Autism

Recognition, referral, diagnosis and management of adults on the autism spectrum

National Clinical Guideline Number X

National Collaborating Centre for Mental Health
Commissioned by the
National Institute for Health and Clinical Excellence

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1 PREFACE

This guideline has been developed to advise on autism in adults. The guideline recommendations have been developed by a multidisciplinary team of healthcare professionals, 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 people with autism while also emphasising the importance of the experience of care for 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, and future revisions of this guideline will incorporate new scientific evidence as it develops. The guideline makes a number of research recommendations specifically to address gaps in the evidence base. In the meantime, it is hoped that the guideline will assist clinicians, 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 incorporate 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 limitation 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 people with Autism Spectrum Conditions. However, there will always be some people and situations for which 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 person an Autism Spectrum Condition, 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 of the 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 Clinical Excellence (NICE) 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 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 The National Collaborating Centre for Mental Health

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.

1.1.5 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 set 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.

1.1.6 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 will monitor the extent to which Primary Care Trusts, trusts responsible for mental health and social care, and Health Authorities have implemented these guidelines.

1.2 THE NATIONAL AUTISM IN ADULTS GUIDELINE

1.2.1 Who has developed this guideline?

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included people with Autism and carers, and professionals from psychiatry, clinical psychology, general practice, nursing, paediatrics, social care, education 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 Patient and 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 adults with an Autism Spectrum Condition 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, adults with Autism Spectrum Conditions.

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 treatment and management of in adults. It aims to:

- improve access and engagement with treatment and services for people with Autism Spectrum Conditions

- evaluate the role of specific psychological, psychosocial and pharmacological interventions in the treatment of Autism Spectrum Conditions
- evaluate the role of psychological and psychosocial interventions in combination with pharmacological interventions in the treatment of Autism Spectrum Conditions
- evaluate the role of specific service-level interventions for people with Autism Spectrum Conditions
- integrate the above to provide best-practice advice on the care of individuals with Autism Spectrum Conditions
- 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 summary of the clinical practice and research recommendations, and a general introduction to guidelines and to the methods used to develop them. Chapter 4 to Chapter 8 provide the evidence that underpins the recommendations about the treatment and management of Autism in adults.

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. On the CD-ROM, full details about the included studies can be found in Appendix 14. Where meta-analyses were conducted, the data are presented using forest plots in Appendix 15 (see Text Box 1 for details).

Text Box 1: Appendices on CD-ROM

Clinical study characteristics tables	Appendix 14
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2 INTRODUCTION TO AUTISM SPECTRUM CONDITIONS IN ADULTS

2.1 THE AUTISM SPECTRUM

2.1.1 History

Autism was first described in 1943 by Leo Kanner in Baltimore (Kanner, 1943) and was independently described by Hans Asperger in 1944 in Vienna (Asperger, 1944) Both of these clinical descriptions described an overlapping core set of features (social difficulties alongside highly repetitive behaviour) but in Asperger's account the children had good intelligence and good language skills, whereas in Kanner's account there was greater variability in IQ and language development. The children described by Asperger got little attention because Asperger's account was written in German. Two significant efforts to bring this account to the English speaking medical world were by Lorna Wing in a seminal article (Wing, 1981) and Uta Frith in a seminal book (Frith, 1991). Whilst autism was listed in DSM-III, Asperger Syndrome was not, although it was finally included in DSM-IV in 1994.

In the 1950s and 1960s autism was often attributed to purely environmental factors (such as unemotional parenting) (Bettelheim, 1968). The purely environmental theory was overturned in the 1970s by Rutter (Rutter, 1978) who argued that associated phenomena such as epilepsy could not be attributed to environmental factors such as parenting style and instead indicated abnormalities of brain function, that the parents themselves were not bad parents, and that the higher concordance of autism in identical twins than in non-identical twins indicated a genetic cause (Folstein & Rutter, 1977). The idea that autism involves atypical brain development is now firmly established (Courchesne *et al.*, 2001) and that it involves many genes is also no longer in doubt (Geschwind, 2008).

In the 1950s through to the 1980s autism was mostly considered to be categorical (either present or absent) and quite rare (4 in 10,000 children) (Rutter, 1978). These two views were overturned by Lorna Wing who found in her own epidemiological study that when partial syndromes were included, autism was much more common than had previously been realized, and that autism could come by degrees, warranting the term "the autistic spectrum" (Wing, 1988). Today we recognize at least 1% of the population have an autism spectrum condition (Baird *et al.,* 2006; Baron-Cohen *et al.*, 2009a) so that it is now regarded as relatively common.

