2004) – Tremor subscale • Study-specific report of adverse event (Gringras et al., 2012; Marcus et al., 2009; Owen et al., 2009) – Any treatment-emergent extrapyramidal symptom, Extrapyramidal disorder, Muscle rigidity, Muscle spasms, Tremor, Psychomotor hyperactivity, Hyperkinesia, Hypokinesia, and Seizures subscales • Study-specific side effect checklist (Hasanzadeh et al., 2012; Rupp, 2002) – Dyskinesia, Slowed movement, Twitches, and Muscle rigidity subscales
	Musculoskeletal and connective tissue disorders	• Study-specific open-ended questioning for adverse events (Harfterkamp et al., 2012) – Myalgia subscale
	Blood pressure and heart related conditions	• Physical exam: Diastolic blood pressure (in mm Hg); Pulse (in bpm); Systolic blood pressure (in mm Hg) • Study-specific outcome measure (Shea et al., 2004) – Tachycardia subscale • Study-specific report of adverse event (Handen et al., 2009) – Blood and lymphatic system disorders total • Study-specific side effect checklist (Rupp, 2002) – Tachycardia subscale
	Vascular disorders	• Study-specific report of adverse event (Handen et al., 2009) – Vascular disorders total
	Liver conditions	• Laboratory assessment: Change in alanine transaminase
	Renal and urinary symptoms	• Non-systematic assessment (Johnson & Johnson Pharmaceutical Research & Development, 2011) – Enuresis subscale • Study-specific report of adverse event (Handen et al., 2009; Marcus et al., 2009; Owen et al., 2009) – Renal and urinary disorders total, and Enuresis subscale • Study-specific side effect checklist (Rupp, 2002) – Enuresis subscale
	Injury, poisoning and procedural complications	• Study-specific report of adverse event (Handen et al., 2009) – Injury, poisoning and procedural complications total
	Investigations	• Study-specific report of adverse event (Handen et al., 2009) – Investigations total

10.2 HARMS ASSOCIATED WITH PSYCHOSOCIAL INTERVENTIONS

10.2.1 Studies considered

No studies met inclusion criteria for full-text retrieval for adverse events associated with psychosocial interventions.

10.3 HARMS ASSOCIATED WITH PHARMACOLOGICAL INTERVENTIONS

10.3.1 Studies considered

Twenty-three studies from the search met the eligibility criteria for full-text retrieval. Of these, 19 RCTs provided relevant clinical evidence and were included in the review. All of these studies examined adverse events associated with pharmacological interventions as an indirect outcome. Though for one study (CAMPBELL1978 [Campbell et al., 1978]) data could only be extracted for adverse events (and not for positive treatment effects) so the study characteristics for this study are categorised as if adverse events were the direct outcome (target of the intervention). All studies were published in peer-reviewed journals between 1978 and 2012. In addition, four studies were excluded from the analysis. The reasons for exclusion were that safety data could not be extracted or the paper was a systematic review with no useable data and any meta-analysis not appropriate to extract. Further information about both included and excluded studies can be found in Appendix 12f.

Two anticonvulsant trials (HELLINGS2005, HOLLANDER2010[107]) examined adverse events.

One antidepressant trial (KING2009[108]) examined adverse events.

One antihistamine trial (AKHONDZADEH2004[109]) examined adverse events.

One antioxidant trial (HARDAN2012[110]) examined adverse events.

Nine antipsychotic trials (CAMPBELL1978, JOHNSON&JOHNSON2011, LUBY2006, MARCUS2009, MIRAL2008, NAGARAJ2006, OWEN2009, RUPPRISPERIDONE2001, SHEA2004[111]) examined adverse events.

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[107] See Section 7.3.2 for direct outcomes from HELLINGS2005 and HOLLANDER2010.20
[108] See Section 6.3.7 for direct outcomes from KING2009.
[109] See Section 7.3.2 for direct outcomes from AKHONDZADEH2004.
[110] See Section 7.3.2 for direct outcomes from HARDAN2012.
[111] See Chapter 7, Section 7.3.2, for direct outcomes from JOHNSON&JOHNSON2011, MARCUS2009, OWEN2009, RUPPRISPERIDONE2001 and SHEA2004; see Section 6.3.3 for direct outcomes from LUBY2006, MIRAL2008 and NAGARAJ2006.

One antiviral trial (KING2001[112]) examined adverse events.

One cognitive enhancer trial (AKHONDZADEH2008[113]) examined adverse events.

One melatonin trial (GRINGRAS2012[114]) examined adverse events.

One opioid antagonist trial (CAMPBELL1993[115]) examined adverse events.

Finally, one selective noradrenaline reuptake inhibitor (SNRI) trial (ELILILLY2009[116]) examined adverse events.

10.3.2 Clinical evidence

Adverse events associated with anticonvulsants

Both of the included anticonvulsant trials (HELLINGS2005, HOLLANDER2010) involved a comparison between divalproex and placebo in children with autism (see Table 142).

Table 314: Study information table for included trials for adverse events associated with anticonvulsants

Comparison	Divalproex versus placebo
No. trials (N)	2 (63)
Study IDs	(1) HELLINGS2005 (2) HOLLANDER2010
Study design	(1)-(2) RCT
% female	(1) 33 (2) 16
Mean age (years)	(1) 11.2 (2) 9.5
IQ	(1) 54 (assessed using variable IQ tests) (2) 63.3 (assessed using the LIPS-R)
Dose/intensity (mg/hours)	(1) Final planned dose of 20 mg/kg/day (mean valproic acid through blood levels were 77.8 mcg/mL at week 8) (2) Not reported
Setting	(1)-(2) Outpatient
Length of treatment (weeks)	(1) 8 (2) 12
Continuation phase (length and inclusion criteria)	(1) 8 (2) 12

Evidence for adverse events associated with divalproex and the quality of the evidence is presented in Table 304. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

[112] See Chapter 7, Section 7.3.2, for direct outcomes from KING2001.
[113] See Chapter 7, Section 7.3.2, for direct outcomes from AKHONDZADEH2008.
[114] See Chapter 8, Section 8.8.3, for direct outcomes from GRINGRAS2012.
[115] See Chapter 7, Section 7.3.2, for direct outcomes from CAMPBELL1993.
[116] See Chapter 8, Section 8.7.5, for direct outcomes from ELILILLY20009.

Table 315: Evidence summary table for adverse events associated with anticonvulsants

	Divalproex versus placebo			
Outcome	Any adverse event	More than one adverse event	Discontinuation due to adverse event	Weight gain
Outcome measure	Number of participants experiencing any side effect during the trial (measured using checklist derived from PDR)	Number of participants experiencing more than one adverse event during the trial (measured using physical examination)	Number of participants who discontinued due to adverse event	Number of kilograms or pounds that participants gained during the trial
Study ID	HELLINGS2005	HOLLANDER2010	(1) HELLINGS2005 (2) HOLLANDER2010	
Effect size (CI; p value)	RR 1.19 (0.88, 1.61; p = 0.25)	RR 1.72 (0.40, 7.32; p = 0.46)	RR 2.37 (0.26, 21.43; p = 0.44)	SMD 0.29 (-0.24, 0.82; p = 0.28)
Heterogeneity (chi²; p value; I²)	Not applicable		Chi^2 = 0.01, df = 1; p = 0.92; I^2 = 0%	Chi^2 = 0.97, df = 1; p = 0.32; I^2 = 0%
Quality of the evidence (GRADE)	Very low[1,2,3]			
Number of studies/participants	K = 1; N = 30	K = 1; N = 27	K = 2; N = 57	
Forest plot	1.33.1; Appendix 13			

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded for strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.

There was no evidence for statistically significant adverse events associated with divalproex (see Table 304).

Adverse events associated with antidepressants

The one included antidepressant trial compared citalopram with placebo (KING2009) in children with autism (see Table 78).

Evidence for adverse events associated with citalopram and the quality of the evidence is presented in Table 317, Table 318, Table 319 and Table 320. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was evidence for a number of statistically significant adverse events associated with citalopram. Participants receiving citalopram were more likely to experience any adverse event during the trial than participants receiving placebo (see Table 317). There was also increased risk with citalopram for: increased energy level (see

Table 317, participants receiving citalopram were nearly twice more likely to experience increased energy than participants receiving placebo); disinhibited, impulsive, or intrusive behaviour (see Table 317, participants receiving citalopram were nearly three times more likely to experience disinhibited behaviour than participants receiving placebo); decreased attention and concentration (see Table 318, participants receiving citalopram were over four and a half times more likely to experience decreased attention than participants receiving placebo); hyperactivity (see Table 318, participants receiving citalopram were over four and a half times more likely to experience hyperactivity than participants receiving placebo); stereotypy (see Table 318, participants receiving citalopram were over eight times more likely to experience stereotypy than participants receiving placebo); diarrhoea or loose stools (see Table 318, participants receiving citalopram were twice more likely to experience diarrhoea than participants receiving placebo); any insomnia (see Table 319, participants receiving citalopram were nearly twice more likely to experience insomnia than participants receiving placebo); initial insomnia or difficulty falling asleep (see Table 319, participants receiving citalopram were over two and a half times more likely to experience difficulty falling asleep than participants receiving placebo); and other skin or subcutaneous tissue disorder (see Table 320, participants receiving citalopram were over nine times more likely to experience skin or subcutaneous tissue disorder, other than rash, than participants receiving placebo).

Table 316: Study information table for included trials for adverse events associated with antidepressants

	Citalopram versus placebo
No. trials (N)	1 (149)
Study IDs	KING2009
Study design	RCT
% female	14
Mean age (years)	9.4
IQ	Not reported (58% IQ>70)
Dose/intensity (mg/hours)	Final dose of citalopram 16.5 mg/day; final dose of placebo 18.5 mg/day
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Table 317: Evidence summary table for adverse events associated with antidepressants

	Citalopram versus placebo							
Outcome	Any adverse event	Nightmares	Increased energy level	Anger or irritability	Aggression or hostility	Headache or migraine	Restlessness or difficulty settling down	Disinhibited, impulsive, or intrusive behaviour
Outcome measure	Safety Monitoring Uniform Report Form (Greenhill et al., 2004)							
Study ID	KING2009							
Effect size (CI; p value)	RR 1.12 (1.02, 1.23; p = 0.02)	RR 11.45 (0.64, 203.38; p = 0.10)	RR 1.94 (1.13, 3.33; p = 0.02)	RR 1.44 (0.76, 2.73; p = 0.26)	RR 1.36 (0.71, 2.60; P = 0.35)	RR 1.56 (0.75, 3.25; p = 0.23)	RR 1.93 (0.82, 4.57; p = 0.13)	RR 2.92 (1.11, 7.68; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable							
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,3,4]	Very low[1,2,3]	Very low[1,3,4]				Very low[1,2,3]
Number of studies/participants	K = 1; N = 149							
Forest plot	1.33.2; Appendix 13							

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to serious imprecision as number of events <300.
[3]Downgraded for strongly suspected publication bias as authors are consultants to pharmaceutical companies.
[4]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 318: Evidence summary table for adverse events associated with antidepressants (continued 1)

	Citalopram versus placebo							
Outcome	Silliness	Anxiety	Mood lability	Increased speech	Decreased attention and concentration	Hyperactivity	Stereotypy	Diarrhoea or loose stools
Outcome measure	Safety Monitoring Uniform Report Form (Greenhill et al., 2004)							
Study ID	KING2009							
Effect size (CI; p value)	RR 0.94 (0.40, 2.17; p = 0.88)	RR 0.93 (0.38, 2.27; p = 0.87)	RR 0.81 (0.32, 2.06; p = 0.66)	RR 2.08 (0.66, 6.62; p = 0.21)	RR 4.68 (1.05, 20.96; p = 0.04)	RR 4.68 (1.05, 20.96; p = 0.04)	RR 8.33 (1.07, 64.95; p = 0.04)	RR 2.20 (1.06, 4.54; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable							
Quality of the evidence (GRADE)	Very low[1,2,3]				Very low[1,3,4]			
Number of studies/participants	K = 1; N = 149							
Forest plot	1.33.2; Appendix 13							

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded for strongly suspected publication bias as authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.

Table 319: Evidence summary table for adverse events associated with antidepressants (continued 2)

	Citalopram versus placebo						
Outcome	Abdominal discomfort	Vomiting or nausea	Any insomnia	Initial insomnia or difficulty falling asleep	Midcycle or other insomnia	Cold, flu or other systemic infection	Decreased appetite
Outcome measure	Safety Monitoring Uniform Report Form (Greenhill et al., 2004)						
Study ID	KING2009						
Effect size (CI; p value)	RR 1.50 (0.68, 3.30; p = 0.31)	RR 2.43 (0.99, 5.98; p = 0.05)	RR 1.71 (1.03, 2.86; p = 0.04)	RR 2.53 (1.11, 5.74; p = 0.03)	RR 1.50 (0.68, 3.30; p = 0.31)	RR 1.24 (0.82, 1.87; p = 0.30)	RR 1.15 (0.52, 2.53; p = 0.74)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Very low[1,2,3]		Very low[1,3,4]		Very low[1,2,3]		
Number of studies/participants	K = 1; N = 149						
Forest plot	1.33.2; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded for strongly suspected publication bias as authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.

Table 320: Evidence summary table for adverse events associated with antidepressants (continued 3)

	Citalopram versus placebo						
Outcome	Increased appetite	Rash	Other skin or subcutaneous tissue disorder	Fatigue	Allergies	Cough	Any serious adverse event
Outcome measure	Safety Monitoring Uniform Report Form (Greenhill et al., 2004)						
Study ID	KING2009						
Effect size (CI; p value)	RR 0.91 (0.35, 2.38; p = 0.85)	RR 1.56 (0.68, 3.60; p = 0.30)	RR 9.37 (1.22, 72.12; p = 0.03)	RR 1.04 (0.46, 2.35; p = 0.92)	RR 1.42 (0.70, 2.88; p = 0.33)	RR 2.08 (0.75, 5.80; p = 0.16)	RR 3.12 (0.13, 75.42; p = 0.48)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Very low[1,2,3]		Very low[1,3,4]	Very low[1,2,3]			
Number of studies/participants	K = 1; N = 149						
Forest plot	1.33.2; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded for strongly suspected publication bias as authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.

Adverse events associated with antihistamines

The antihistamine trial (AKHONDZADEH2004) compared combined cyproheptadine and haloperidol with combined placebo and haloperidol in children with autism (see Table 321).

Table 321: Study information table for included trial for adverse events associated with antihistamines

	Cyproheptadine and haloperidol versus placebo and haloperidol
No. trials (N)	1 (40)
Study IDs	AKHONDZADEH2004
Study design	RCT
% female	40
Mean age (years)	6.7
IQ	Not reported
Dose/intensity (mg/hours)	Planned final dose of haloperidol = 0.05 mg/ kg/day Planned final dose of cyproheptadine = 0.2 mg/ kg/day Planned final dose of placebo not reported
Setting	Outpatient
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	8

Evidence for adverse events associated with cyproheptadine and the quality of the evidence is presented in Table 322 and Table 323. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There was no evidence for any statistically significant adverse events associated with cyproheptadine (as an adjunct to haloperidol) (see Table 322 and Table 323).

Table 322: Evidence summary table for adverse events associated with antihistamines

	Cyproheptadine and haloperidol versus placebo and haloperidol					
Outcome	Extrapyramidal symptoms	Trouble swallowing	Stiffness	Slow movement	Constipation	Diarrhoea
Outcome measure	Extrapyramidal Symptoms Rating Scale: total	Study-specific side effect checklist				
Study ID	AKHONDZADEH2004					
Effect size (CI; p value)	RR 0.33 (0.08, 1.46; p = 0.14)	RR 0.50 (0.10, 2.43; p = 0.39)	RR 0.33 (0.04, 2.94; p = 0.32)	RR 0.33 (0.04, 2.94; p = 0.32)	RR 2.00 (0.41, 9.71; p = 0.39)	RR 0.67 (0.12, 3.57; p = 0.64)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]					
Number of studies/participants	K = 1; N = 40					
Forest plot	1.33.3; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 323: Evidence summary table for adverse events associated with antihistamines *(continued)*

	Cyproheptadine and haloperidol versus placebo and haloperidol				
Outcome	Increased appetite	Morning drowsiness	Day time drowsiness	Restlessness	Fatigue
Outcome measure	Study-specific side effect checklist				
Study ID	AKHONDZADEH2004				
Effect size (CI; p value)	RR 2.25 (0.83, 6.13; p = 0.11)	RR 1.50 (0.28, 8.04; p = 0.64)	RR 0.50 (0.05, 5.08; p = 0.56)	RR 0.25 (0.03, 2.05; p = 0.20)	RR 1.50 (0.28, 8.04; p = 0.64)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	Very low[1,2]				
Number of studies/participants	K = 1; N = 40				
Forest plot	1.33.3; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Adverse events associated with antioxidants

The antioxidant trial (HARDAN2012) compared N-acetylcysteine with placebo in children with autism (see Table 324).

Table 324: Study information table for included trial for adverse events associated with antioxidants

	N-acetylcysteine versus placebo
No. trials (N)	1 (33)
Study IDs	HARDAN2012
Study design	RCT
% female	6
Mean age (years)	7.1 (based on N = 29)
IQ	Not reported
Dose/intensity (mg/hours)	Final dose of 2,700 mg/day (3 doses of 900 mg)
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for adverse events associated with N-acetylcysteine and the quality of the evidence is presented in Table 325 and Table 326. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

There is no evidence for statistically significant adverse events associated with N-acetylcysteine (see Table 325 and Table 326).