A final historical note: in the 1970s the symptoms were described as a "triad of impairments" (Wing, 1976) that included social difficulties, communication difficulties, and imagination difficulties (together with strongly repetitive behaviour). In the planned DSM-V criteria the triad will be reduced to a dyad (two core dimensions): Social and

communication difficulties will be collapsed into a single dimension called social-communication difficulties, to reflect that these are so intertwined that they cannot be easily disentangled. Imagination difficulties will be dropped because some people on the autism spectrum show excellent imagination in relation to the arts (drawing, in particular) and imagination is not easily operationalised; so the strongly repetitive behaviour (incorporating difficulties in adapting to change and unusually narrow interests) becomes the second major dimension.

People on the autism spectrum lie in the intersection of these two dimensions, meaning they show both features. These are shown in Figure 1. Showing just one of these features do not warrant a diagnosis on the autism spectrum, and the co-occurrence of the two dimensions means the autism spectrum can still be viewed as a syndrome:

Figure 1: The two main dimensions in the diagnosis of the autism spectrum. *Reproduced with permission (Baron-Cohen 2008).*

2.1.2 Terminology

A variety of terms are used which can lead to some confusion. These include subgroup diagnostic categories such as autism, Asperger Syndrome, pervasive developmental disorders, atypical autism. In the planned DSM-V (2012/2013) these will all be subsumed under a single overarching diagnostic term: autism spectrum disorder (ASD). Intellectual Disorder (or what in the UK is termed learning disability) and Language Disorder will be separately coded, to reflect that these can co-occur with ASD. In the UK some authors prefer to use the term Autism Spectrum Condition (ASC) since some people with the condition themselves see themselves as neurologically different (and in need of a diagnosis to access support) but not necessarily 'disordered'. In the US many authors are keen to retain the term 'disorder' to reflect severity and how the symptoms interfere in everyday functioning. In this guideline we have opted to avoid the debate over whether to use ASD or ASC and instead simply use the term 'the autism spectrum'.

This guideline is concerned with the diagnosis and management of adults on the autism spectrum in the community and in prison. In the UK this new focus on adults on the autism spectrum comes follows on the heels of the Autism Act (HMSO, 2009) in Parliament, and the Autism Strategy (DH, 2010) from the Department of Health, recognizing that this group has been overlooked in terms of identification and support services.

2.1.3 Features and presentation

The Autism Spectrum is characterized by difficulties in two domains: (A) social-communication and (B) strongly repetitive behaviour/ **difficulties** adjusting to rapid and unexpected change/unusually narrow interests.

Regarding the **social communication difficulties**, these can be manifest in many different ways, including the following (note that none of these are necessary or inevitably a part of autism, and different features may be evident in different individuals with autism):

- Atypical eye contact (staring at people for too long or not looking at people's eyes enough)
- Intrusions into others' personal space (standing too close to someone else, talking too loud, touching people inappropriately)
- Reduced interest in socializing
- Difficulties understanding others' behaviour, motives, and intentions
- Difficulties reading other people's facial expressions or vocal intonation
- Difficulties taking turns in conversation/tendency towards monologue
- Difficulties making small talk/maintaining a conversation
- Social naiveté and vulnerability to exploitation
- Bluntness/lack of diplomacy
- Difficulties reading between the lines/picking up hints
- Difficulties taking another person's perspective
- Difficulties resolving conflict
- Difficulties anticipating what might offend others (faux pas)
- Lack of social awareness
- Difficulties keeping track of what the listener/reader needs to know
- Difficulties making/keeping friends
- Difficulties understanding other people's expectations
- Difficulties conforming
- Difficulties judging what might be relevant or irrelevant to others
- Difficulties coping with/interacting in social groups
- Unable to tell white lies
- Difficulties coping with ambiguity in language
- Becoming obsessed with a person to an intrusive extent
- Social anxiety
- Loneliness (and risk of depression)
- Reduced empathy

Regarding the **difficulties adjusting to rapid and unexpected change/strongly repetitive behaviour, and unusually narrow interests**, these can be manifest in many different ways, including the following:

- Avoiding crowded places

- Difficulties multi tasking
- Doing one thing at a time
- Narrow deep interests, rather than broad superficial interests
- Preference for repetition and routine
- Tantrums or anxiety at change
- Need for sameness (eating the same foods, wearing the same clothes, taking the same routes, going to the same places) and avoidance of novelty
- Preference for predictability and predictable events (fans spinning, washing machines spinning, trains going down tracks,
- Attention to detail
- Development of 'obsessional interests'
- Need for strict order and precision

Historically, classic autism (also called Kanner's autism, or infantile autism, or Autistic Disorder) and Asperger Syndrome have shared the same two diagnostic difficulties above, but in classic autism the child was late to develop language (no single words by 2 years old, no phrase speech by 3 years old), and there may be additional learning difficulties (i.e., IQ may be in the below average range). In contrast, in Asperger Syndrome, language developed on time (when a history is taken) and IQ is always above 70, if not above average (i.e., no sign of learning difficulty). Whilst these two subgroups are delineated in DSM-IV (1994), as mentioned earlier the plan in DSM-V (2012) is to collapse these into a single category called Autism Spectrum Disorder (whilst flagging up levels of severity and associated disabilities such as learning difficulties or language delay).

2.1.4 Development, course and prognosis

Difficulties related to the autism spectrum start early: if a developmental history is taken it is usually evident that there were social difficulties as early as the second year of life (from 18 months old) in terms of mixing with other children and adjusting to social groups and change. Average age of diagnosis of classic autism is in primary school (by 6 years old) (Frith, 1989) whereas Asperger Syndrome is often not diagnosed until secondary school (by 14 years old) or even older (early adulthood or later) (Attwood, 1997). This is often because classic autism entails some developmental delays and so is more noticeable even to an untrained observer, whereas in Asperger Syndrome (AS) the good language and cognitive skills may mean the person can cope academically and in primary school the social demands may be less challenging (the peer group may be more tolerant of a child who does not conform). In addition, primary schools are typically smaller communities (200 children) whereas a secondary school is typically much bigger (from 600 to 2000), which significantly increases the social load.

Teenagers with AS may be difficult for teachers to cope with because the student with AS typically wants to do what *they* are interested in rather than what the teacher expects them to do (lack of social conformity). The student can appear disruptive to a class setting, and their refusal to accept statements ("do it because I told you to") without logical reasons may mean the student is seen as challenging. Students with AS can end

up losing motivation educationally and dropping out, underperforming in terms of school leaving qualifications. They are also at risk of being bullied, verbally or physically, because of being 'loners' and not fitting in; and some teenagers with AS retaliate, turning from victim to bullying themselves. Some adolescents with AS develop secondary depression and may feel suicidal, as well as showing social anxiety if expected to do group presentations (Tantam, 2000).

Some individuals manage to get through adolescence without a diagnosis because their families 'cushion' them by doing everything for them or tolerating their idiosyncrasies, and the person only starts to experience difficulties at the transition to independence (e.g., going to university) where they cannot make friends, becoming depressed and isolated. They may therefore only seek a diagnosis in their late teens or early twenties. Others may not seek a diagnosis until mid life when they have had a series of failed relationships (including marriage(s)) and failed jobs (including getting disciplined for having a difficult attitude towards co-workers, not being a 'team player', or simply not being promoted). A study by the National Autistic Society (UK) found that 90% of adults on the autism spectrum are unemployed despite having skills that mean they could be working, although many might require supported or sheltered employment.

2.1.5 Impairment, disability, secondary problems

The autism spectrum is very wide, ranging from individuals with limited self-help or independence or academic or verbal skills through to individuals who are in the gifted range of intelligence and fully independent but who are socially clumsy. This wide spectrum means that how 'symptoms' present in different individuals may be very different, in part a function of the extent to which the individual can fall back on general cognitive ability to devise coping strategies and the extent to which they are motivated to try to mask their disability in order to try to fit in.

Autism Spectrum Conditions can co-exist with many other diagnoses, including depression, social anxiety, obsessive compulsive disorder, attention deficit and hyperactivity disorder, Tourette's syndrome/tic disorder, eating disorder (anorexia), gender identity disorder, and even psychosis.

2.1.6 Issues of particular importance

Whereas detection and diagnosis of childhood autism now largely occurs by early childhood (age 3-6 years old), diagnosis of Asperger Syndrome is often overlooked until as late as adulthood, and can easily be misdiagnosed as simple depression or as a personality disorder. A developmental history is key to making this differentiation. This Guideline is in part a response to the under-diagnosis in adults.

Sensory and gastro-intestinal issues are also very common (the former possibly being seen in as many as 90% of cases (Baron-Cohen *et al.*, 2009b) and the latter in about a third of cases). These should be assessed because they have major implications for management.

It is important that autism is seen not only as a medical diagnosis where the NHS has responsibilities, but also a social-care responsibility (in the areas of education, housing, and employment). The issue of autism rights is now also an important social issue and professionals need to be sensitive to the view that many individuals on the autism spectrum regard themselves as an excluded minority whose rights have been overlooked by a 'neurotypical' majority. Alongside using medical diagnostic terminology to define themselves, they also use the key concept of 'neurodiversity' to remind society that there are many different routes along which the brain can develop, that one is not necessarily better or worse than another, and that society has to adapt to make space for this diversity.

2.2 INCIDENCE AND PREVALENCE

Childhood prevalence studies suggest the autism spectrum occurs in approximately 1% of the population, and that for every 2 known cases, there are 3 undiagnosed cases who might need a diagnosis at some point in their lives (Baron-Cohen *et al.,* 2009a). This suggests ASC is now much more common than was previously thought, since in 1978 prevalence of autism was reported to be 4 per 10,000 (Rutter, 1978). This dramatic change in prevalence is thought to largely reflect greater awareness, growth of services and a widening of diagnostic criteria to include AS, which was only brought into the international classification system in 1994. See Figure 2 for a schematic representation of this dramatic increase in diagnosis:

Figure 2: The rising prevalence of cases on the autism spectrum. Along the Y (vertical) axis are number of cases on the autism spectrum per 10,000 in the population. *Reproduced from Baron-Cohen (2008) with permission.*

2.3 DIFFERENTIAL DIAGNOSIS

Because Obsessive Compulsive Disorder (OCD) also involves unusually repetitive behaviour it is important to highlight the key difference between OCD and people on the autism spectrum. This is that that the obsessions in people on the autism spectrum do not necessarily cause anxiety (they are not 'egodystonic') and in OCD social development was not necessarily atypical in childhood.

Because personality disorders also involve social difficulties it is important to highlight the key difference between people on the autism spectrum and those with personality disorders. This is that personality disorders do not typically involve the 'obsessive' narrow interests or resistance to change. In addition, although people on the autism spectrum and those with psychopathy (or antisocial personality disorder) both involve empathy deficits, in people on the autism spectrum it is the *cognitive* component of empathy that is impaired ('theory of mind' or recognizing what others may be thinking or feeling) whilst *affective* empathy (having an appropriate emotional reaction to/caring

about other's feelings) may be intact, whereas in psychopathy the cognitive component of empathy is intact (enabling them to deceive and manipulate others) whilst affective empathy is impaired (they do not care about other's suffering, for example).

The autism spectrum can co-occur with other conditions involving 'rigid' behaviour and cognition such as eating disorders or gender identity disorder, and a dual diagnosis might be appropriate if the difficulties on the autism spectrum predate the second diagnosis. Emotional difficulties such as social anxiety disorder or depression are also common in people on the autism spectrum and are usefully seen as secondary to the autism spectrum difficulties since the autism spectrum difficulties often develop first and cause social difficulties including social isolation, which can give rise to the anxiety and depression.

2.4 AETIOLOGY

As mentioned earlier, there is no longer any doubt that difficulties on the autism spectrum are strongly genetic (Geschwind, 2008). This evidence comes from both twin studies, family genetic studies, and molecular genetic studies. To date hundreds of molecular genetic associations have been reported, and it is not yet clear which genes are necessary and sufficient to cause which type of autism spectrum outcome. The autism spectrum is not 100% genetic (estimates of heritability are between 60-90%) leaving room for a gene-environment interaction, but the environmental factors are not yet known. The idea that the environmental factor was MMR vaccine damage is no longer tenable. Potential environmental factors include the foetal sex steroid hormones (themselves under genetic influence) (Auyeung *et al*., 2009) and social training/experience (Lovaas & Smith 1988).

The autism spectrum is also now clearly understood to be neurodevelopmental, meaning that there are differences in the pattern of brain development from the earliest point. For example, early brain overgrowth has been documented in the first 2 years of life (Courchesne *et al.,* 2001), and in later 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 gist or holistic information (Belmonte *et al.,* 2004).