Table 325: Evidence summary table for adverse events associated with antioxidants

	N-acetylcysteine versus placebo							
Outcome	Any gastrointestinal side effect	Constipation	Nausea	Diarrhoea	Increased appetite	Loss of appetite	Akathisia	Increased motor activity
Outcome measure	DOTES							
Study ID	HARDAN2012							
Effect size (CI; p value)	RR 1.68 (0.92, 3.09; p = 0.09)	RR 1.61 (0.31, 8.24; p = 0.57)	RR 2.14 (0.66, 6.97; p = 0.21)	RR 3.21 (0.38, 27.40; p = 0.29)	RR 5.33 (0.28, 102.26; p = 0.27)	RR 0.71 (0.14, 3.66; p = 0.69)	RR 3.20 (0.14, 72.62; p = 0.47)	RR 0.71 (0.14, 3.66; p = 0.69)
Heterogeneity (chi²; p value; I²)	Not applicable							
Quality of the evidence (GRADE)	Very low[1,2]							
Number of studies/participants	K = 1; N = 29							
Forest plot	1.33.4; Appendix 13							

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 326: Evidence summary table for adverse events associated with antioxidants *(continued)*

	N-acetylcysteine versus placebo						
Outcome	Tremor	Dizziness	Excitement/agitation	Depressed affect	Nasal congestion	Increased salivation	Sweating
Outcome measure	DOTES						
Study ID	HARDAN2012						
Effect size (CI; p value)	RR 0.36 (0.02, 8.07; p = 0.52)	RR 0.36 (0.02, 8.07; p = 0.52)	RR 0.71 (0.14, 3.66; p = 0.69)	RR 3.20 (0.14, 72.62; p = 0.47)	RR 0.71 (0.25, 2.01; p = 0.52)	RR 0.21 (0.01, 4.09; p = 0.31)	RR 0.36 (0.02, 8.07; p = 0.52)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Very low[1,2]						
Number of studies/participants	K = 1; N = 29						
Forest plot	1.33.4; Appendix 13						
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).							

Adverse events associated with antipsychotics

Five of the antipsychotic trials (JOHNSON&JOHNSON2011, LUBY2006, NAGARAJ2006, RUPPRISPERIDONE2001, SHEA2004) compared risperidone with placebo, and two studies compared aripiprazole with placebo (MARCUS2009, OWEN2009) in children with autism. Data from two trials also allowed for a comparison of low dose antipsychotics (0.125-0.175 mg/day risperidone [JOHNSON&JOHNSON2011]; 5 mg/day aripiprazole [MARCUS2009]) with placebo. One of the antipsychotic trials (MIRAL2008) compared risperidone with haloperidol. Finally, one of the antipsychotic trials (CAMPBELL1978) compared haloperidol and behaviour therapy with placebo and behaviour therapy (see Table 327).

Table 327: Study information table for included trials for adverse events associated with antipsychotics

	Antipsychotic (risperidone or aripiprazole) versus placebo	**Risperidone versus haloperidol**	**Haloperidol and behaviour therapy versus placebo and behaviour therapy**
No. trials (N)	7 (657)	1 (30)	1 (42)
Study IDs	(1) JOHNSON&JOHNSON2011 (2) LUBY2006 (3) MARCUS2009 (4) NAGARAJ2006 (5) OWEN2009 (6) RUPPRISPERIDONE2001 (7) SHEA2004	MIRAL2008	CAMPBELL1978
Study design	(1)-(7) RCT	RCT	RCT
% female	(1) 13 (2) 26 (3) 11 (4) 13 (5) 12 (6) 19 (7) 23	17	20
Mean age (years)	(1) 9.3 (2) 4 (3) 9.7 (4) 5 (5) 9.3 (6) 8.8 (7) 7.5	10.5	4.5
IQ	(1)-(3) Not reported (4) Not reported (28% with mild LD; 28% with moderate LD) (5)-(7) Not reported	Not reported	Not reported
Dose/intensity (mg/hours)	(1) Low dose risperidone:0.125 mg (if <45 kg) or 0.175 mg (if ≥45 kg); High dose risperidone: 1.25 mg (if <45 kg)	Final dose of 2.6 mg/day for risperidone and	Final dose of 1.65 mg/day for haloperidol;

	or 1.75 mg (if ≥45 kg) (2) Mean final of risperidone = 1.14 mg/day (3) Fixed doses of 5 mg/day or 10 mg/day or 15 mg/day (3 active treatment arms) (4) Planned final dose = 1 mg/day (5) 2-15 mg/day (6) Final dose of 1.8 mg/day of risperidone and 2.4 mg/day of placebo (7) Final dose of 1.48 mg/day	haloperidol	3.95 mg/day for placebo
Setting	(1) Not reported (2) Outpatient (3) Research setting (4) Outpatient (5) Not reported (6) Study was conducted across five university sites (7) Outpatient	Not reported	Inpatient
Length of treatment (weeks)	(1) 6 (2) 24 (3) 8 (4) 26 (5)-(7) 8	10	8
Continuation phase (length and inclusion criteria)	(1) 26 (including open-label phase; however, data cannot be extracted for follow-up as all participants received risperidone resulting in no control group for 6-month outcome measures) (2) 24 (3) 8 (4) 26 (5) 8 (6) 8 (in the studies included in RUPPRISPERIDONE2002, an open-label 16-week extension is reported in Aman and colleagues [2005] and 95-week open-label follow-up phase in Anderson and colleagues [2007], but efficacy or safety data are not extractable for this follow-up) (7) 8	12 (including a 1-2-week screening phase)	12 (including 2-week placebo washout at the beginning and 2 weeks of placebo and behaviour therapy at the end of the trial)

Evidence for adverse events associated with antipsychotics and the quality of the evidence is presented in Table 328, Table 329, Table 330, Table 331, Table 332, Table 333, Table 334, Table 335, Table 336 and Table 337. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 328: Evidence summary table for adverse events associated with antipsychotics

	Antipsychotic versus placebo						
Outcome	Any side effect	Discontinuation due to adverse events	Discontinuation due to drooling	Discontinuation due to sedation	Discontinuation due to tremor	Clinically relevant (≥7%) weight gain	Weight gain
Outcome measure	Non-systematic assessment, study-specific outcome measure or study-specific report	Study-specific report				Weight assessment	Non-systematic assessment, study-specific outcome measure or study-specific report
Study ID	(1) MARCUS2009 OWEN2009 (2) CAMPBELL1978 (3) JOHNSON& JOHNSON2011 SHEA2004	OWEN2009	MARCUS2009			MARCUS2009 OWEN2009	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011 SHEA2004
Effect size (CI; p value)	(1)+(2)+(3) RR 1.27 (1.14, 1.42; p <0.00001) (1) *Aripiprazole* RR 1.23 (1.08, 1.41; p = 0.002) (2) *Haloperidol* RR 3.20 (1.45, 7.05; p = 0.004) (3) *Risperidone* RR 1.17 (0.98, 1.39; p = 0.07)	*Aripiprazole* RR 1.81 (0.46, 7.16; p = 0.40)	*Aripiprazole* RR 2.19 (0.12, 41.76; p = 0.60)	*Aripiprazole* RR 4.70 (0.27, 80.88; p = 0.29)	*Aripiprazole* RR 2.82 (0.15, 51.50; p = 0.48)	*Aripiprazole* RR 3.80 (1.79, 8.05; p = 0.0005)	(1)+(2) RR 2.43 (0.85, 6.98; p = 0.10) (1) *Aripiprazole* RR 2.16 (0.27, 17.17; p = 0.47) (2) *Risperidone* RR 2.55 (0.75, 8.66; p = 0.13)
Heterogeneity (chi²; p value; I²)	Heterogeneity: Chi² = 6.67,	Not applicable				Chi² = 0.30, df = 1; p = 0.59;	Chi² = 0.26, df = 2; p = 0.88;

	df = 4; p = 0.15; I^2 = 40% Test for subgroup differences: Chi^2 = 5.98, df = 2; p = 0.05, I^2 = 66.5%			I^2 = 0%	I^2 = 0%
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,3,4]		Very low[1,3,5]	Very low[1,3,4]
Number of studies/participants	K = 5; N = 528	K = 1; N = 98	K = 1; N = 216	K = 2; N = 313	K = 3; N = 391
Forest plot	1.33.5; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to serious inconsistency as I^2 value indicates moderate heterogeneity.
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[5]Downgraded due to serious imprecision as number of events <300.

Table 329: Evidence summary table for adverse events associated with antipsychotics (continued 1)

	Antipsychotic versus placebo						
Outcome	Weight gain (in kg)	BMI change (kg/m-squared)	Clinically relevant prolactin elevation (above upper limit of normal for age and gender)	Prolactin concentration (ng/ml)	Any treatment-emergent extrapyramidal symptom	Extrapyramidal symptoms	Extrapyramidal disorder
Outcome measure	Weight assessment		Laboratory assessment		Study-specific report of adverse event	AIMS: total	Study-specific report of adverse event
Study ID	(1) MARCUS2009 (2) JOHNSON &JOHNSON2011 LUBY2006 NAGARAJ2006 RUPPRISPERIDONE2001 SHEA2004	MARCUS2009	MARCUS2009 OWEN2009	LUBY2006 RUPPRISPERIDONE2001	MARCUS2009 OWEN2009	JOHNSON &JOHNSON2011	MARCUS2009 OWEN2009
Effect size (CI; p value)	(1)+(2) SMD 0.69 (0.51, 0.88; p <0.00001) (1) *Aripiprazole* SMD 0.48 (0.16, 0.80; p = 0.003) (2) *Risperidone* SMD 0.80 (0.57, 1.03; p <0.00001)	*Aripiprazole* SMD 0.31 (-0.00, 0.63; p = 0.05)	*Aripiprazole* RR 0.19 (0.04, 0.98; p = 0.05)	*Risperidone* SMD 1.80 (1.38, 2.22; p <0.00001)	*Aripiprazole* RR 1.89 (0.98, 3.67; p = 0.06)	*Risperidone* SMD -0.46 (-0.89, -0.03; p = 0.04)	*Aripiprazole* RR 6.02 (0.70, 51.91; p = 0.10)
Heterogeneity (chi²; p value; I^2)	Heterogeneity: Chi² = 3.91, df = 5; p = 0.56; I^2 = 0% Test for subgroup differences: Chi² = 2.52,	Not applicable	Chi² = 0.82, df = 1; p = 0.37; I^2 = 0%	Chi² = 1.61, df = 1; p = 0.21; I^2 = 38%	Chi² = 0.00, df = 1; p = 0.97; I^2 = 0%	Not applicable	Chi² = 0.19, df = 1; p = 0.66; I^2 = 0%

	df = 1; p = 0.11; I^2 = 60.3%						
Quality of the evidence (GRADE)	Low[1,2]	Very low[1,2,3]	Very low[1,2,4]	Low[1,5]	Very low[1,2,6]	Very low[1,2,5]	Very low[1,2,6]
Number of studies/participants	K = 6; N = 541	K = 1; N = 216	K = 2; N = 313	K = 2; N = 124	K = 2; N = 313	K = 1; N = 92	K = 2; N = 313
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)
[4]Downgraded due to serious imprecision as number of events <300.
[5]Downgraded due to serious imprecision as N <400.
[6]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 330: Evidence summary table for adverse events associated with antipsychotics (continued 2)

	Antipsychotic versus placebo						
Outcome	Fasting glucose (mg/dL) change score	Fasting glucose (≥115 mg/dL)	Fasting triglycerides (≥120 mg/dL for females or 160 mg/dL for males)	Insulin resistance (HOMA-IR) change score	Leptin (mg/L) change score	Diastolic blood pressure (mm Hg) change scores	Systolic blood pressure (mm Hg) change scores
Outcome measure	Laboratory assessment					Physical exam	
Study ID	JOHNSON &JOHNSON2011	MARCUS2009 OWEN2009 (effect not estimable)	MARCUS2009 OWEN2009	JOHNSON &JOHNSON2011	LUBY2006 RUPPRISPERIDONE2001	SHEA2004	
Effect size (CI; p value)	Risperidone SMD 0.02 (-0.49,	Aripiprazole RR 1.57 (0.08,	Aripiprazole RR 1.80 (0.74,	Risperidone SMD -0.12 (-0.63,	Risperidone SMD 0.64 (0.24, 1.04; p = 0.002)	Risperidone SMD 0.15 (-	Risperidone SMD 0.44 (-

	0.53; p = 0.93)	32.11; p = 0.77)	4.35; p = 0.19)	0.40; p = 0.65)		0.29, 0.60; p = 0.50)	0.01, 0.89; p = 0.05)
Heterogeneity (chi2; p value; I2)	Not applicable		Chi^2 = 0.63, df = 1; p = 0.43; I^2 = 0%	Not applicable	Chi^2 = 0.97, df = 1; p = 0.33; I^2 = 0%	Not applicable	
Quality of the evidence (GRADE)	Very low1,2,3	Very low1,2,4		Very low1,2,3	Low1,5	Very low1,2,3	
Number of studies/participants	K = 1; N = 68	K = 2; N = 313		K = 1; N = 65	K = 2; N = 104	K = 1; N = 78	
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[3]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5)
[4]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[5]Downgraded due to serious imprecision as N <400.

Table 331: Evidence summary table for adverse events associated with antipsychotics (continued 3)

	Antipsychotic versus placebo						
Outcome	Pulse (bpm) change score	Somnolence/ Drowsiness	Fatigue	Lethargy	Sedation	Upper respiratory tract infection	Rhinitis/rhinorrhea
Outcome measure	Physical exam	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist		Study-specific report of adverse event	Non-systematic assessment or study-specific report	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist	Study-specific outcome measure or study-specific report
Study ID	SHEA2004	(1) MARCUS2009 OWEN2009 (2) JOHNSON&JOHNSON2011 RUPPRISPERIDONE2001 SHEA2004		MARCUS2009	(1) MARCUS2009 OWEN2009 (2) JOHNSON&	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001	(1) MARCUS2009 (2) SHEA2004

					JOHNSON2011	SHEA2004	
Effect size (CI; p value)	*Risperidone* SMD 0.70 (0.24, 1.15; p = 0.003)	(1)+(2) RR 4.81 (2.85, 8.13; p <0.00001) (1) *Aripiprazole* RR 2.98 (1.07, 8.31; p = 0.04) (2) *Risperidone* RR 5.71 (3.08, 10.60; p <0.00001)	(1)+(2) RR 3.16 (1.95, 5.13; p <0.00001) (1) *Aripiprazole* RR 8.33 (2.11, 32.90; p = 0.003) (2) *Risperidone* RR 2.25 (1.38, 3.68; p = 0.001)	*Aripiprazole* RR 6.58 (0.39, 110.35; p = 0.19)	(1)+(2) RR 4.94 (1.94, 12.58; p = 0.0008) (1) *Aripiprazole* RR 4.25 (1.57, 11.51; p = 0.005) (2) *Risperidone* RR 11.03 (0.66, 183.98; p = 0.09)	(1)+(2) RR 1.78 (0.97, 3.25; p = 0.06) (1) *Aripiprazole* RR 0.65 (0.16, 2.58; p = 0.54) (2) *Risperidone* RR 2.45 (1.21, 4.96; p = 0.01)	(1)+(2) RR 2.62 (1.02, 6.77; p = 0.05) (1) *Aripiprazole* RR 2.47 (0.32, 19.30; p = 0.39) (2) *Risperidone* RR 2.68 (0.93, 7.71; p = 0.07)
Heterogeneity (chi²; p value; I²)	Not applicable	Heterogeneity: Chi² = 2.78, df = 4; p = 0.60; *I²* = 0% Test for subgroup differences: Chi² = 1.14, df = 1; p = 0.29; *I²* = 12.2%	Heterogeneity: Chi² = 4.18, df = 4; p = 0.38; *I²* = 4% Test for subgroup differences: Chi² = 3.08, df = 1; p = 0.08, *I²* = 67.5%	Not applicable	Heterogeneity: Chi² = 0.45, df = 2; p = 0.80; *I²* = 0% Test for subgroup differences: Chi² = 0.39, df = 1; p = 0.53; *I²* = 0%	Heterogeneity: Chi² = 4.91, df = 4; p = 0.30; *I²* = 19% Test for subgroup differences: Chi² = 2.82, df = 1; p = 0.09; *I²* = 64.6%	Chi² = 0.00, df = 1; p = 0.94; *I²* = 0%
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,2,4]		Very low[1,2,5]	Very low[1,2,4]	Very low[1,2,5]	Very low[1,2,4]
Number of studies/participants	K = 1; N = 78	K = 5; N = 588		K = 1; N = 216	K = 3; N = 409	K = 5; N = 588	K = 2; N = 295
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[3]Downgraded due to serious imprecision as N <400.
[4]Downgraded due to serious imprecision as number of events <300.
[5]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm

(RR 0.75/1.25)

Table 332: Evidence summary table for adverse events associated with antipsychotics (continued 4)

	Antipsychotic versus placebo						
Outcome	Nasal congestion	Nasopharyngitis	Nose bleed	Coughing	Increased appetite	Decreased appetite	Abdominal pain/stomach ache
Outcome measure	Study-specific report or study-specific side effect checklist	Non-systematic assessment or study-specific report	Non-systematic assessment or study-specific report	Non-systematic assessment, study-specific outcome measure or study-specific report	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist	Study-specific report or study-specific side effect checklist	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist
Study ID	(1) MARCUS2009 OWEN2009 (2) RUPPRISPERIDONE 2001	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011 (effect size not estimable)	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001 SHEA2004	(1) MARCUS2009 (2) RUPPRISPERIDONE 2001	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001 SHEA2004
Effect size (CI; p value)	(1)+(2) RR 1.42 (0.92, 2.19; p = 0.11) (1) Aripiprazole RR 2.37 (0.52, 10.77; p = 0.26) (2) Risperidone RR 1.30 (0.84, 2.02; p = 0.24)	(1)+(2) RR 1.65 (0.68, 3.97; p = 0.27) (1) Aripiprazole RR 1.61 (0.55, 4.71; p = 0.38) (2)	(1)+(2) RR 3.20 (0.40, 25.77; p = 0.27) (1) Aripiprazole RR 3.45 (0.19, 61.28;	(1)+(2) RR 1.63 (0.65, 4.12; p = 0.30) (1) Aripiprazole RR 1.85 (0.43, 8.01;	(1)+(2) RR 3.01 (1.73, 5.24; p = 0.0001) (1) Aripiprazole RR 2.11 (0.89, 5.01; p = 0.09) (2) Risperidone RR 3.83 (1.84, 8.01; p = 0.0003)	(1)+(2) RR 1.43 (0.50, 4.13; P = 0.51) (1) Aripiprazole RR 4.02 (0.54, 29.98; P = 0.17) (2) Risperidone RR 0.62 (0.16, 2.47; P = 0.50)	(1)+(2) RR 1.35 (0.69, 2.64; p = 0.39) (1) Aripiprazole RR 2.16 (0.27, 17.17; p = 0.47) (2) Risperidone RR 1.25 (0.61, 2.54; p = 0.54)

		Risperidone RR 1.72 (0.37, 8.07; p = 0.49)	p = 0.40) (2) Risperidone RR 2.90 (0.14, 58.81; p = 0.49)	p = 0.41) (2) Risperidone RR 1.46 (0.45, 4.79; p = 0.53)			
Heterogeneity (chi2; p value; I2)	Heterogeneity: $Chi^2 = 0.73$, df = 2; p = 0.70; $I^2 = 0\%$ Test for subgroup differences: $Chi^2 = 0.56$, df = 1; p = 0.45; $I^2 = 0\%$	Heterogeneity: $Chi^2 = 1.21$, df = 2; p = 0.55; $I^2 = 0\%$ Test for subgroup differences: $Chi^2 = 0.00$, df = 1; p = 0.95; $I^2 = 0\%$	$Chi^2 = 0.01$, df = 1; p = 0.94; $I^2 = 0\%$	$Chi^2 = 0.06$, df = 1; p = 0.80; $I^2 = 0\%$	Heterogeneity: $Chi^2 = 3.29$, df = 4; p = 0.51; $I^2 = 0\%$ Test for subgroup differences: $Chi^2 = 1.06$, df = 1; p = 0.30; $I^2 = 6.0\%$	$Chi^2 = 2.41$, df = 1; p = 0.12; $I^2 = 58\%$	$Chi^2 = 4.44$, df = 3; p = 0.22; $I^2 = 32\%$ Test for subgroup differences: $Chi^2 = 0.24$, df = 1; p = 0.62; $I^2 = 0\%$
Quality of the evidence (GRADE)	Very low[1,2]	Very low[1,2,3]			Very low[1,3,4]	Very low[1,2,5]	Very low[1,2]
Number of studies/participants	K = 3; N = 413	K = 3; N = 409	K = 2; N = 312	K = 3; N = 391	K = 5; N = 588	K = 2; N = 316	K = 4; N = 491
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.
[5]Downgraded due to serious inconsistency as I2 value indicates moderate heterogeneity.

Table 333: Evidence summary table for adverse events associated with antipsychotics (continued 5)

	Antipsychotic versus placebo						
Outcome	Abdominal discomfort	Vomiting	Nausea	Gastroenteritis viral	Constipation	Diarrhoea	Fever
Outcome measure	Non-systematic assessment	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist	Non-systematic assessment, study-specific report or study-specific side effect checklist	Study-specific report of adverse event	Non-systematic assessment, study-specific outcome measure, or study-specific side effect checklist	Non-systematic assessment, study-specific report or study-specific side effect checklist	Non-systematic assessment, study-specific outcome measure or study-specific report
Study ID	JOHNSON& JOHNSON2011	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001 SHEA2004	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001	MARCUS2009	JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001 SHEA2004	(1) OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 SHEA2004
Effect size (CI; p value)	*Risperidone* RR 0.08 (0.00, 1.56; p = 0.10)	(1)+(2) RR 1.50 (0.97, 2.34; p = 0.07) (1) *Aripiprazole* RR 2.19 (0.95, 5.03; p = 0.07) (2) *Risperidone* RR 1.23 (0.74, 2.07; p = 0.42)	(1)+(2) RR 1.30 (0.51, 3.37; p = 0.58) (1) *Aripiprazole* RR 2.47 (0.32, 19.30; p = 0.39) (2) *Risperidone* RR 1.02 (0.34, 3.00; p = 0.98)	*Aripiprazole* RR 3.45 (0.19, 61.28; p = 0.40)	*Risperidone* RR 2.53 (1.19, 5.39; p = 0.02)	(1)+(2) RR 0.83 (0.43, 1.59; p = 0.58) (1) *Aripiprazole* RR 0.85 (0.24, 2.98; p = 0.80) (2) *Risperidone* RR 0.82 (0.39, 1.75; p = 0.61)	(1)+(2) RR 2.25 (1.04, 4.87; p = 0.04) (1) *Aripiprazole* RR 6.66 (1.13, 39.20; p = 0.04) (2) *Risperidone* RR 1.26

							(0.53, 3.02; p = 0.60)
Heterogeneity (chi²; p value; I²)	Not applicable	Heterogeneity: Chi² = 2.25, df = 4; p = 0.69; I^2 = 0% Test for subgroup differences: Chi² = 1.31, df = 1; p = 0.25; I^2 = 23.6%	Heterogeneity: Chi² = 0.92, df = 2; p = 0.63; I^2 = 0% Test for subgroup differences: Chi² = 0.56, df = 1; p = 0.45, I^2 = 0%	Not applicable	Chi² = 0.81, df = 2; p = 0.67; I^2 = 0%	Heterogeneity: Chi² = 0.08, df = 2; p = 0.96; I^2 = 0% Test for subgroup differences: Chi² = 0.00, df = 1; p = 0.96; I^2 = 0%	Heterogeneity: Chi² = 3.68, df = 3; p = 0.30; I^2 = 19% Test for subgroup differences: Chi² = 2.72, df = 1; p = 0.10; I^2 = 63.3%
Quality of the evidence (GRADE)	Very low[1,2,3]		Very low[1,2]	Very low[1,2,3]	Low[1,4]	Very low[1,2]	Very low[1,3,4]
Number of studies/participants	K = 1; N = 96	K = 5; N = 588	K = 3; N = 412	K = 1; N = 216	K = 3; N = 275	K = 3; N = 293	K = 4; N = 488
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.

Table 334: Evidence summary table for adverse events associated with antipsychotics (continued 6)

	Antipsychotic versus placebo						
Outcome	Influenza-like symptoms	Insomnia	Hypersomnia	Sleep problems	Headache	Dizziness	Increased salivation
Outcome measure	Study-specific outcome measure	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist	Non-systematic assessment or study-specific report	Study-specific side effect checklist	Non-systematic assessment, study-specific outcome measure, study-specific report or study-specific side effect checklist	Study-specific side effect checklist	Study-specific outcome measure or study-specific report
Study ID	SHEA2004	(1) OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001 SHEA2004	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	RUPPRISPERIDONE 2001	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE 2001 SHEA2004	RUPPRISPERIDONE 2001	(1) MARCUS2009 (2) SHEA2004
Effect size (CI; p value)	*Risperidone* RR 1.95 (0.38, 10.04; p = 0.42)	(1)+(2) RR 0.59 (0.34, 1.04; p = 0.07) (1) *Aripiprazole* RR 0.80 (0.19, 3.38; p = 0.76) (2) *Risperidone* RR 0.56 (0.31, 1.03; p = 0.06)	(1)+(2) RR 2.01 (0.33, 12.16; p = 0.45) (1) *Aripiprazole* RR 3.45 (0.19, 61.28; p = 0.40) (2) *Risperidone* RR 1.15 (0.11, 12.20; p = 0.91)	*Risperidone* RR 1.27 (0.58, 2.80; p = 0.55)	(1)+(2) RR 1.10 (0.65, 1.88; p = 0.72) (1) *Aripiprazole* RR 0.85 (0.35, 2.07; p = 0.73) (2) *Risperidone* RR 1.31 (0.67, 2.57; p = 0.43)	*Risperidone* RR 4.16 (0.93, 18.64; p = 0.06)	(1)+(2) RR 3.60 (0.82, 15.82; p = 0.09) (1) *Aripiprazole* RR 3.40 (0.45, 25.70; p = 0.24) (2) *Risperidone* RR 3.90 (0.46, 33.36; p = 0.21)

Heterogeneity (chi²; p value; I²)	Not applicable	Heterogeneity: Chi² = 2.40, df = 3; p = 0.49; *I²* = 0% Test for subgroup differences: Chi² = 0.19, df = 1; p = 0.66; *I²* = 0%	Chi² = 0.35, df = 1; p = 0.55; *I²* = 0%	Not applicable	Heterogeneity: Chi² = 5.55, df = 4; p = 0.24; *I²* = 28% Test for subgroup differences: Chi² = 0.57, df = 1; p = 0.45; *I²* = 0%	Not applicable	Chi² = 0.01, df = 1; p = 0.93; *I²* = 0%
Quality of the evidence (GRADE)	Very low[1,2,3]	Low[1,4]	Very low[1,2,3]	Very low[1,2]	Very low[1,2,3]	Very low[1,2]	Very low[1,2,3]
Number of studies/participants	K = 1; N = 79	K = 4; N = 372	K = 2; N = 312	K = 1; N = 100	K = 5; N = 588	K = 1; N = 100	K = 2; N = 295
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.

Table 335: Evidence summary table for adverse events associated with antipsychotics (continued 7)

	Antipsychotic versus placebo						
Outcome	Drooling	Dry mouth	Increased thirst	Tachycardia	Anorexia	Anxiety	Depression
Outcome measure	Study-specific report or study-specific side effect checklist	Study-specific side effect checklist	Non-systematic assessment, study-specific report or study-specific side effect checklist	Study-specific outcome measure or study-specific side effect checklist	Study-specific outcome measure	Study-specific side effect checklist	Non-systematic assessment
Study ID	(1) MARCUS2009 OWEN2009 (2)	RUPPRISPERIDONE2001	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	RUPPRISPERIDONE2001 SHEA2004	SHEA2004	RUPPRISPERIDONE2001	JOHNSON & JOHNSON2

	RUPPRISPERIDONE2001		RUPPRISPERIDONE2001				011
Effect size (CI; p value)	(1)+(2) RR 6.04 (2.10, 17.39; p = 0.0009) (1) *Aripiprazole* RR 9.65 (1.24, 74.91; p = 0.03) (2) *Risperidone* RR 4.51 (1.37, 14.86; p = 0.01)	*Risperidone* RR 1.87 (0.68, 5.20; p = 0.23)	(1)+(2) RR 1.46 (0.57, 3.74; p = 0.43) (1) *Aripiprazole* RR 1.55 (0.18, 12.93; p = 0.69) (2) *Risperidone* RR 1.44 (0.51, 4.09; p = 0.50)	*Risperidone* RR 7.77 (1.45, 41.72; p = 0.02)	*Risperidone* RR 3.90 (0.46, 33.36; p = 0.21)	*Risperidone* RR 1.25 (0.59, 2.62; p = 0.56)	*Risperidone* RR 2.90 (0.14, 58.81; p = 0.49)
Heterogeneity (chi²; p value; I²)	Heterogeneity: Chi² = 0.44, df = 2; p = 0.80; *I²* = 0% Test for subgroup differences: Chi² = 0.40, df = 1; p = 0.53; *I²* = 0%	Not applicable	Heterogeneity: Chi² = 0.28, df = 2; p = 0.87; *I²* = 0% Test for subgroup differences: Chi² = 0.00, df = 1; p = 0.95; *I²* = 0%	Chi² = 0.09, df = 1; p = 0.76; *I²* = 0%	Not applicable		
Quality of the evidence (GRADE)	Low[1,2]	Very low[1,3]		Low[1,2]	Very low[1,3,4]	Very low[1,3]	Very low[1,3,4]
Number of studies/participants	K = 3; N = 413	K = 1; N = 100	K = 3; N = 412	K = 2; N = 179	K = 1; N = 79	K = 1; N = 100	K = 1; N = 96
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to serious imprecision as number of events <300.
[3]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[4]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.

Table 336: Evidence summary table for adverse events associated with antipsychotics (continued 8)

	Antipsychotic versus placebo						
Outcome	Apathy	Aggression	Agitation	Restlessness	Psychomotor hyperactivity	Tremor	Dyskinesia/Hyperkinesia
Outcome measure	Study-specific outcome measure	Non-systematic assessment or study-specific report	Non-systematic assessment	Non-systematic assessment, study-specific report or study-specific side effect checklist	Non-systematic assessment or study-specific report	Study-specific outcome measure, study-specific report or study-specific side effect checklist	Study-specific report or study-specific side effect checklist
Study ID	SHEA2004	(1) OWEN2009 (2) JOHNSON& JOHNSON2011	JOHNSON& JOHNSON2011	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001	(1) OWEN2009 (2) JOHNSON& JOHNSON2011	(1) MARCUS2009 OWEN2009 (2) RUPPRISPERIDONE2001 SHEA2004	(1) OWEN2009 (2) RUPPRISPERIDONE2001
Effect size (CI; p value)	*Risperidone* RR 10.73 (0.61, 187.79; p = 0.10)	(1)+(2) RR 0.20 (0.04, 1.11; p = 0.07) (1) *Aripiprazole* RR 0.27 (0.03, 2.29; p = 0.23) (2) *Risperidone* RR 0.12 (0.01, 2.35; p = 0.16)	*Risperidone* RR 0.29 (0.03, 3.05; p = 0.30)	(1)+(2) RR 0.63 (0.25, 1.57; p = 0.32) (1) *Aripiprazole* RR 0.32 (0.08, 1.32; p = 0.12) (2) *Risperidone* RR 1.07 (0.29, 3.93; p = 0.92)	(1)+(2) RR 0.56 (0.13, 2.47; p = 0.44) (1) *Aripiprazole* RR 0.53 (0.05, 5.67; p = 0.60) (2) *Risperidone* RR 0.57 (0.08, 3.90; p = 0.57)	(1)+(2) RR 8.99 (2.40, 33.64; p = 0.001) (1) *Aripiprazole* RR 10.42 (1.33, 81.48; p = 0.03) (2) *Risperidone* RR 7.79 (1.46, 41.70; p = 0.02)	(1)+(2) RR 1.51 (0.47, 4.82; p = 0.49) (1) *Aripiprazole* RR 0.35 (0.01, 8.48; p = 0.52) (2) *Risperidone* RR 2.08 (0.55, 7.87; p = 0.28)
Heterogeneity (chi²; p value; I²)	Not applicable	$Chi^2 = 0.19$, df = 1; p = 0.66; $I^2 = 0\%$	Not applicable	Heterogeneity: $Chi^2 = 1.57$, df = 3; p = 0.67; $I^2 = 0\%$ Test for subgroup differences: $Chi^2 = 1.52$, df = 1; p = 0.22; $I^2 = 34.2\%$	$Chi^2 = 0.00$, df = 1; p = 0.96; $I^2 = 0\%$	Heterogeneity: $Chi^2 = 0.06$, df = 3; p = 1.00; $I^2 = 0\%$ Test for subgroup differences: $Chi^2 = 0.05$, df = 1; p = 0.83; $I^2 = 0\%$	Heterogeneity: $Chi^2 = 1.02$, df = 1; p = 0.31; $I^2 = 2\%$ Test for subgroup differences: $Chi^2 = 1.02$, df = 1; p = 0.31; $I^2 = 1.6\%$
Quality of the	Very low[1,2,3]					Very low[1,3,4]	Very low[1,2]

evidence (GRADE)							
Number of studies/participants	K = 1; N = 79	K = 2; N = 193	K = 1; N = 96	K = 4; N = 509	K = 2; N = 193	K = 4; N = 492	K = 2; N = 197
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300

Table 337: Evidence summary table for adverse events associated with antipsychotics (continued 9)

	Antipsychotic versus placebo						
Outcome	Hypokinesia	Muscle rigidity	Muscle spasms	Enuresis	Skin irritation/Rash	Earache/Ear infection	Sore throat
Outcome measure	Study-specific report of adverse event	Study-specific report or study-specific side effect checklist	Study-specific report of adverse event	Non-systematic assessment, study-specific report or study-specific side effect checklist	Non-systematic assessment, study-specific report or study-specific side effect checklist	Non-systematic assessment or study-specific side effect checklist	Study-specific side effect checklist
Study ID	OWEN2009	(1) OWEN2009 (2) RUPPRISPERIDONE2001	OWEN2009	(1) MARCUS2009 OWEN2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001	JOHNSON& JOHNSON2011 RUPPRISPERIDONE2001	RUPPRISPERIDONE2001
Effect size (CI; p value)	*Aripiprazole* RR 3.19 (0.13, 76.36; p = 0.47)	(1)+(2) RR 4.54 (0.79, 26.12; p = 0.09) (1) *Aripiprazole* RR 3.19 (0.13, 76.36; p = 0.47)	*Aripiprazole* RR 0.35 (0.01, 8.48;	(1)+(2) RR 1.14 (0.67, 1.93; p = 0.63) (1) *Aripiprazole* RR 0.92 (0.28, 3.05; p = 0.89)	(1)+(2) RR 1.66 (0.76, 3.60; p = 0.20) (1) *Aripiprazole* RR 1.24 (0.14, 10.81; p = 0.85)	*Risperidone* RR 0.85 (0.22, 3.30; P = 0.82)	*Risperidone* RR 5.20 (0.63, 42.96; p = 0.13)

		(2) *Risperidone* RR 5.20 (0.63, 42.96; p = 0.13)	p = 0.52)	(2) *Risperidone* RR 1.21 (0.68, 2.18; p = 0.52)	(2) *Risperidone* RR 1.74 (0.76, 4.01; p = 0.19)		
Heterogeneity (chi²; p value; I^2)	Not applicable	Chi² = 0.06, df = 1; p = 0.80; I^2 = 0%	Not applicable	Heterogeneity: Chi² = 1.39, df = 3; p = 0.71; I^2 = 0% Test for subgroup differences: Chi² = 0.16, df = 1; p = 0.69; I^2 = 0%	Heterogeneity: Chi² = 0.20, df = 2; p = 0.90; I^2 = 0% Test for subgroup differences: Chi² = 0.08, df = 1; p = 0.77; I^2 = 0%	Chi² = 0.98, df = 1; P = 0.32; I^2 = 0%	Not applicable
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,2]	Very low[1,2,3]	Very low[1,2]			
Number of studies/participants	K = 1; N = 97	K = 2; N = 197	K = 1; N = 97	K = 4; N = 509	K = 3; N = 412	K = 2; N = 196	K = 1; N = 100
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.

There was evidence for a large number of statistically significant adverse events associated with antipsychotics. A meta-analysis with five studies revealed increased risk of experiencing any side effect for participants receiving aripiprazole, haloperidol or risperidone relative to participants receiving placebo (see Table 328). There was increased risk of weight gain with antipsychotics, with participants receiving aripiprazole being nearly four times more likely to show clinically significant (≥7%) weight gain than participants receiving placebo (K = 2; N = 313; see Table 328), and participants receiving aripiprazole or risperidone showing moderate weight gain as measured by continuous weight in kg (K = 6; N = 541; see Table 329). There was also evidence from a five study meta-analysis for elevated risk of increased appetite, with participants receiving aripiprazole or risperidone being over three times more likely to experience increased appetite than participants receiving placebo (see Table 332). In addition, there was evidence from three studies for an increased risk of constipation with participants receiving risperidone being over two and a half times more likely to experience constipation than participants receiving placebo (see Table 333).