2.5 IDENTIFICATION AND ASSESSMENT

The process for identification and assessment is well understood but is limited by the availability of well-validated tools for case identification and the lack of **specialist** services to undertake the necessary assessments. The **identification** and assessment process should include a case identification phase followed by a detailed diagnostic assessment if needed. Screening instruments need to be age-appropriate, severity-appropriate, and brief, but are not themselves diagnostic. A typical diagnostic assessment may take at least 2 hours in carefully documenting the developmental

history, in order to make the differential diagnoses above. Diagnostic assessment is often within a multi-disciplinary team but at a minimum is by a qualified clinician, usually a clinical psychologist, psychiatrist or neurologist. In the case of children this is also often conducted by a paediatrician together with a speech therapist.

2.6 CURRENT CARE AND TREATMENT IN ENGLAND AND WALES

The Autism Act (HMSO, 2009) and the subsequence Autism Strategy (DH, 2010) required all NHS trusts to define an autism spectrum care pathway by the end of 2011, particularly for adults on the autism spectrum, since in many areas the childhood pathways are already well established. Only a few specialist services for the assessment and diagnosis of adults with autism currently exist in the UK and fewer are in a position to provide appropriate interventions. The number of adults with autism in contact with specialist mental health services is not well understood but probably includes a significant number of people whose autism is unrecognised. Developing these care pathways represents a considerable challenge as there are many parts of the UK where there is insufficient training/knowledge about the autism spectrum and that it may take some time to put in place a care pathway in all regions.

2.6.1 NHS

Such care pathways need to start with identification/diagnosis and end with a full package of support to meet the needs of the individual, and take into account that the patient might need support right across their life. At present the level of training and knowledge of autism is limited amongst primary care professionals and will need specific attention if the recommendations developed in this guideline are to be of real benefit. **Access** to treatment for adults with autism is also limited and may extend beyond mental health care to access to physical health care.

2.6.2 Other services

The NHS needs to work closely with Social Care and Education since ASC does not just affect mental health but has an impact on independent living (housing, employment, social networks, leisure, shopping, travel) and education at all levels (school, college/university). Care pathways should therefore include liaison with these other agencies and with Disability Resource Centres in colleges or with HR in the workplace.

2.7 ECONOMIC COST

Autism has lifetime consequences and significant economic impact because of the enormous implications for the individual with the disorder and their family members or carers. The economic burden of Autism Spectrum Conditions is considerable due to the increase in prevalence. Baird and colleagues (2006) estimated that 116 in every 10,000 children aged 9-10 years have an Autism Spectrum Condition which is substantially higher than the estimates in the past. Some of this increase in prevalence is attributed to greater awareness of ASC, changes in diagnostic criteria and improvements in identification.

Knapp and colleagues (2009) estimated the cost of supporting children with autisms to be £2.7billion each year; for adults these costs amount to £25 billion each year in the UK (in 2005/06 prices), which averages out at £500 each year for every person in the country. These cost estimates excluded benefits but included lost employment for the individual and hence lost productivity to the society. The study took into account age, level of intellectual disability, place of residence and lost productivity. Ninety percent of the overall cost of supporting individuals with autism relate to supporting adults. The public sector covers the major component of costs of supporting people with autism. The study estimated that out of the total cost of £25 billion of supporting adults with autism 59% is attributed to publicly funded services, 36% to lost employment for the individual with autism, and the remaining 5% to family expenses (Knapp *et al.,* 2009).

Adults with autism have high needs of support at the place of residence. The proportion of people with autism with intellectual disability living in institutional facilities is considerably higher than people without intellectual disability (Knapp *et al.*, 2009). Baird and colleagues (2006) estimate that 55% of people with autism have intellectual disability. The major component of the total cost (£25bn) of supporting adults with autism is attributed to the cost of supporting intellectually disabled adults, which is almost two thirds (£17 billion) of the total cost. A large proportion of people with autism with intellectual disability lived in residential care (52%), supported living accommodation (7%), or hospitals (6%) (Knapp *et al.,* 2009). These places of residence constitute major components of cost associated with supporting people with autism, as the annual costs per person are very high, ranging from approximately £87,500 for supported accommodation to £98,000 for living in hospital.

One study found that very few people with autism go into work given little or no support available to them (Howlin *et al.,* 2005). It is estimated that only 12% of non-intellectually disabled adults with autism have full-time jobs (Barnard *et al.,* 2001). The unemployment rate among non-intellectually disabled adults with autism is 88% and this has huge costs to the economy in terms of lost productivity. This productivity loss is conspicuous as non-intellectually disabled adults with autism could be employed using supported employment programmes. Järbrink and Knapp (2001) demonstrated that the lack of supported employment programmes for people with autism has negative resource consequences for the economy.