There were mixed results for effects of antipsychotics on prolactin levels. There was an effect in favour of the experimental group for clinically relevant prolactin elevation (above upper limit of normal for age and gender) with participants receiving aripiprazole showing a just over 80% risk reduction in clinically significant prolactin relative to participants receiving placebo (K = 2; N = 313; see Table 329). However, for participants receiving risperidone a large and statistically significant adverse effect was observed for a continuous measure of prolactin concentration (K = 2; N = 124; see Table 329).

There were also mixed results for effects of antipsychotics on motor symptoms. There was single study evidence in favour of the experimental group (risperidone) for extrapyramidal symptoms as measured by the AIMS total score (see Table 329). However, there was evidence from a four study meta-analysis for increased risk of tremor associated with antipsychotics, with participants who received aripiprazole or risperidone being nearly nine times more likely to experience tremor than participants who received placebo (see Table 336).

There was evidence from a meta-analysis with five studies for increased risk of somnolence or drowsiness and fatigue, with participants receiving aripiprazole or risperidone nearly five times more likely to experience drowsiness, and over three times more likely to experience fatigue, than participants receiving placebo (see Table 331). There was also evidence from a meta-analysis with three studies for increased risk of sedation, with participants receiving aripiprazole or risperidone nearly five times more likely to experience sedation than participants receiving placebo (see Table 331).

There was evidence from a four study meta-analysis for increased risk of fever associated with antipsychotics, with participants receiving aripiprazole or

risperidone being more than twice as likely to experience fever than participants receiving placebo (see Table 333).

There was evidence from three studies for an increased risk of drooling associated with antipsychotics, with participants who received aripiprazole or risperidone being over six times more likely to experience drooling than participants receiving placebo (see Table 335).

There was evidence from a meta-analysis with two studies for a moderate and statistically significant adverse effect of risperidone on leptin concentration (see Table 330), and for an increased risk of rhinitis/rhinorrhea with participants who received risperidone or aripiprazole being over two and a half times more likely to experience rhinitis than participants receiving placebo (see Table 331). There was also evidence from a two study meta-analysis for an increased risk of tachycardia associated with risperidone, with participants who received risperidone being nearly eight times more likely to experience tachycardia than participants who received placebo (see Table 335).

Finally, there was single study evidence for a moderate and statistically significant adverse effect of risperidone on pulse (see Table 331).

Evidence for adverse events associated with low dose antipsychotics and the quality of the evidence is presented in Table 338, Table 339, Table 340, Table 341, Table 342, Table 343 and Table 344. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 338: Evidence summary table for adverse events associated with low dose antipsychotics

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo						
Outcome	Any side effect	Discontinuation due to sedation	Discontinuation due to drooling	Discontinuation due to tremor	Any treatment-emergent extrapyramidal symptoms	Extrapyramidal symptoms	Extrapyramidal disorder
Outcome measure	Non-systematic assessment or study-specific report of adverse event	Study-specific report of adverse event				AIMS: total	Study-specific report of adverse event
Study ID	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	MARCUS2009				JOHNSON& JOHNSON2011	MARCUS2009
Effect size (CI; p value)	(1)+(2) RR 1.03 (0.84, 1.26; p = 0.77) (1) *Aripiprazole (5 mg/day)* RR 1.22 (1.00, 1.48; p = 0.05) (2) *Risperidone (0.125-0.175 mg/day)* RR 0.67 (0.40, 1.12; p = 0.12)	*Aripiprazole (5 mg/day)* RR 2.94 (0.12, 70.61; p = 0.51)	*Aripiprazole (5 mg/day)* RR 2.94 (0.12, 70.61; p = 0.51)	*Aripiprazole (5 mg/day)* RR 4.91 (0.24, 99.74; p = 0.30)	*Aripiprazole (5 mg/day)* RR 1.96 (0.80, 4.83; p = 0.14)	*Risperidone (0.125-0.175 mg/day)* SMD -0.37 (-0.87, 0.13; p = 0.14)	*Aripiprazole (5 mg/day)* RR 4.91 (0.24, 99.74; p = 0.30)
Heterogeneity (chi²; p value; I^2)	Chi^2 = 5.60, df = 1; p = 0.02; I^2 = 82%	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2,3,4]	Very low[1,3,4]				Very low[1,4,5]	Very low[1,3,4]
Number of studies/ participants	K = 2; N = 168	K = 1; N = 103				K = 1; N = 63	K = 1; N = 103

Forest plot	1.33.5; Appendix 13

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious inconsistency as I^2 value indicates substantial to considerable heterogeneity.
[3]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[4]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[5]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 339: Evidence summary table for adverse events associated with low dose antipsychotics (continued 1)

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo						
Outcome	Tremor	Clinically relevant (≥7%) weight gain	Weight gain	Weight gain (in kg)	BMI change (kg/m-squared)	Increased appetite	Decreased appetite
Outcome measure	Study-specific report of adverse event	Weight assessment	Non-systematic assessment or study-specific report of adverse event	Weight assessment		Non-systematic assessment or study-specific report of adverse event	Study-specific report of adverse event
Study ID	MARCUS2009		(1) MARCUS2009 (2) JOHNSON&JOHNSON2011		MARCUS2009	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	MARCUS2009
Effect size (CI; p value)	*Aripiprazole (5 mg/day)* RR 8.83 (0.49, 159.93; p = 0.14)	*Aripiprazole (5 mg/day)* RR 4.17 (1.51, 11.54; p = 0.006)	(1)+(2) RR 2.52 (0.67, 9.51; p = 0.17) (1) *Aripiprazole (5 mg/day)* RR 3.92 (0.45, 33.92; p = 0.21) (2) *Risperidone (0.125-0.175 mg/day)* RR	(1)+(2) SMD 0.45 (0.13, 0.76; p = 0.005) (1) *Aripiprazole (5 mg/day)* SMD 0.46 (0.07, 0.85; p = 0.02) (2) *Risperidone (0.125-0.175 mg/day)*	*Aripiprazole (5 mg/day)* SMD 0.28 (-0.11, 0.66; p = 0.16)	(1)+(2) RR 3.95 (1.36, 11.51; p = 0.01) (1) *Aripiprazole (5 mg/day)* RR 4.90 (1.13, 21.29; p = 0.03) (2) *Risperidone (0.125-0.175 mg/day)* RR	*Aripiprazole (5 mg/day)* RR 4.90 (0.59, 40.53; p = 0.14)

			1.75 (0.31, 9.79; p = 0.52)	SMD 0.42 (-0.11, 0.96; p = 0.12)		2.92 (0.61, 13.96; p = 0.18)	
Heterogeneity (chi²; p value; I^2)	Not applicable		Chi^2 = 0.33, df = 1; p = 0.56; I^2 = 0%	Chi^2 = 0.01, df = 1; p = 0.91; I^2 = 0%	Not applicable	Chi^2 = 0.23, df = 1; p = 0.63; I^2 = 0%	Not applicable
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,3,4]	Very low[1,2,3]	Very low[1,3,5]	Very low[1,3,6]	Very low[1,3,4]	Very low[1,2,3]
Number of studies/ participants	K = 1; N = 103		K = 2; N = 168	K = 2; N = 160	K = 1; N = 103	K = 2; N = 168	K = 1; N = 103
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious imprecision as number of events <300.
[5]Downgraded due to serious imprecision as N <400.
[6]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).

Table 340: Evidence summary table for adverse events associated with low dose antipsychotics (continued 2)

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo						
Outcome	Fasting glucose (mg/dL) (Change Score)	Fasting glucose (≥115 mg/dL)	Fasting triglycerides (≥120 mg/dL for females or 160 mg/dL for males)	Insulin Resistance (HOMA-IR) (Change Score)	Aggression	Agitation	Depression
Outcome measure	Laboratory assessment				Non-systematic assessment		
Study ID	JOHNSON& JOHNSON2011	MARCUS2009		JOHNSON&JOHNSON2011			
Effect size (CI; p value)	*Risperidone (0.125-0.175 mg/day)* SMD 0.03 (-0.55, 0.62; p = 0.91)	*Aripiprazole (5 mg/day)* Effect size not estimable as zero events in both groups	*Aripiprazole (5 mg/day)* RR 2.94 (0.62, 13.90; p = 0.17)	*Risperidone (0.125-0.175 mg/day)* SMD -0.30 (-0.90, 0.30; p = 0.33)	*Risperidone (0.125-0.175 mg/day)* RR 0.23 (0.01, 4.66; p = 0.34)	*Risperidone (0.125-0.175 mg/day)* RR 0.23 (0.01, 4.66; p = 0.34)	*Risperidone (0.125-0.175 mg/day)* Effect size not estimable as zero events in both groups
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Very low[1,2,3]	Not applicable	Very low[1,3,4]	Very low[1,2,3]	Very low[1,3,4]		Not applicable
Number of studies/ participants	K = 1; N = 45	K = 1; N = 103		K = 1; N = 43	K = 1; N = 65		
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as N <400 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (SMD -0.5/0.5).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 341: Evidence summary table for adverse events associated with low dose antipsychotics (continued 3)

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo						
Outcome	Abdominal discomfort	Abdominal pain (upper)	Constipation	Nausea	Vomiting	Gastroenteritis viral	Diarrhoea
Outcome measure	Non-systematic assessment	Non-systematic assessment or study-specific report of adverse event	Non-systematic assessment	Non-systematic assessment or study-specific report of adverse event		Study-specific report of adverse event	Non-systematic assessment
Study ID	JOHNSON& JOHNSON2011	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	JOHNSON& JOHNSON2011	(1) MARCUS2009 (2) JOHNSON&JOHNSON2011		MARCUS2009	JOHNSON& JOHNSON2011
Effect size (CI; p value)	*Risperidone (0.125-0.175 mg/day)* RR 0.17 (0.01, 3.09; p = 0.23)	(1)+(2) RR 2.44 (0.37, 15.99; p = 0.35) (1) *Aripiprazole (5 mg/day)* RR 1.96 (0.18, 20.97; p = 0.58) (2) *Risperidone (0.125-0.175 mg/day)* RR 3.48 (0.15, 82.48; p = 0.44)	*Risperidone (0.125-0.175 mg/day)* RR 0.39 (0.02, 9.16; p = 0.56)	(1)+(2) RR 1.07 (0.15, 7.39; p = 0.95) (1) *Aripiprazole (5 mg/day)* RR 0.98 (0.06, 15.26; p = 0.99) (2) *Risperidone (0.125-0.175 mg/day)* RR 1.17 (0.08, 17.86; p = 0.91)	(1)+(2) RR 1.21 (0.42, 3.44; p = 0.72) (1) *Aripiprazole (5 mg/day)* RR 1.23 (0.35, 4.31; p = 0.75) (2) *Risperidone (0.125-0.175 mg/day)* RR 1.17 (0.17, 7.79; p = 0.87)	*Aripiprazole (5 mg/day)* RR 2.94 (0.12, 70.61; p = 0.51)	*Risperidone (0.125-0.175 mg/day)* RR 1.17 (0.08, 17.86; p = 0.91)
Heterogeneity (chi²; p value; I²)	Not applicable	Chi^2 = 0.08, df = 1; p = 0.78; I^2 = 0%	Not applicable	Chi^2 = 0.01, df = 1; p = 0.93; I^2 = 0%	Chi^2 = 0.00, df = 1; p = 0.97; I^2 = 0%	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2,3]						
Number of studies/participants	K = 1; N = 65	K = 2; N = 168	K = 1; N = 65	K = 2; N = 168		K = 1; N = 103	K = 1; N = 65
Forest plot	1.33.5; Appendix 13						

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.

Table 342: Evidence summary table for adverse events associated with low dose antipsychotics (continued 4)

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo						
Outcome	Pyrexia	Drooling	Increased salivation	Thirst	Fatigue	Lethargy	Somnolence
Outcome measure	Non-systematic assessment or study-specific report of adverse event	Study-specific report of adverse event		Non-systematic assessment or study-specific report of adverse event		Study-specific report of adverse event	Non-systematic assessment or study-specific report of adverse event
Study ID	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011	MARCUS2009		(1) MARCUS2009 (2) JOHNSON&JOHNSON2011		MARCUS2009	(1) MARCUS2009 (2) JOHNSON& JOHNSON2011
Effect size (CI; p value)	(1)+(2) RR 6.87 (0.36, 129.70; p = 0.20) (1) *Aripiprazole (5 mg/day)* RR6.87 (0.36, 129.70; p = 0.20) (2) *Risperidone (0.125-0.175 mg/day)* Effect size not estimable as zero events in both groups	*Aripiprazole (5 mg/day)* RR4.91 (0.24, 99.74; p = 0.30)	*Aripiprazole (5 mg/day)* RR0.98 (0.06, 15.26; p = 0.99)	(1)+(2) RR 2.94 (0.32, 27.36; p = 0.34) (1) *Aripiprazole (5 mg/day)* RR2.94 (0.32, 27.36; p = 0.34) (2) *Risperidone (0.125-0.175 mg/day)* Effect size not estimable as zero events in both groups	(1)+(2) RR 4.91 (0.24, 99.74; p = 0.30) (1) *Aripiprazole (5 mg/day)* RR4.91 (0.24, 99.74; p = 0.30) (2) *Risperidone (0.125-0.175 mg/day)* Effect size not estimable as zero events in both groups	*Aripiprazole (5 mg/day)* RR8.83 (0.49, 159.93; p = 0.14)	(1)+(2) RR 1.32 (0.33, 5.26; p = 0.69) (1) *Aripiprazole (5 mg/day)* RR1.96 (0.38, 10.24; p = 0.42) (2) *Risperidone (0.125-0.175 mg/day)* RR 0.39 (0.02, 9.16; p = 0.56)

Heterogeneity (chi²; p value; I²)	Not applicable				Chi² = 0.80, df = 1; p = 0.37; *I²* = 0%
Quality of the evidence (GRADE)	Very low[1,2,3]				
Number of studies/ participants	K = 2; N = 168	K = 1; N = 103	K = 2; N = 168	K = 1; N = 103	K = 2; N = 168
Forest plot	1.33.5; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.

Table 343: Evidence summary table for adverse events associated with low dose antipsychotics (continued 5)

Low dose antipsychotic (risperidone or aripiprazole) versus placebo							
Outcome	Sedation	Headache	Ear infection	Upper respiratory tract infection	Cough	Rhinorrhea	Nasal congestion
Outcome measure	Non-systematic assessment or study-specific report of adverse event		Non-systematic assessment	Non-systematic assessment or study-specific report of adverse event		Study-specific report of adverse event	
Study ID	(1) MARCUS2009 (2) JOHNSON&JOHNSON2011		JOHNSON& JOHNSON2011	(1) MARCUS2009 (2) JOHNSON&JOHNSON2011		MARCUS2009	
Effect size (CI; p value)	(1)+(2) RR 3.01 (0.94, 9.62; p = 0.06) (1) *Aripiprazole (5 mg/day)* RR 2.94 (0.84, 10.25; p = 0.09) (2) *Risperidone (0.125-*	(1)+(2) RR 0.90 (0.28, 2.86; p = 0.85) (1) *Aripiprazole (5 mg/day)* RR 1.47 (0.26, 8.44; p = 0.66) (2) *Risperidone (0.125-*	*Risperidone (0.125-0.175 mg/day)* Effect size not estimable as zero events in both groups	(1)+(2) RR 2.49 (0.36, 17.01; p = 0.35) (1) *Aripiprazole (5 mg/day)* RR 4.91 (0.24, 99.74; p = 0.30) (2) *Risperidone (0.125-*	(1)+(2) RR 3.92 (0.87, 17.59; p = 0.07) (1) *Aripiprazole (5 mg/day)* RR 3.92 (0.87, 17.59; p = 0.07) (2) *Risperidone (0.125-*	*Aripiprazole (5 mg/day)* RR 1.96 (0.18, 20.97; p = 0.58)	*Aripiprazole (5 mg/day)* RR 0.98 (0.06, 15.26; p = 0.99)

	0.175 mg/day) RR 3.48 (0.15, 82.48; p = 0.44)	*0.175 mg/day)* RR 0.58 (0.11, 2.96; p = 0.52)		*0.175 mg/day)* RR 1.17 (0.08, 17.86; p = 0.91)	*0.175 mg/day)* Effect size not estimable as zero events in both groups		
Heterogeneity (chi²; p value; I²)	Chi² = 0.01, df = 1 (P = 0.92); *I²* = 0%	Chi² = 0.58, df = 1; p = 0.45; *I²* = 0%	Not applicable	Chi² = 0.49, df = 1; p = 0.48; *I²* = 0%	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2,3]		Not applicable	Very low[1,2,3]			
Number of studies/ participants	K = 2; N = 168		K = 1; N = 65	K = 2; N = 168		K = 1; N = 103	
Forest plot	1.33.5; Appendix 13						
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.							

Table 344: Evidence summary table for adverse events associated with low dose antipsychotics (continued 6)

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo				
Outcome	Nasopharyngitis	Nose bleed	Akathisia	Insomnia	Hypersomnia
Outcome measure	Non-systematic assessment or study-specific report of adverse event			Non-systematic assessment	Non-systematic assessment or study-specific report of adverse event
Study ID	(1) MARCUS2009 (2) JOHNSON&JOHNSON2011			JOHNSON& JOHNSON2011	(1) MARCUS2009 (2) JOHNSON&JOHNSON2011
Effect size (CI; p value)	(1)+(2) RR 2.09 (0.65, 6.79; p = 0.22) (1) *Aripiprazole (5 mg/day)* RR 2.94	Effect size not estimable as zero events in both groups	(1)+(2) RR 0.35 (0.06, 2.14; p = 0.25) (1) *Aripiprazole (5 mg/day)* RR 0.33	*Risperidone (0.125-0.175 mg/day)* RR 0.23 (0.01, 4.66; p = 0.34)	(1)+(2) RR 2.12 (0.38, 11.88; p = 0.39) (1) *Aripiprazole (5 mg/day)* RR6.87 (0.36, 129.70;

	(0.62, 13.90; p = 0.17) (2) *Risperidone (0.125-0.175 mg/day)* RR 1.17 (0.17, 7.79; p = 0.87)		(0.04, 3.04; p = 0.33) (2) *Risperidone (0.125-0.175 mg/day)* RR 0.39 (0.02, 9.16; p = 0.56)		p = 0.20) (2) *Risperidone (0.125-0.175 mg/day)* RR 0.39 (0.02, 9.16; p = 0.56)
Heterogeneity (chi²; p value; I²)	Chi² = 0.55, df = 1; p = 0.46; *I²* = 0%	Not applicable	Chi² = 0.01, df = 1; p = 0.93; *I²* = 0%	Not applicable	Chi² = 1.72, df = 1; p = 0.19; *I²* = 42%
Quality of the evidence (GRADE)	Very low[1,2,3]	Not applicable	Very low[1,2,3]		Very low[1,2,3,4]
Number of studies/participants	K = 2; N = 168			K = 1; N = 65	
Forest plot	1.33.5; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious inconsistency as I2 value indicates moderate heterogeneity.

Table 345: Evidence summary table for adverse events associated with low dose antipsychotics (continued 7)

	Low dose antipsychotic (risperidone or aripiprazole) versus placebo			
Outcome	Psychomotor hyperactivity	Enuresis	Rash	Clinically relevant prolactin elevation (above upper limit of normal)
Outcome measure	Non-systematic assessment	Non-systematic assessment or study-specific report of adverse event		Study-specific report of adverse event
Study ID	JOHNSON&JOHNSON2011	(1) MARCUS2009 (2) JOHNSON&JOHNSON2011		MARCUS2009
Effect size (CI; p value)	*Risperidone (0.125-0.175 mg/day)* RR 0.58 (0.06, 6.12; p = 0.65)	(1)+(2) RR 1.61 (0.29, 9.04; p = 0.59) (1) *Aripiprazole (5 mg/day)* RR0.33 (0.01, 7.85; p = 0.49) (2) *Risperidone (0.125-0.175 mg/day)* RR 5.81 (0.29,	(1)+(2) RR 1.61 (0.29, 9.04; p = 0.59) (1) *Aripiprazole (5 mg/day)* RR0.33 (0.01, 7.85; p = 0.49) (2) *Risperidone (0.125-0.175 mg/day)* RR 5.81 (0.29,	*Aripiprazole (5 mg/day)* RR 0.20 (0.01, 3.99; p = 0.29)

		116.41; p = 0.25)	116.41; p = 0.25)	
Heterogeneity (chi²; p value; I²)	Not applicable	Chi² = 1.67, df = 1; 0 = 0.20; *I²* = 40%	Chi² = 1.67, df = 1; p = 0.20; *I²* = 40%	Not applicable
Quality of the evidence (GRADE)	Very low[1,2,3]	Very low[1,2,3,4]		Very low[1,2,3]
Number of studies/participants	K = 1; N = 65	K = 2; N = 168		K = 1; N = 103
Forest plot	1.33.5; Appendix 13			

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if follow-up duration (=<12 weeks) is sufficient to observe potential longer term adverse events and reliability/validity of some outcome measures unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial funded by pharmaceutical company and/or study drugs were provided by pharmaceutical company and/or authors are consultants to pharmaceutical companies.
[4]Downgraded due to serious inconsistency as I2 value indicates moderate heterogeneity.

There was some evidence that even with low dose antipsychotics there was an increased risk of weight gain. Evidence from a single study revealed that participants who received aripiprazole were over four times more likely to show clinically relevant (equal to or greater than 7%) weight gain. There was also evidence from a meta-analysis with two studies for a small to moderate and statistically significant adverse effect of aripiprazole or risperidone on a continuous measure of weight gain. Finally, there was also evidence from two studies for increased appetite associated with antipsychotics, with participants who received aripiprazole or risperidone being nearly four times more likely to show increased appetite than participants who received placebo (see Table 339).

Evidence for adverse events associated with risperidone relative to haloperidol and the quality of the evidence is presented in Table 346. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 346: Evidence summary table for adverse events associated with antipsychotics (risperidone versus haloperidol)

	Risperidone versus haloperidol		
Outcome	Treatment-emergent extrapyramidal symptoms	Prolactin (change score)	Liver problems (change in alanine transaminase)
Outcome measure	Extrapyramidal Symptoms Rating Scale: Section I	Laboratory assessment	
Study ID	MIRAL2008		
Effect size (CI; p value)	SMD -0.83 (-1.61, -0.05; p = 0.04)	SMD -1.01 (-1.80, -0.22; p = 0.01)	SMD -0.83 (-1.60, -0.05; p = 0.04)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very low[1,2,3]		
Number of studies/participants	K = 1; N = 28		
Forest plot	1.33.5; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient follow-up duration to observe potential longer term adverse effects.
[2]Downgraded due to serious imprecision as N <400.
[3]Downgraded due to strongly suspected publication bias as the study was partly funded by the pharmaceutical company that manufactured the drug tested.

There was single study evidence for a contrasting adverse event profile associated with risperidone and haloperidol. There was evidence for large and statistically significant effects in favour of risperidone for extrapyramidal symptoms (as measured by the Extrapyramidal Symptoms Rating Scale) and for liver problems (as measured by change in alanine transaminase). However, there was evidence for a large and statistically significant effect in favour of haloperidol for prolactin concentration (see Table 346).

Adverse events associated with antivirals

The one included antiviral trial (KING2001) compared amantadine hydrochloride (Symmetrel® syrup) with taste- and colour-matched placebo (see Table 157).

Table 347: Study information table for included trial for adverse events associated with antivirals

	Amantadine hydrochloride versus placebo
No. trials (N)	1 (39)
Study IDs	KING2001
Study design	RCT
% female	13
Mean age (years)	7.0
IQ	Not reported
Dose/intensity (mg/hours)	Planned intensity of 2.5 mg/kg (single dose) per day for first week of treatment period and 5 mg/kg (two doses) per day for remaining 3 weeks of treatment
Setting	Outpatient
Length of treatment (weeks)	4
Continuation phase (length and inclusion criteria)	5 (4-week double-blind treatment period was preceded by a 1-week single-blind placebo run-in phase [single dose of 2.5 mg/kg per day])

Evidence for adverse events associated with amantadine hydrochloride and the quality of the evidence is presented in Table 348. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 348: Evidence summary table for adverse events associated with antivirals

	Amantadine hydrochloride versus placebo		
Outcome	Any adverse event	Insomnia	Antisocial behaviour
Outcome measure	Study-specific report of adverse event		
Study ID	KING2001		
Effect size (CI; p value)	RR 1.05 (0.71, 1.56; p = 0.80)	RR 2.11 (0.43, 10.19; p = 0.35)	RR 0.53 (0.11, 2.55; p = 0.43)
Heterogeneity (chi²; p value; I²)	Not applicable		
Quality of the evidence (GRADE)	Very kow[1,2,3]		
Number of studies/participants	K = 1; N = 39		
Forest plot	1.33.6; Appendix 13		

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 5 weeks is sufficient follow-up duration to observe longer-term adverse events and reliability/validity of measure is unclear.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as the trial is funded by a pharmaceutical company.

There was no evidence for statistically significant adverse events associated with amantadine hydrochloride (see Table 348).

Adverse events associated with cognitive enhancers

The one included cognitive enhancers trial (AKHONDZADEH2008) compared combined piracetam and risperidone with combined placebo and risperidone (see Table 159).

Table 349: Study information table for included trial of adverse events associated with cognitive enhancers

	Piracetam and risperidone versus placebo and risperidone
No. trials (N)	1 (40)
Study IDs	AKHONDZADEH2008
Study design	RCT
% female	25
Mean age (years)	6.8
IQ	Not reported
Dose/intensity (mg/hours)	Fixed final dose of risperidone 2 mg/day (for children weighing 10-40 kg) and 3 mg/day (for children weighing >40 kg) and fixed final dose of piracetam of 800 mg/day
Setting	Outpatient
Length of treatment (weeks)	10
Continuation phase (length and inclusion criteria)	10

Evidence for adverse events associated with piracetam (as an adjunct to risperidone) and the quality of the evidence is presented in Table 350 and Table 351. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 350: Evidence summary table for adverse events associated with cognitive enhancers

	Piracetam and risperidone versus placebo and risperidone				
Outcome	Any treatment-emergent extrapyramidal symptom	Constipation	Nervousness	Day time drowsiness	Morning drowsiness
Outcome measure	Extrapyramidal Symptoms Rating Scale	Study-specific side effect checklist			
Study ID	AKHONDZADEH2008				
Effect size (CI; p value)	RR 0.75 (0.32, 1.77; p = 0.51)	RR 1.33 (0.34, 5.21; p = 0.68)	RR 0.50 (0.05, 5.08; p = 0.56)	RR 0.78 (0.36, 1.68; p = 0.52)	RR 1.38 (0.71, 2.68; p = 0.35)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	Very low[1,2]				
Number of studies/participants	K = 1; N = 40				
Forest plot	1.33.7; Appendix 13				

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as not clear if 10 weeks a sufficient follow-up duration to observe potential longer-term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 351: Evidence summary table for adverse events associated with cognitive enhancers *(continued)*

	Piracetam and risperidone versus placebo and risperidone			
Outcome	Increased appetite	Loss of appetite	Dry mouth	Fatigue
Outcome measure	Study-specific side effect checklist			
Study ID	AKHONDZADEH2008			
Effect size (CI; p value)	RR 1.17 (0.48, 2.86; p = 0.74)	RR 1.00 (0.07, 14.90; p = 1.00)	RR 1.33 (0.34, 5.21; p = 0.68)	RR 1.67 (0.46, 6.06; p = 0.44)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Very low[1,2]			
Number of studies/participants	K = 1; N = 40			
Forest plot	1.33.7; Appendix 13			
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as not clear if 10 weeks a sufficient follow-up duration to observe potential longer-term adverse events. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).				

There was no evidence for any statistically significant adverse events associated with piracetam, as an adjunct to risperidone (see Table 350 and Table 351).

Adverse events associated with melatonin

The one included melatonin trial (GRINGRAS2012) compared melatonin with placebo (see Table 284).

Table 352: Study information table for included trial of adverse events associated with melatonin

	Melatonin versus placebo
No. trials (N)	1 (63)
Study IDs	GRINGRAS2012
Study design	RCT
% female	29
Mean age (years)	8.7
IQ	Not reported
Dose/intensity (mg/hours)	Planned intensity of initial dose of 0.5 mg at randomisation, increased every week for four weeks (if necessary) in three dose increments: 2 mg, 6 mg to a maximum of 12 mg. Formulation was immediate-release
Setting	Outpatient
Length of treatment (weeks)	12
Continuation phase (length and inclusion criteria)	12

Evidence for adverse events associated with melatonin and the quality of the evidence is presented in Table 353, Table 354 and Table 355. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 353: Evidence summary table for adverse events associated with melatonin

	Melatonin versus placebo				
Outcome	Coughing	Mood swings	Vomiting	Increased excitability	Headache
Outcome measure	Study-specific report of adverse event				
Study ID	GRINGRAS2012				
Effect size (CI; p value)	RR 0.51 (0.22, 1.17; p = 0.11)	RR 1.28 (0.49, 3.39; p = 0.61)	RR 1.10 (0.44, 2.77; p = 0.84)	RR 0.92 (0.31, 2.70; p = 0.87)	RR 1.10 (0.17, 7.33; p = 0.92)
Heterogeneity (chi²; p value; I²)	Not applicable				
Quality of the evidence (GRADE)	Very low[1,2]				
Number of studies/participants	K = 1; N = 63				
Forest plot	1.33.8; Appendix 13				
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient duration to observe potential longer-term adverse events. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).					

Table 354: Evidence summary table for adverse events associated with melatonin (continued 1)

	Melatonin versus placebo					
Outcome	Rash	Somnolence	Fatigue	Hypothermia	Increased activity	Nausea
Outcome measure	Study-specific report of adverse event					
Study ID	GRINGRAS2012					
Effect size (CI; p value)	RR 1.47 (0.36, 6.03; p = 0.60)	RR 0.66 (0.17, 2.53; p = 0.54)	RR 0.18 (0.02, 1.44; p = 0.11)	RR 0.55 (0.05, 5.76; p = 0.62)	RR 1.10 (0.24, 5.04; p = 0.90)	RR 0.55 (0.05, 5.76; p = 0.62)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]					
Number of studies/participants	K = 1; N = 63					
Forest plot	1.33.8; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient duration to observe potential longer-term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

Table 355: Evidence summary table for adverse events associated with melatonin (continued 2)

	Melatonin versus placebo					
Outcome	Dizziness	Breathlessness	Hung-over feeling	Tremor	Seizures	Other
Outcome measure	Study-specific report of adverse event					
Study ID	GRINGRAS2012					
Effect size (CI; p value)	RR 0.22 (0.01, 4.39; p = 0.32)	Effect size not estimable as zero events in both groups	RR 3.29 (0.14, 77.82; p = 0.46)	Effect size not estimable as zero events in both groups	RR 0.37 (0.02, 8.65; p = 0.53)	RR 0.82 (0.53, 1.30; p = 0.40)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]	Not applicable	Very low[1,2]	Not applicable	Very low[1,2]	
Number of studies/participants	K = 1; N = 63					
Forest plot	1.33.8; Appendix 13					

There was no evidence for statistically significant adverse events associated with melatonin (see Table 353, Table 354 and Table 355).

Adverse events associated with opioid antagonists

The one included opioid antagonists trial (CAMPBELL1993) compared naltrexone with placebo (see Table 163).

Table 356: Study information table for included trial of adverse events associated with opioid antagonists

	Naltrexone versus placebo
No. trials (N)	1 (45)
Study IDs	CAMPBELL1993
Study design	RCT
% female	17
Mean age (years)	4.9
IQ	Full-scale IQ not reported. For N = 37: 22% severe LD; 24% moderate LD; 38% mild LD; 13% borderline; 3% normal IQ. For N = 38 adaptive and language DQs (as measured by Gesell Developmental Schedules) were reported as 51.5 for adaptive behaviour and 28.7 for language
Dose/intensity (mg/hours)	Optimal dose of 1 mg/kg/day
Setting	Inpatient
Length of treatment (weeks)	3
Continuation phase (length and inclusion criteria)	6 (including 2-week placebo washout period at beginning of trial and 1-week post-treatment placebo period)

Evidence for adverse events associated with naltrexone and the quality of the evidence is presented in Table 357 and Table 358. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 357: Evidence summary table for adverse events associated with opioid antagonists

	Naltrexone versus placebo					
Outcome	Any side effect	Aggressiveness	Self-injurious behaviour	Hyperactivity	Temper tantrums	Stereotypies
Outcome measure	Study-specific side effect checklist					
Study ID	CAMPBELL1993					
Effect size (CI; p value)	RR 1.45 (0.74, 2.87; p = 0.28)	RR 0.63 (0.20, 2.00; p = 0.43)	RR 0.39 (0.04, 3.98; p = 0.43)	RR 0.52 (0.10, 2.80; p = 0.45)	RR 1.57 (0.15, 15.92; p = 0.71)	RR 0.52 (0.10, 2.80; p = 0.45)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2,3]					
Number of studies/participants	K = 1; N = 41					
Forest plot	1.33.9; Appendix 13					
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as outcome measure designed specifically for the study with no independent reliability or validity ratings, and it is unclear if 6 weeks is a sufficient follow-up duration to observe potential longer-term side effects. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [3]Downgraded due to strongly suspected publication bias as potential conflict of interest because drug and placebo were supplied by the manufacturer.						

Table 358: Evidence summary table for adverse events associated with opioid antagonists *(continued)*

	Naltrexone versus placebo					
Outcome	Irritability	Decreased verbal production (transient)	Slight sleepiness	Falling asleep	Decreased appetite	Vomiting
Outcome measure	Study-specific side effect checklist					
Study ID	CAMPBELL1993					
Effect size (CI; p value)	RR 1.17 (0.22, 6.30; p = 0.85)	RR 2.38 (0.10, 55.06; p = 0.59)	RR 2.38 (0.10, 55.06; p = 0.59)	RR 3.96 (0.20, 77.63; p = 0.36)	RR 3.96 (0.20, 77.63; p = 0.36)	RR 5.54 (0.30, 100.86; p = 0.25)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the	Very low[1,2,3]					

evidence (GRADE)	
Number of studies/participants	K = 1; N = 41
Forest plot	1.33.9; Appendix 13
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as outcome measure designed specifically for the study with no independent reliability or validity ratings, and it is unclear if 6 weeks is a sufficient follow-up duration to observe potential longer-term side effects. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25). [3]Downgraded due to strongly suspected publication bias as potential conflict of interest because drug and placebo were supplied by the manufacturer.	

There was no evidence for any statistically significant adverse events associated with naltrexone (see Table 357 and Table 358).

Adverse events associated with SNRIs

The SNRI trial (ELILILLY2009) compared atomoxetine with placebo in children with autism (see Table 74).

Table 359: Study information table for included trial of adverse events associated with SNRIs

	Atomoxetine versus placebo
No. trials (N)	1 (97)
Study IDs	ELILILLY2009
Study design	RCT
% female	14
Mean age (years)	9.9
IQ	92.9 (assessed using the WISC-III)
Dose/intensity (mg/hours)	Planned final dose of 1.2 mg/kg/day
Setting	Not reported
Length of treatment (weeks)	8
Continuation phase (length and inclusion criteria)	28 weeks (8-week double-blind phase followed by 20-week open-label continuation phase; however, data only extracted for the double-blind phase as no control group data available for open-label continuation)

Evidence for adverse events associated with atomoxetine and the quality of the evidence is presented in Table 360, Table 361 and Table 362. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 360: Evidence summary table for adverse events associated with SNRIs

	Atomoxetine versus placebo					
Outcome	Any adverse event	Discontinuation due to adverse events	Abdominal pain	Upper abdominal pain	Diarrhoea	Nausea
Outcome measure	Study-specific open-ended questioning for adverse events					
Study ID	ELILILLY2009					
Effect size (CI; p value)	RR 1.24 (0.97, 1.59; p = 0.08)	RR 3.13 (0.12, 78.66; p = 0.49)	RR 1.36 (0.32, 5.76; p = 0.68)	RR 3.06 (0.88, 10.63; p = 0.08)	RR 0.34 (0.04, 3.16; p = 0.34)	RR 3.57 (1.27, 10.08; p = 0.02)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2,3]					Very low[1,2,4]
Number of studies/participants	K = 1; N = 97					
Forest plot	1.33.10; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 8 weeks is sufficient follow-up duration to observe potential longer-term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial run and reported by pharmaceutical company.
[4]Downgraded due to serious imprecision as number of events <300.

Table 361: Evidence summary table for adverse events associated with SNRIs (continued 1)

	Atomoxetine versus placebo					
Outcome	Vomiting	Fatigue	Pyrexia	Influenza	Deceased appetite	Myalgia
Outcome measure	Study-specific open-ended questioning for adverse events					
Study ID	ELILILLY2009					
Effect size (CI; p value)	RR 1.43 (0.49, 4.19; p = 0.52)	RR 2.81 (0.96, 8.21; p = 0.06)	RR 0.15 (0.01, 2.75; p = 0.20)	RR 7.14 (0.38, 134.69; p = 0.19)	RR 4.42 (1.34, 14.55; p = 0.01)	RR 7.14 (0.38, 134.69; p = 0.19)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2,3]				Very low[1,2,4]	Very low[1,2,3]
Number of studies/participants	K = 1; N = 97					
Forest plot	1.33.10; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 8 weeks is sufficient follow-up duration to observe potential longer-term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial run and reported by pharmaceutical company.
[4]Downgraded due to serious imprecision as number of events <300.

Table 362: Evidence summary table for adverse events associated with SNRIs (continued 2)

	Atomoxetine versus placebo					
Outcome	Dizziness	Headache	Psychomotor hyperactivity	Aggression	Early morning awakening	Initial insomnia
Outcome measure	Study-specific open-ended questioning for adverse events					
Study ID	ELILILLY2009					
Effect size (CI; p value)	RR 3.06 (0.33, 28.42; p = 0.32)	RR 1.36 (0.63, 2.93; p = 0.43)	RR 0.26 (0.03, 2.20; p = 0.21)	RR 0.68 (0.12, 3.89; p = 0.67)	RR 11.22 (0.64, 197.60; p = 0.10)	RR 0.61 (0.15, 2.42; p = 0.48)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2,3]					
Number of studies/participants	K = 1; N = 97					
Forest plot	1.33.10; Appendix 13					

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 8 weeks is sufficient follow-up duration to observe potential longer-term adverse events.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias as trial run and reported by pharmaceutical company.

There was single study evidence for an increased risk of nausea associated with SNRIs, with participants who received atomoxetine being over three and a half times more likely to experience nausea than participants who received placebo (see Table 360). There was also evidence for decreased appetite associated with atomoxetine, with participants who received the drug being nearly four and a half times more likely to report decreased appetite than participants who received placebo (see Table 361).

10.4 HARMS ASSOCIATED WITH BIOMEDICAL INTERVENTIONS

10.4.1 Studies considered

Seven studies from the search met the eligibility criteria for full-text retrieval. All of these trials provided relevant clinical evidence and were included in the review and examined adverse events associated with biomedical interventions as an indirect outcome. All studies were published in peer-reviewed journals between 2009 and 2012.

Two medical procedure trials (ROSSIGNOL2009, SAMPANTHAVIVAT2012[117]) examined adverse events.

Five nutritional interventions trials (ADAMS2011, BENT2011, HANDEN2009, HASANZADEH2012, WHITELEY2010[118]) examined adverse events.

10.4.2 Clinical evidence

Adverse events associated with medical procedures

The two included medical procedure trials (ROSSIGNOL2009, SAMPANTHAVIVAT2012) compared HBOT and attention-placebo control condition (see Table 92).

Table 363: Study information table for included trial of adverse events associated with medical procedures

	HBOT versus attention-placebo
No. trials (N)	2 (122)
Study IDs	(1) ROSSIGNOL2009 (2) SAMPANTHAVIVAT2012
Study design	(1)-(2) RCT
% female	(1) 16 (2) 17
Mean age (years)	(1) 4.9

[117] See Section 7.4.2 for direct outcomes from ROSSIGNOL2009 and see Section 6.4.3 for direct outcomes from SAMPANTHAVIVAT2012.
[118] See Section 6.4.3 and Section 6.4.5, respectively, for direct outcomes from ADAMS2011 and WHITELEY2010; see Section 7.4.2 for direct outcomes from BENT2011 and HASANZADEH2012; see Section 8.8.5 for direct outcomes from HANDEN2009.

	(2) 5.9
IQ	(1)-(2) Not reported
Dose/intensity (mg/hours)	(1) Planned intensity of 40 hours (10 hours/week) (2) Planned intensity of 20 hours (5 hours/week)
Setting	(1)-(2) Not reported
Length of treatment (weeks)	(1)-(2) 4
Continuation phase (length and inclusion criteria)	(1)-(2) 4

Evidence for adverse events associated with HBOT and the quality of the evidence is presented in Table 364. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 364: Evidence summary table for adverse events associated with medical procedures

	HBOT versus attention-placebo	
Outcome	Any adverse event	Minor-grade ear barotrauma
Outcome measure	Study-specific daily treatment logbooks	Not reported
Study ID	ROSSIGNOL2009	SAMPANTHAVIVAT2012
Effect size (CI; p value)	RR 1.32 (0.24, 7.35; p = 0.75)	RR 3.67 (1.14, 11.79; p = 0.03)
Heterogeneity (chi²; p value; I²)	Not applicable	
Quality of the evidence (GRADE)	Very low[1,2,3]	Low[4,5]
Number of studies/participants	K = 1; N = 62	K = 1; N = 58
Forest plot	1.34.1; Appendix 13	

Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 4 weeks sufficient follow-up duration to detect potential longer-term adverse events and adverse events were recorded by the intervention administrator who was non-blind to treatment assignment and to other potentially confounding factors.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).
[3]Downgraded due to strongly suspected publication bias because of a potential conflict of interest as study funded by the International Hyperbarics Association and authors profit from the use of hyperbaric treatment in their clinical practices.
[4]Downgraded for serious risk of bias – high risk of detection bias as unclear if 4 weeks was a sufficient follow-up duration to observe potential longer-term adverse events and outcome measure and outcome assessor/s not reported so blinding, and reliability and validity unclear.
[5]Downgraded due to serious imprecision as number of events <300.

There was no evidence from one study (ROSSIGNOL2009) for statistically significant adverse events associated with HBOT. However, another single study (SAMPANTHAVIVAT2012) found evidence for statistically significant adverse events associated with HBOT, with participants who received HBOT being over three and a half times more likely to experience minor-grade ear barotrauma during the trial than participants who received sham HBOT (see Table 364).

Adverse events associated with nutritional interventions

One of the nutritional intervention trials (ADAMS2011) compared a multivitamin/mineral supplement with placebo. One of the included nutritional intervention trials (BENT2011) compared omega-3 fatty acid supplement with placebo. One of the trials (HANDEN2009) compared oral human immunoglobulin

with placebo. HANDEN2009 was a four-armed trial and included three active intervention arms (low dose [140 mg/day], moderate dose [420 mg/day] or high dose [840 mg/day]). Initial analysis compared high dose with low dose groups; however, as no statistically significant differences were found for adverse event outcomes the groups were combined (across dosages) and compared with placebo. One of the nutritional intervention trials (HASANZADEH2012) compared combined ginkgo biloba and risperidone with combined placebo and risperidone. Finally, the last included nutritional intervention trial (WHITELEY2010) compared a gluten-free and casein-free diet with treatment as usual (see Table 365).

Evidence for adverse events associated with nutritional interventions and the quality of the evidence is presented in Table 366, Table 367, Table 368, Table 369, Table 370, Table 371, Table 372, Table 373 and Table 374. The full evidence profiles and associated forest plots can be found in Appendix 17 and Appendix 13, respectively.

Table 365: Study information table for included trials of adverse events associated with nutritional interventions

	Multivitamin/mineral supplement versus placebo	Omega-3 fatty acids versus placebo	Immunoglobulin versus placebo	Ginkgo biloba and risperidone versus placebo and risperidone	Gluten-free and casein-free diet versus treatment as usual
No. trials (N)	1 (141)	1 (27)	1 (125)	1 (47)	1 (72)
Study IDs	ADAMS2011	BENT2011	HANDEN2009	HASANZADEH2012	WHITELEY2010
Study design	RCT	RCT	RCT	RCT	RCT
% female	11	11	14	17	11
Mean age (years)	10.8	5.8	7.3	6.4	8.2
IQ	Not reported	77.5 (assessed using the Stanford-Binet Intelligence Scales)	Not reported	Not reported	Not reported
Dose/intensity (mg/hours)	One dose a day at lunchtime (formulation of vitamin/mineral supplement based on 60 lb which was adjusted up or down according to body weight up to a maximum of 100 lb: 1000 IU vitamin A; 600 mg vitamin C; 300 IU vitamin D3; 150 IU vitamin E; 70 mg mixed tocopherols; 20 mg B1, 20 mg B2, 15 mg niacin and 10 mg niacinamide B3; 15 mg B5; 40 mg B6; 500 mcg B12; 100 mcg folic acid; 550 mcg folinic acid; 150 mcg biotin; 250 mcg	1.3 g of omega-3 fatty acids per day (with 1.1 g of EPA and DHA) administered as two daily doses (with 650 mg of omega-3 fatty acids, 350 mg of EPA and 230 mg of DHA per dose)	Planned intensity of 140 mg/day, 420 mg/day or 840 mg/day for low, moderate and high dose arms respectively	Planned final dose of 2 or 3 mg/day of risperidone (for children weighing 10-30 kg and >30 kg respectively) and 80 or 120 mg/day of ginkgo biloba (for children weighing <30 kg and >30 kg respectively)	Unknown (compliance not recorded)

	choline; 100 mcg inositol; 3.6 mg mixed carotenoids; 50 mg coenzyme Q10; 50 mg N-acetylcysteine; 100 mg calcium; 70 mcg chromium; 100 mcg iodine; 500 mcg lithium; 100 mg magnesium; 3 mg manganese; 150 mcg molybdenum; 50 mg potassium; 22 mcg selenium; 500 mg sulphur; 12 mg zinc)				
Setting	Outpatient	Outpatient	Not reported	Outpatient	Home
Length of treatment (weeks)	13	12	12	10	35 (data extracted for 8-month intervention as after this point duration was variable across participants)
Continuation phase (length and inclusion criteria)	13	12	12	10	104 (experimental group received diet and control group received treatment as usual for 8 months, at 8 months interim assessment of change in scores for the experimental group on one of several measures [ADOS, GARS, VABS, ADHD Rating Scale-IV] against pre-defined statistical thresholds as evidence of improvement, if

					threshold exceeded both groups allocated to receive diet and re-assessed at 20 months, if threshold not exceeded experimental and control group continued to receive their respective interventions and then re-assessed at 12 months, if experimental group exceeded threshold at 12 months both groups received diet intervention and re-assessed at 24 months, if threshold not exceed then both groups stopped trial)

Table 366: Evidence summary table for adverse events associated with nutritional interventions (multivitamin/mineral)

	Multivitamin/mineral supplement versus placebo			
Outcome	Discontinuation due to adverse events	Discontinuation due to diarrhoea	Discontinuation due to increased stimming	Discontinuation due to behaviour problems
Outcome measure	Discontinuation due to adverse event			
Study ID	ADAMS2011			
Effect size (CI; p value)	RR 0.57 (0.14, 2.31; p = 0.44)	RR 0.32 (0.03, 3.00; p = 0.32)	RR 0.32 (0.01, 7.72; p = 0.48)	RR 1.92 (0.18, 20.66; p = 0.59)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Low[1]			
Number of studies/participants	K = 1; N = 141			
Forest plot	1.34.2; Appendix 13			
Note. [1]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).				

There was no evidence for statistically significant adverse events associated with a multivitamin/mineral supplement (see Table 366).

There was also no evidence for statistically significant adverse events associated with an omega-3 fatty acid supplement (see Table 367).

There was no evidence for statistically significant adverse effects associated with immunoglobulin where the dosages were combined (see Table 368 and Table 370), or for any differences in the adverse events associated with low relative to high immunoglobulin dosage.

Table 367: Evidence summary table for adverse events associated with nutritional interventions (omega-3)

	Omega-3 fatty acids versus placebo						
Outcome	Any adverse event	Rash	Upper respiratory infection	Nose bleeds	Gastrointestinal symptoms	Hyperactivity	Self-stimulatory behaviour
Outcome measure	Study-specific report of adverse event						
Study ID	BENT2011						
Effect size (CI; p value)	RR 1.16 (0.40, 3.41; p = 0.79)	RR 4.67 (0.24, 88.96; p = 0.31)	RR 2.80 (0.12, 63.20; p = 0.52)	RR 2.80 (0.12, 63.20; p = 0.52)	RR 2.80 (0.12, 63.20; p = 0.52)	RR 0.13 (0.01, 2.36; p = 0.17)	RR 0.31 (0.01, 7.02; p = 0.46)
Heterogeneity (chi²; p value; I²)	Not applicable						
Quality of the evidence (GRADE)	Very low[1,2]						
Number of studies/participants	K = 1; N = 27						
Forest plot	1.34.2; Appendix 13						
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient follow-up duration to observe potential longer-term adverse effects and reliability/validity of outcome measure is unclear. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).							

Table 368: Evidence summary table for adverse events associated with nutritional interventions (immunoglobulin)

	Immunoglobulin versus placebo					
Outcome	Any side effect	Discontinuation due to adverse events	Infections or infestations	Gastrointestinal disorders	Psychiatric disorders	Respiratory, thoracic or mediastinal disorders
Outcome measure	Study-specific report of adverse event					
Study ID	HANDEN2009					
Effect size (CI; p value)	RR 0.94 (0.76, 1.15; p = 0.54)	RR 2.31 (0.30, 18.03; p = 0.43)	RR 0.95 (0.64, 1.41; p = 0.79)	RR 1.32 (0.72, 2.42; p = 0.37)	RR 0.93 (0.40, 2.16; p = 0.87)	RR 1.24 (0.44, 3.45; p = 0.68)
Heterogeneity (chi²; p value; I²)	Not applicable					

Quality of the evidence (GRADE)	Low[1,2]	Very low[1,3]
Number of studies/participants	K = 1; N = 125	
Forest plot	1.34.2; Appendix 13	
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient follow-up duration to observe potential longer-term adverse effects and reliability/validity of outcome measure is unclear. [2]Downgraded due to serious imprecision as number of events <300. [3]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).		

Table 369: Evidence summary table for adverse events associated with nutritional interventions (immunoglobulin continued 1)

	Immunoglobulin versus placebo					
Outcome	Skin or subcutaneous tissue disorders	General disorders or administration site conditions	Nervous system disorders	Injury, poisoning or procedural complications	Investigations	Metabolism or nutrition disorders
Outcome measure	Study-specific report of adverse event					
Study ID	HANDEN2009					
Effect size (CI; p value)	RR 1.32 (0.40, 4.37; p = 0.65)	RR 1.48 (0.34, 6.50; p = 0.60)	RR 5.05 (0.30, 86.01; p = 0.26)	RR 1.65 (0.20, 13.58; p = 0.64)	RR 0.99 (0.11, 9.17; p = 0.99)	RR 0.99 (0.11, 9.17; p = 0.99)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]					
Number of studies/participants	K = 1; N = 125					
Forest plot	1.34.2; Appendix 13					
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient follow-up duration to observe potential longer-term adverse effects and reliability/validity of outcome measure is unclear. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).						

Table 370: Evidence summary table for adverse events associated with nutritional interventions (immunoglobulin continued 2)

	Immunoglobulin versus placebo					
Outcome	Eye disorders	Blood or lymphatic system disorders	Renal or urinary disorders	Ear or labyrinth disorders	Immune system disorders	Vascular disorders
Outcome measure	Study-specific report of adverse event					
Study ID	HANDEN2009					
Effect size (CI; p value)	RR 2.36 (0.13, 44.42; p = 0.57)	RR 0.33 (0.02, 5.12; p = 0.43)	RR 0.07 (0.00, 1.37; p = 0.08)	RR 1.01 (0.04, 24.19; p = 0.99)	RR 1.01 (0.04, 24.19; p = 0.99)	RR 1.01 (0.04, 24.19; p = 0.99)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]					
Number of studies/participants	K = 1; N = 125					
Forest plot	1.34.2; Appendix 13					
Note. [1]Downgraded for serious risk of bias – high risk of detection bias as unclear if 12 weeks is sufficient follow-up duration to observe potential longer-term adverse effects and reliability/validity of outcome measure is unclear. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).						

Table 371: Evidence summary table for adverse events associated with nutritional interventions (ginkgo biloba)

	Ginkgo biloba and risperidone versus placebo and risperidone					
Outcome	Day time drowsiness	Morning drowsiness	Constipation	Dizziness	Slow movement	Nervousness
Outcome measure	Study-specific side effect checklist					
Study ID	HASANZADEH2012					
Effect size (CI; p value)	RR 0.89 (0.35, 2.26; p = 0.81)	RR 5.21 (0.26, 102.98; p = 0.28)	RR 1.04 (0.23, 4.65; p = 0.96)	RR 0.35 (0.04, 3.11; p = 0.34)	RR 2.09 (0.20, 21.48; p = 0.54)	RR 5.22 (0.66, 41.32; p = 0.12)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]					

Number of studies/participants	K = 1; N = 47
Forest plot	1.34.2; Appendix 13
Note. [1]Downgraded for serious risk of bias – risk of detection bias is unclear/unknown for adverse event outcomes as it is unclear if 10 weeks is a sufficient follow-up duration to observe potential longer-term adverse events, the reliability and validity of the checklist used to record adverse events is unclear, and the checklist is based on parental report and parents will be non-blind to other potentially confounding factors. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).	

Table 372: Evidence summary table for adverse events associated with nutritional interventions (ginkgo biloba continued 1)

	Ginkgo biloba and risperidone versus placebo and risperidone					
Outcome	Restlessness	Increased appetite	Loss of appetite	Fatigue	Diarrhoea	Twitches
Outcome measure	Study-specific side effect checklist					
Study ID	HASANZADEH2012					
Effect size (CI; p value)	RR 0.63 (0.17, 2.33; p =0.48)	RR 0.63 (0.27, 1.44; p = 0.27)	RR 0.78 (0.20, 3.12; p = 0.73)	RR 2.61 (0.56, 12.13; p = 0.22)	RR 1.04 (0.23, 4.65; p = 0.96)	RR 7.29 (0.40, 133.82; p = 0.18)
Heterogeneity (chi²; p value; I²)	Not applicable					
Quality of the evidence (GRADE)	Very low[1,2]					
Number of studies/participants	K = 1; N = 47					
Forest plot	1.34.2; Appendix 13					
Note. [1]Downgraded for serious risk of bias – risk of detection bias is unclear/unknown for adverse event outcomes as it is unclear if 10 weeks is a sufficient follow-up duration to observe potential longer-term adverse events, the reliability and validity of the checklist used to record adverse events is unclear, and the checklist is based on parental report and parents will be non-blind to other potentially confounding factors. [2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).						

Table 373: Evidence summary table for adverse events associated with nutritional interventions (ginkgo biloba continued 2)

	Ginkgo biloba and risperidone versus placebo and risperidone			
Outcome	Dry mouth	Trouble swallowing	Sore throat/tongue	Abdominal pain
Outcome measure	Study-specific side effect checklist			
Study ID	HASANZADEH2012			
Effect size (CI; p value)	RR 1.04 (0.07, 15.72; p = 0.98)	RR 0.35 (0.04, 3.11; p = 0.34)	RR 0.21 (0.03, 1.65; p = 0.14)	RR 0.70 (0.13, 3.79; p = 0.67)
Heterogeneity (chi²; p value; I²)	Not applicable			
Quality of the evidence (GRADE)	Very low[1,2]			
Number of studies/participants	K = 1; N = 47			
Forest plot	1.34.2; Appendix 13			

Note. [1]Downgraded for serious risk of bias – risk of detection bias is unclear/unknown for adverse event outcomes as it is unclear if 10 weeks is a sufficient follow-up duration to observe potential longer-term adverse events, the reliability and validity of the checklist used to record adverse events is unclear, and the checklist is based on parental report and parents will be non-blind to other potentially confounding factors.
[2]Downgraded due to very serious imprecision as number of events <300 and 95% CI crosses both line of no effect and measure of appreciable benefit or harm (RR 0.75/1.25).

There was no evidence for statistically significant adverse events associated with ginkgo biloba as an adjunct to risperidone (see Table 371, Table 372 and Table 373).

Table 374: Evidence summary table for adverse events associated with nutritional interventions (gluten-free and casein-free diet)

	Gluten-free and casein-free diet versus treatment as usual
Outcome	Any side effect
Outcome measure	Outcome measure not reported
Study ID	WHITELEY2010
Effect size (CI; p value)	Effect size not estimable as zero events in both groups
Heterogeneity (chi²; p value; I²)	Not applicable
Quality of the evidence (GRADE)	Not applicable
Number of studies/participants	K = 1; N = 72
Forest plot	1.34.2; Appendix 13

For the gluten-free and casein-free diet adverse event effect size could not be estimated but no adverse events were reported in either group (see Table 374).

10.5CLINICAL EVIDENCE SUMMARY

There was single study evidence for statistically significant harms associated with the antidepressant citalopram, including: increased energy level; disinhibited, impulsive or intrusive behaviour; decreased attention and concentration; hyperactivity; stereotypy; diarrhoea; any insomnia and initial insomnia or difficulty falling asleep; skin or subcutaneous tissue disorder.

There was also single study evidence for an increased risk of nausea and decreased appetite associated with atomoxetine.

There was meta-analysis evidence for statistically significant harms associated with antipsychotics as follows: increased risk of any adverse event, increased risk of clinically relevant weight gain, continuous measure of weight gain, increased appetite, constipation, prolactin concentration, leptin change score, pulse change score, somnolence/drowsiness, fatigue, sedation, rhinitis, fever, tachycardia, drooling, and tremor. There was also evidence for statistically significant adverse events associated with low dose antipsychotics as follows: clinically relevant weight gain, continuous measure of weight gain and increased appetite.

Finally, there was single study evidence for an increased risk of minor-grade ear barotrauma associated with HBOT.

10.6FROM EVIDENCE TO RECOMMENDATIONS

The GDG considered the adverse event data together with the clinical and cost efficacy evidence. Given that there was no evidence for positive treatment effects on core autism features associated with antidepressants (see Chapter 6), and there was

evidence for significant harms associated with citalopram, the GDG concluded that there was not sufficient evidence to recommend antidepressants targeted at core features of autism in children and young people (see Chapter 6 for recommendation).

There was very limited evidence for positive treatment effects of HBOT on core autism features, with only single study evidence for a statistically significant effect on clinician-rated global improvement (see Chapter 6). Given that there was evidence for an increased risk of minor-grade ear barotrauma associated with HBOT, the GDG concluded that there was not sufficient evidence to recommend HBOT targeted at core features of autism, or for any other purpose, in children and young people (see Chapter 6 for recommendation).

There was evidence for positive treatment effects of antipsychotic medication on behaviour that challenges (see Chapter 7). However, there was also evidence for significant harms associated with risperidone or aripiprazole and the mechanisms by which these drugs exerted any beneficial effect was unclear from the data reviewed. It was also unclear whether the effects were mediated by a change in any psychotic symptoms, reduced levels of anxiety or more general sedation. Therefore, the GDG's judgement was that antipsychotics may be considered for the treatment and management of behaviour that challenges, including irritability, lethargy and social withdrawal, stereotypic behaviour, hyperactivity and noncompliance, and inappropriate speech, in children and young people with autism. However, due to the concerns regarding side effects associated with antipsychotic use, and the lack of data about long-term effects, the GDG concluded that where antipsychotics are used for the treatment of behaviour that challenges in children and young people with autism the clinician should consider starting with a low dose and there should be regular review of the benefits of the drug, any side effects, with particular emphasis on monitoring weight gain and the minimum effective dose should be chosen to maintain improvement in the target behaviour. The GDG were of the view that treatment should not be continued after 6 weeks in the absence of clear evidence of important clinical benefit (see Chapter 7 for recommendations)

There was either no or very little evidence to answer the subquestions about subgroups of children and young people with autism (for example, looked-after children, those from immigrant groups and those with sensory difficulties) or features of the interventions (for example, intensity and duration). In the absence of evidence, the GDG did not discuss these issues further.

11 SUMMARY OF RECOMMENDATIONS

11.1 RECOMMENDATIONS

11.1.1 General principles of care

Access to health and social care services

11.1.1.1 Ensure that all children and young people with autism have full access to health and social care services, including mental health services, regardless of their intellectual ability or any coexisting diagnosis.

Organisation and delivery of services

11.1.1.2 The overall configuration and development of local services (including health, mental health, learning disability, education and social care services) for children and young people with autism, should be coordinated by a local autism multi-agency strategy group (for people with autism of all ages) in line with Autism in children and young people (covering identification and diagnosis) (NICE clinical guideline 128) and Autism in adults (NICE clinical guideline 142).

11.1.1.3 The assessment, management and coordination of care for children and young people with autism should be provided through local specialist community-based multidisciplinary teams ('local autism teams') which should include professionals from health, mental health, learning disability, education and social care services in line with Autism in children and young people (covering identification and diagnosis) (NICE clinical guideline 128) and Autism in adults (NICE clinical guideline 142).

11.1.1.4 Local autism teams should ensure that every child or young person diagnosed with autism has a case manager or key worker to manage and coordinate treatment, care, support and transition to adult care in line with Autism in children and young people (covering identification and diagnosis) (NICE clinical guideline 128).

11.1.1.5 Local autism teams should provide (or organise) the interventions and care recommended in this guideline for children and young people with autism who have particular needs, including:

- looked-after children and young people
- those from immigrant groups
- those with regression in skills
- those with coexisting conditions such as:
  - severe visual and hearing impairments

- other medical problems including epilepsy or sleep and elimination problems
- motor disorders including cerebral palsy
- intellectual disability
- severe communication impairment, including lack of spoken language, or complex language disorders
- mental health problems.

11.1.1.6 Local autism teams should have a key role in the delivery and coordination of:

- specialist care and interventions for children and young people with autism, including those living in specialist residential accommodation
- advice, training and support for other health and social care professionals and staff (including in residential and community settings) who may be involved in the care of children and young people with autism
- advice and interventions to promote functional adaptive skills including communication and daily living skills
- assessing and managing behaviour that challenges
- assessing and managing coexisting conditions
- reassessing needs throughout childhood and adolescence, taking particular account of transition to adult services
- supporting access to leisure and enjoyable activities
- supporting access to and maintaining contact with educational, housing and employment services
- providing support for families (including siblings) and carers, including offering short breaks and other respite care
- producing local protocols for:
  - information sharing, communication and collaborative working among healthcare, education and social care services, including arrangements for transition to adult services
  - shared care arrangements with primary care providers and ensuring that clear lines of communication between primary and secondary care are maintained.

11.1.1.7 Refer children and young people with autism to a regional or national autism service if there is a lack of:

- local skills and competencies needed to provide interventions and care for a child or young person with a complex coexisting condition, such as a severe sensory or motor impairment or mental health problem, or
- response to the therapeutic interventions provided by the local autism team.

Knowledge and competence of health and social care professionals

11.1.1.8 Health and social care professionals working with children and young people with autism in any setting should receive training in autism awareness and skills in managing autism, which should include:

- the nature and course of autism
- the nature and course of behaviour that challenges in children and young people with autism
- recognition of common coexisting conditions, including:
  - mental health problems such as anxiety and depression
  - physical health problems such as epilepsy
  - sleep problems
  - other neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD)
- the importance of key transition points, such as changing schools or health or social care services
- the child or young person's experience of autism and its impact on them
- the impact of autism on the family (including siblings) or carers
- the impact of the social and physical environment on the child or young person
- how to assess risk (including self-harm, harm to others, self-neglect, breakdown of family or residential support, exploitation or abuse by others) and develop a risk management plan
- the changing needs that arise with puberty (including the child or young person's understanding of intimate relationships and related problems that may occur, for example, misunderstanding the behaviour of others)
- how to provide individualised care and support and ensure a consistent approach is used across all settings
- skills for communicating with a child or young person with autism.

Making adjustments to the social and physical environment and processes of care

11.1.1.9 Take into account the physical environment in which children and young people with autism are supported and cared for. Minimise any negative impact by:

- providing visual supports, for example, words, pictures or symbols that are meaningful for the child or young person
- making reasonable adjustments or adaptations to the amount of personal space given
- considering individual sensory sensitivities to lighting, noise levels and the colour of walls and furnishings.

11.1.1.10 Make adjustments or adaptations to the processes of health or social care, for example, arranging appointments at the beginning or end of the day to minimise waiting time, or providing single rooms for children and young people who may need a general anaesthetic in hospital (for example, for dental treatment).

Information and involvement in decision-making

11.1.1.11 Provide children and young people with autism, and their families and carers, with information about autism and its management and the support available on an ongoing basis, suitable for the child or young person's needs and developmental level. This may include:

- contact details for local and national organisations that can provide:
  - support and an opportunity to meet other people, including families or carers, with experience of autism
  - information on courses about autism
  - advice on welfare benefits, rights and entitlements
  - information about educational and social support and leisure activities
- information about services and treatments available
- information to help prepare for the future, for example, transition to adult services.

11.1.1.12 Make arrangements to support children and young people with autism and their family and carers during times of increased need, including major life changes such as puberty, starting or changing schools, or the birth of a sibling.

11.1.1.13 Explore with children and young people with autism, and their families and carers, whether they want to be involved in shared decision-making and continue to explore these issues at regular intervals. If children and young people express interest, offer a collaborative approach to treatment and care that takes their preferences into account.

11.1.2 Families and carers

11.1.2.1 Offer all families (including siblings) and carers verbal and written information about their right to:

- short breaks and other respite care
- a formal carer's assessment of their own physical and mental health needs, and how to access these.

11.1.2.2 Offer families (including siblings) and carers an assessment of their own needs, including whether they have:

- personal, social and emotional support
- practical support in their caring role, including short breaks and emergency plans

- a plan for future care for the child or young person, including transition to adult services.

11.1.2.3 When the needs of families and carers have been identified, discuss help available locally and, taking into account their preferences, offer information, advice, training and support, especially if they:

- need help with the personal, social or emotional care of the child or young person, including age-related needs such as self-care, relationships or sexuality
- are involved in the delivery of an intervention for the child or young person in collaboration with health and social care professionals.

11.1.3 Specific interventions for the core features of autism

Psychosocial interventions

11.1.3.1 Consider a specific social-communication intervention for the core features of autism in children and young people that includes play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication in the child or young person. Strategies should:

- be adjusted to the child or young person's developmental level
- aim to increase the parents', carers', teachers' or peers' understanding of, and sensitivity and responsiveness to, the child or young person's patterns of communication and interaction
- include techniques of therapist modelling and video-interaction feedback
- include techniques to expand the child or young person's communication, interactive play and social routines.

The intervention should be delivered by a trained professional. For pre-school children consider parent, carer or teacher mediation. For school-aged children consider peer mediation.

Pharmacological and dietary interventions

11.1.3.2 Do not use the following interventions for the management of core features of autism in children and young people:

- antipsychotics
- antidepressants
- anticonvulsants
- exclusion diets (such as gluten- or casein-free diets).

11.1.4 Interventions for behaviour that challenges

Anticipating and preventing behaviour that challenges

11.1.4.1 Assess factors that may increase the risk of behaviour that challenges in routine assessment and care planning in children and young people with autism, including:

- impairments in communication that may result in difficulty understanding situations or in expressing needs and wishes
- coexisting physical disorders, such as pain or gastrointestinal disorders
- coexisting mental health problems such as anxiety or depression and other neurodevelopmental conditions such as ADHD
- the physical environment, such as lighting and noise levels
- the social environment, including home, school and leisure activities
- changes to routines or personal circumstances
- developmental change, including puberty
- exploitation or abuse by others
- inadvertent reinforcement of behaviour that challenges
- the absence of predictability and structure.

11.1.4.2 Develop a care plan with the child or young person and their families or carers that outlines the steps needed to address the factors that may provoke behaviour that challenges, including:

- treatment, for example, for coexisting physical, mental health and behavioural problems
- support, for example, for families or carers
- necessary adjustments, for example, by increasing structure and minimising unpredictability.

Assessment and initial intervention for behaviour that challenges

11.1.4.3 If a child or young person's behaviour becomes challenging, reassess factors identified in the care plan and assess for any new factors that could provoke the behaviour.

11.1.4.4 Offer the following to address factors that may trigger or maintain behaviour that challenges:

- treatment for physical disorders, or coexisting mental health and behavioural problems
- interventions aimed at changing the environment, such as:
  - providing advice to families and carers
  - making adjustments or adaptations to the physical surroundings (see recommendation 5.5.1.9).

11.1.4.5 If behaviour remains challenging despite attempts to address the underlying possible causes, consult senior colleagues and undertake a multidisciplinary review.

11.1.4.6 At the multidisciplinary review, take into account the following when choosing an intervention for behaviour that challenges:

- the nature, severity and impact of the behaviour
- the child or young person's physical and communication needs and capabilities
- the environment
- the support and training that families, carers or staff may need to implement the intervention effectively
- the preferences of the child or young person and the family or carers
- the child or young person's experience of, and response to, previous interventions.

Psychosocial interventions for behaviour that challenges

11.1.4.7 If no coexisting mental health or behavioural problem, physical disorder or environmental problem has been identified as triggering or maintaining the behaviour that challenges, offer the child or young person a psychosocial intervention (informed by a functional assessment of behaviour) as a first-line treatment.

11.1.4.8 The functional assessment should identify:

- factors that appear to trigger the behaviour
- patterns of behaviour
- the needs that the child or young person is attempting to meet by performing the behaviour
- the consequences of the behaviour (that is, the reinforcement received as a result of the behaviour).

11.1.4.9 Psychosocial interventions for behaviour that challenges should include:

- clearly identified target behaviour
- a focus on outcomes that are linked to quality of life
- assessment and modification of environmental factors that may contribute to initiating or maintaining the behaviour
- a clearly defined intervention strategy that takes into account the developmental level and coexisting problems of the child or young person
- a specified timescale to meet intervention goals (to promote modification of intervention strategies that do not lead to change within a specified time)
- a systematic measure of the target behaviour taken before and after the intervention to ascertain whether the agreed outcomes are being met
- consistent application in all areas of the child or young person's environment (for example, at home and at school)
- agreement among parents, carers and professionals in all settings about how to implement the intervention.

Pharmacological interventions for behaviour that challenges

11.1.4.10 Consider antipsychotic medication[119] for managing behaviour that challenges in children and young people with autism when psychosocial or other interventions are insufficient or could not be delivered because of the severity of the behaviour. Antipsychotic medication should be initially prescribed and monitored by a paediatrician or psychiatrist who should:

- identify the target behaviour
- decide on an appropriate measure to monitor effectiveness, including frequency and severity of the behaviour and a measure of global impact
- review the effectiveness and any side effects of the medication after 3–4 weeks
- stop treatment if there is no indication of a clinically important response at 6 weeks.

11.1.4.11 If antipsychotic medication is prescribed:

- start with a low dose
- use the minimum effective dose needed
- regularly review the benefits of the antipsychotic medication and any adverse events.

11.1.4.12 When choosing antipsychotic medication, take into account side effects, acquisition costs, the child or young person's preference (or that of their parent or carer where appropriate) and response to previous treatment with an antipsychotic.

11.1.4.13 When prescribing is transferred to primary or community care, the specialist should give clear guidance to the practitioner who will be responsible for continued prescribing about:

- the selection of target behaviours
- monitoring of beneficial and side effects
- the potential for minimally effective dosing
- the proposed duration of treatment
- plans for stopping treatment.

11.1.5 Interventions for life skills

11.1.5.1 Offer children and young people with autism support in developing coping strategies and accessing community services, including developing skills to access public transport, employment and leisure facilities.

11.1.6 Interventions for autism that should not be used

11.1.6.1 Do not use the following interventions to manage autism in any context in children and young people:

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[119] At the time of publication (August 2013), no antipsychotic medication had a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

- secretin
- chelation
- hyperbaric oxygen therapy.

11.1.7 Interventions for coexisting problems

11.1.7.1 Offer psychosocial and pharmacological interventions for the management of coexisting mental health or medical problems in children and young people with autism in line with NICE guidance for children and young people, including:

- Attention deficit hyperactivity disorder (ADHD) (NICE clinical guideline 72)
- Conduct disorders in children and young people (NICE clinical guideline 158)
- Constipation in children and young people (NICE clinical guideline 99)
- Depression in children and young people (NICE clinical guideline 28)
- Epilepsy (NICE clinical guideline 137)
- Obsessive-compulsive disorder (OCD) and body dysmorphic disorder (BDD) (NICE clinical guideline 31)
- Post-traumatic stress disorder (PTSD) (NICE clinical guideline 26).

11.1.7.2 Consider the following for children and young people with autism and anxiety who have the verbal and cognitive ability to engage in a cognitive behavioural therapy (CBT) intervention:

- group CBT adjusted to the needs of children and young people with autism
- individual CBT for children and young people who find group-based activities difficult.

11.1.7.3 Consider adapting the method of delivery of CBT for children and young people with autism and anxiety to include:

- emotion recognition training
- greater use of written and visual information and structured worksheets
- a more cognitively concrete and structured approach
- simplified cognitive activities, for example, multiple-choice worksheets
- involving a parent or carer to support the implementation of the intervention, for example, involving them in therapy sessions
- maintaining attention by offering regular breaks
- incorporating the child or young person's special interests into therapy if possible.

Interventions for sleep problems

11.1.7.4 If a child or young person with autism develops a sleep problem offer an assessment that identifies:

- what the sleep problem is (for example, delay in falling asleep, frequent waking, unusual behaviours, breathing problems or sleepiness during the day)
- day and night sleep patterns, and any change to those patterns
- whether bedtime is regular
- what the sleep environment is like for example:
  - the level of background noise
  - use of a blackout blind
  - a television or computer in the bedroom
  - whether the child shares the room with someone
- presence of comorbidities especially those that feature hyperactivity or other behavioural problems
- levels of activity and exercise during the day
- possible physical illness or discomfort (for example, reflux, ear or tooth ache, constipation or eczema)
- effects of any medication
- any other individual factors thought to enhance or disturb sleep, such as emotional relationships or problems at school
- the impact of sleep and behavioural problems on parents or carers and other family members.

11.1.7.5 If the child or young person with autism snores loudly, chokes or appears to stop breathing while sleeping, refer to a specialist to check for obstructive sleep apnoea.

11.1.7.6 Develop a sleep plan (this will often be a specific sleep behavioural intervention) with the parents or carers to help address the identified sleep problems and to establish a regular night-time sleep pattern. Ask the parents or carers to record the child or young person's sleep and wakefulness throughout the day and night over a 2-week period. Use this information to modify the sleep plan if necessary and review the plan regularly until a regular sleep pattern is established.

11.1.7.7 Do not use a pharmacological intervention to aid sleep unless:

- sleep problems persist despite following the sleep plan
- sleep problems are having a negative impact on the child or young person and their family or carers.

If a pharmacological intervention is used to aid sleep it should:

- only be used following consultation with a specialist paediatrician or psychiatrist with expertise in the management of autism or paediatric sleep medicine
- be used in conjunction with non-pharmacological interventions

- be regularly reviewed to evaluate the ongoing need for a pharmacological intervention and to ensure that the benefits continue to outweigh the side effects and risks.

11.1.7.8 If the sleep problems continue to impact on the child or young person or their parents or carers, consider:

- referral to a paediatric sleep specialist, and
- short breaks and other respite care for one night or more. Short breaks may need to be repeated regularly to ensure that parents or carers are adequately supported. Agree the frequency of breaks with them and record this in the care plan.

11.1.7.9 Do not use omega-3 fatty acids to manage sleep problems in children and young people with autism.

Speech and language problems

11.1.7.10 Do not use neurofeedback to manage speech and language problems in children and young people with autism.

11.1.7.11 Do not use auditory integration training to manage speech and language problems in children and young people with autism.

11.1.8 Transition to adult services

11.1.8.1 Local autism teams should ensure that young people with autism who are receiving treatment and care from child and adolescent mental health services (CAMHS) or child health services are reassessed at around 14 years to establish the need for continuing treatment into adulthood.

11.1.8.2 If continuing treatment is necessary, make arrangements for a smooth transition to adult services and give information to the young person about the treatment and services they may need.

11.1.8.3 The timing of transition may vary locally and individually but should usually be completed by the time the young person is 18 years. Variations should be agreed by both child and adult services.

11.1.8.4 As part of the preparation for the transition to adult services, health and social care professionals should carry out a comprehensive assessment of the young person with autism.

11.1.8.5 The assessment should make best use of existing documentation about personal, educational, occupational, social and communication functioning, and should include assessment of any coexisting conditions, especially depression, anxiety, ADHD, obsessive-compulsive disorder (OCD) and global delay or intellectual disability in line with Autism in adults (NICE clinical guideline 142).

11.1.8.6 For young people aged 16 or older whose needs are complex or severe, use the care programme approach (CPA) in England, or care and treatment plans in Wales, as an aid to transfer between services.

11.1.8.7 Involve the young person in the planning and, where appropriate, their parents or carers.

11.1.8.8 Provide information about adult services to the young person, and their parents or carers, including their right to a social care assessment at age 18.

11.1.8.9 During transition to adult services, consider a formal meeting involving health and social care and other relevant professionals from child and adult services.

11.2 RESEARCH RECOMMENDATIONS

11.2.1 A key worker approach for children and young people with autism and their families

What is the value of a key worker approach (defined by protocol and delivered in addition to usual care) for children and young people with autism in terms of parental satisfaction, functioning and stress and child psychopathology?

Why this is important

Autism is well characterised as a chronic disorder with lifelong disability in some individuals, yet the current health management structure is usually organised around single episodes of care. The theory and practice of management of chronic illness, as well as widely expressed service-user opinion, indicate that a chronic care model for the organisation of autism services could be appropriate and cost effective.

A key worker approach for children and young people with autism and their families should be formally evaluated in a randomised controlled trial (RCT) reporting short- and medium-term outcomes (including cost-effectiveness) with a follow-up of at least 6 months and again at 12 months. The outcomes (parental satisfaction, functioning and stress and child psychopathology) should be assessed by structured clinical interviews, parent- and self-reports using validated questionnaires and objective measures of behaviour. The study needs to be large enough to determine the presence of clinically important effects, and mediators and moderators (in particular the child or young person's age) should be investigated.

11.2.2 Managing behaviour that challenges in children and young people with autism

Is a group-based parent training intervention for parents or carers of children and young people with autism clinically and cost effective in reducing early and emerging behaviour that challenges in the short- and medium-term compared with treatment as usual?

Why this is important

Behaviour that challenges is common in children and young people with autism but many are referred only when the behaviour has become severely impairing, they pose a threat to themselves or others, or everyday life has broken down. By this time, behavioural interventions may be difficult or impossible and antipsychotic

medication is used despite it being symptomatic in its benefits, having long-term adverse effects and behavioural problems typically recurring after use.

A group-based parent training intervention (such as educating parents to identify triggers and patterns of reinforcement) should be evaluated using an RCT. Primary outcomes should be short- and medium-term reduction in behaviour that challenges. Secondary outcomes should include parental and sibling stress, quality of life and the child or young person's adaptive function. The medium-term use of medication should also be assessed. Cost effectiveness should encompass a wide range of services, such as additional educational support and social services, and health service use by families.

11.2.3 Managing sleep problems in children with autism

Is a sleep hygiene intervention or melatonin clinically and cost effective in the management of sleep onset, night waking and reduced total sleep in children (aged 4–10 years) with autism?

Why this is important

Sleep problems are common in children and young people with autism and have a significant negative impact on them and their parents. However studies of melatonin have used different groups and preparations of melatonin precluding meta-analysis.

The intervention should be evaluated in an RCT in 3 stages: (1) recording sleep onset, night waking and total sleep time over 3 months using actigraphy and a parent-completed diary; (2) for those with a sleep problem, random allocation to sleep hygiene by booklet or professional contact; (3) for those with persistent sleep problems after 3 months, random allocation to prolonged-release melatonin or placebo; after a further 3 months, those on placebo would be offered melatonin.

It should report primary and secondary outcomes followed-up at 12 months for all participants. Primary outcomes should include increased total sleep time and decreased night waking. Secondary outcomes should include improved sleep onset, a change in Aberrant Behaviour Checklist measures of behaviour that challenges, and improvement in parental stress index and satisfaction and the child's cognitive function.

11.2.4 Treating comorbid anxiety in children and young people with autism

What is the comparative clinical and cost effectiveness of pharmacological and psychosocial interventions for anxiety disorders in children and young people with autism?

Why this is important

Early trials of CBT for anxiety in children and young people with autism have been promising but have methodological shortcomings. Furthermore, the common pharmacological approaches have not been evaluated in this population.

A parallel-arm RCT should compare pharmacological and psychosocial interventions with placebo in children and young people with autism and an anxiety disorder. Pharmacological treatment should be with a selective serotonin reuptake inhibitor (SSRI) and dosing should follow research in typically developing children but with the option of evaluating outcomes at lower doses. The SSRI should be blinded with an identical placebo and an 'attention' or other psychosocial control group. The psychosocial intervention should be manualised and based on cognitive behavioural approaches shown to be effective in previous trials. The sample should cover the full age and intellectual range of children and young people and the size powered to deliver precise effect size estimates for both active arms.

Primary outcome measures should be reduction in anxiety symptoms by parent report. Secondary outcomes may include self- and teacher-report, blinded measures such as heart rate and skin conductance, patient satisfaction, changes in adaptive function, quality of life and disruptive behaviour. Adverse effects should be evaluated and an economic evaluation included.

11.2.5 Teacher-, parent- and peer-mediated psychosocial interventions in pre-school children with autism

Are comprehensive early interventions that combine multiple elements and are delivered by parents and teachers (for example, the Learning Experiences – an Alternative Program for Preschoolers and their Parents [LEAP] model) effective in managing the core symptoms of autism and coexisting difficulties (such as adaptive behaviour and developmental skills) in pre-school children?

Why this is important

Many children with autism are diagnosed in the pre-school period when service provision is advice and support to parents and professionals in nursery or early years educational settings. There is evidence from one moderate-sized trial that adequately supervised comprehensive programmes can help manage the core symptoms of autism and coexisting difficulties. However, the quality of the trial was low.

The research programme should be in 4 stages:

1. Develop a manualised programme suitable to UK public service settings (health services, early years education, and so on).

2. Test its feasibility and acceptability in pilot trials with blinded assessment of outcome.

3. Formally evaluate the outcomes on core symptoms of autism and coexisting difficulties in a large-scale trial, including health economic analysis.

4. Conduct a series of smaller trials to determine the elements, length and intensity required to ensure effectiveness of the programme, as well as longer-term outcomes.

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13 ABBREVIATIONS

AAC	alternative and augmentative communication
ABA	applied behaviour analysis
ABC	Aberrant Behavior Checklist
ADHD	attention deficit hyperactivity disorder
ADHD-RS	ADHD rating scale
ADI-R	Autism Diagnostic Interview-Revised
ADIS(-C, -P)	Anxiety Disorders Interview Schedule for DSM-IV(-Child version, -Parent Version)
ADOS(-G, -T)	Autism Diagnostic Observation Schedule (-Generic, -Toddler module)
AEI	Australian Education Index
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AIMS	Abnormal Involuntary Movements Scale
AMHS	adult mental health services
ASA	Autism Screening Algorithm
ASC	Adapted Skillstreaming Checklist
ASD	autism spectrum disorder
ASSIA	Applied Social Services Index and Abstracts
ATEC	Autism Treatment Evaluation Checklist
atm	atmosphere
BASC(-2-PRS)	Behavior Assessment System for Children (2nd edition, Parent Rating Scales)
BPVS	British Picture Vocabulary Scale
BEI	British Education Index
BMJ	*British Medical Journal*
BSQ	Behavior Screening Questionnaire
CAMHS	child and adolescent mental health services
CARS(-BR)	Childhood Autism Rating Scale (adapted for Brazil)
CATS	Children's Automatic Thoughts Scale
CBCL	Child Behavior Checklist
CBT	cognitive behavioural therapy
CCC-2	Children's Communication Checklist-2
CDIs	Communicative Development Inventories
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CFT	Children's Friendship Training
CGAS	Children's Global Assessment Scale
CGI(-AD, -I, -S)	Clinical Global Impressions scale (-Adapted to Global Autism, -Improvement, -Severity)
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMB	combined CBT and melatonin

COMPASS	Collaborative Model for Promoting Competence and Success
CPA	care programme approach
CSBQ	Children's Social Behavior Questionnaire
CSBS-DP	Communication and Symbolic Behavior Scales Developmental Profile
CSHQ	Children's Sleep Habits Questionnaire
CSI	Child Symptom Inventory
CTRS (-R:S)	Conners' Teacher Rating Scale (– Revised: Short Form)
CYBOCS	Children's Yale-Brown Obsessive Compulsive Scale
DARE	Cochrane Database of Abstracts of Reviews of Effects
DAS	Differential Ability Scales
DBC	Developmental Behaviour Checklist
DHA	docosahexaonic acid
DIPAB	Diagnose of Psykotisk Adfærd hos Børn (Diagnosis of Psychotic Behavior in Children
DMSA	dimercaptosuccinic acid
DOTES	Dosage Record and Treatment Emergent Symptom Scale
DSLM	developmental speech and language training through music
DSM(-III, -IV, -TR, -5)	*Diagnostic and Statistical Manual of Mental Disorders* (3rd edition 4th edition, Text Revision, 5th edition)
EBI	early behavioural intervention
ECBI	Eyberg Child Behaviour Inventory
EED	Economic Evaluation Database
EIBI	early intensive behavioural intervention
EIDP	Early Intervention Developmental Profile
Embase	Excerpta Medica Database
EPA	eicosapentanoic acid
EOWPVT(-R)	Expressive One-Word Picture Vocabulary Test (-Revised)
ERIC	Education Resources in Curriculum
ERT	emotion recognition training
ESCS	Early Social Communication Scales
ESDM	Early Start Denver Model
FRT	face recognition training
GARS	Gilliam Autism Rating Scale
GDG	Guideline Development Group
GHQ-28	General Health Questionnaire, 28 items
GMDS	Griffiths Mental Developmental Scale
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBOT	hyperbaric oxygen therapy

HMIC	Health Management Information Consortium
HMSO	Her Majesty's Stationery Office
HOMA-IR	homeostatic model assessment – insulin resistance
HRQoL	health-related quality of life
HTA	Health Technology Assessment
HUI(2, 3)	Health Utility Index (second version, third version)
IBI	intensive behavioural intervention
ICER	incremental cost effectiveness ratio
IBSS	International Bibliography of Social Science
ICD(-9, -10)	*International Classification of Diseases (ninth revision, 10th revision)*
IQ	intelligence quotient
ISRCTN	Internationsal Standard Randomized Controlled Trial Number
ITT	intention to treat
K	number of studies
KBIT-2	Kaufman Brief Intelligence Test – Second Edition
LD	learning disabilities
LEAP	Learning Experiences – an Alternative Program for Preschoolers and Parents
LEAS-C	Levels of Emotional Awareness Scale for Children
LIPS(-R)	Leiter International Performance Scale (-Revised)
MASC	Multidimensional Anxiety Scale for Children
MEDLINE	Medical Literature Analysis and Retrieval System Online
MSEL	Mullen Scales of Early Learning
N	number of participants
N/A	not applicable
NAS	National Autistic Society
NCCMH	National Collaborating Centre for Mental Health
NCCWCH	National Collaborating Centre for Women's and Children's Health
NEPSY-II	A Developmental Neuropsychological Assessment – Second Edition
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	not otherwise specified
OAS(-M)	Overt Aggression Scale-Modified
ODD	oppositional defiant disorder
OIS	optimal information size
OCD	obsessive-compulsive disorder
OR	odds ratio

PACT	parent-mediated communication-focused treatment
PDD	pervasive developmental disorder
PDDBI	Pervasive Development Disorder Behavior Inventory
PedsQL	Pediatric Quality of Life Inventory
PEBM	parent education and behaviour management
PEC	parent education and counselling
PECS	Picture Exchange Communication System
PEP-R	Psychoeducational Profile-Revised
P-ESDM	Parent-mediated Early Start Denver Model
PGI(-I, -R)	Parent Global Impressions (-Improvement, -Revised)
PIQ	performance IQ
PJAM	Precursors of Joint Attention Measure
PLS(-3, -4)	Preschool Language Scales (3rd edition, 4th edition)
PPVT(:R, -III)	Peabody Picture Vocabulary Test (-Revised, 3rd edition)
PSDP	Preschool Developmental Profile
PSI(-3)	Parenting Stress Index (3rd edition)
PsycEXTRA	a grey literature database, which is a companion to PsycINFO
PsycINFO	Psychological Information Database
QALY	quality adjusted life year
QPQ	Quality of Play Questionnaire
QWB-SA	Quality of Well Being Self-Administered scale
RBS(-R)	Repetitive Behavior Scale-Revised
RCT	randomised controlled trial
RDLS	Reynell Developmental Language Scale
RF-RLRS	Ritvo-Freeman Real Life Rating Scale
RIT	reciprocal imitation training
RMT	relational music therapy
RPMT	Responsive Education and Prelinguistic Milieu Training
RQ	review question
RR	relative risk
RUPP	Research Units on Pediatric Psychopharmacology
SCAS(-P)	Spence Children's Anxiety Scale (Parent Version)
SCQ	Social Communication Questionnaire
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
SEN	special educational needs
SENCO	special educational needs coordinator
SIB-R	Scales of Independent Behavior-Revised
SMD	standardised mean difference
SNRI	serotonin and noradrenaline reuptake inhibitor
SNS	social network survey
SOS-M	Secretin Outcome Survey-Modified
SRS	Social Responsiveness Scale

SSA	Social Services Abstracts
SSCI	Social Sciences Citation Index
SSQ	Social Skills Questionnaire
SSRI	selective serotonin reuptake inhibitor
SSRS	Social Skills Rating System
SULP	Social Use of Language Programme
TD	typically developing
TEACCH	Treatment and Education of Autistic and Communication-Handicapped Children
ToM	Theory of Mind test
TPSS	Teacher Perception of Social Skills
VABS	Vineland Adaptive Behavior Scales
VAS	visual analogue scale
WeeFIM	Functional Independence Measure for Children
WISC(-III, IV)	Wechsler Intelligence Scale for Children (3rd edition, 4th edition)
WPPSI-R	Wechsler Preschool and Primary Intelligence Scale-Revised