In the UK, the lifetime costs of an individual with autism without intellectual disability is estimated at £3.1 million (discounted cost £0.7 million); and of an individual with autism and intellectual disability £4.6 million (discounted cost £1.23 million) (Knapp *et al.,* 2009). Ganz (2007) estimated the lifetime per capita incremental societal cost of autism at $3.2 million in the US (discounted estimate). The substantial costs are borne by adult care and lost productivity of individuals with autism and their parents. Knapp and colleagues (2009) converted the US estimate equivalent to £2 million using GDP purchasing power parity and explained that the different methodology, availability of data, different support systems and the assumption of a different discount rate in the USA contributed to the higher estimate of lifetime cost. Ganz (2007) estimated the total annual cost of

autism at $35 billion to USA society. The medical costs were estimated at $29,000 per person per year which included physician and outpatient services, prescription medication, and behavioural therapies; non medical costs were estimated at $38,000 - $43,000 per person per year, depending on the level of disability, including costs of special education, camps, and child care (Ganz, 2006)

The substantial societal cost of autism in adults requires provision of effective interventions that will improve the quality of life of people with autism and their carers and will reduce the costs borne to the health 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 (further information is available in *The Guidelines Manual* [NICE, 2009e]). 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 six basic steps in the process of developing a guideline:

1. Define the scope, which sets the parameters of the guideline and provides a focus and steer for the development work.
2. Define review questions considered important for practitioners and service users.
3. Develop criteria for evidence searching and search for evidence.
4. Design validated protocols for systematic review and apply to evidence recovered by search.
5. Synthesise and (meta-) analyse data retrieved, guided by the review questions, and produce GRADE evidence profiles and summaries.
6. 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 in adults. 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

Guideline topics are selected by the Department of Health and the Welsh Assembly Government, which identify the main areas to be covered by the guideline in a specific remit (see *The Guidelines Manual* [NICE, 2009e] for further information). The NCCMH developed a scope for the guideline based on the remit. The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude
- 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 and the Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCCMH and NICE reviewed the scope in light of comments received, and the revised scope was signed off by the GRP.

3.3 THE GUIDELINE DEVELOPMENT GROUP

The GDG consisted of: professionals in psychiatry, clinical psychology, nursing, social work, and general practice; academic experts in psychiatry and psychology; a service user and carers, and a representative from a service user organisation. The guideline development process was supported by staff from the NCCMH, who undertook the clinical and health economics 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

Eleven GDG meetings were held between 27th July 2010 and 7th September 2011. 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 part of a standing agenda.

3.3.2 Topic groups

The GDG divided its workload along clinically relevant lines to simplify the guideline development process, and GDG members formed smaller topic groups to undertake guideline work in that area of clinical practice. Topic Group 1 covered questions relating to assessment and case identification. Topic Group 2 covered psychological/educational/social interventions. Topic Group 3 covered biomedical interventions and Topic Group 4 covered experience of care. These groups were designed to efficiently manage evidence appraisal prior to presenting it to the GDG as a

whole. Each topic group was chaired by a GDG member with expert knowledge of the topic area (one of the healthcare professionals). Topic groups refined the review questions and the clinical definitions of treatment interventions, reviewed and prepared the evidence with the systematic reviewer before presenting it to the GDG as a whole, and helped the GDG to identify further expertise in the topic. Topic group leaders reported the status of the group's work as part of the standing agenda. They also introduced and led the GDG discussion of the evidence review for that topic and assisted the GDG Chair in drafting the section of the guideline relevant to the work of each topic group.

3.3.3 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 a service user and carers, and a representative from a service user organisation. They contributed as full GDG members to writing the review questions, 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 service user and carer perspective.

3.3.4 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 group 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 6 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 7) 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, sub-questions were generated. Questions submitted by stakeholders were also discussed by the GDG and the rationale for not including any questions was recorded in the minutes. The final list of review questions can be found in Appendix 7.

For questions about interventions, the PICO (Population, Intervention, Comparison and Outcome) framework was used (see Table 1).

Table 1: Features of a well-formulated question on effectiveness intervention – 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?

Questions relating to diagnosis or case identification do not involve an intervention designed to treat a particular condition, therefore the PICO framework was not used. Rather, the questions were designed to pick up key issues specifically relevant to clinical utility, for example their accuracy, reliability, safety and acceptability to the service user.

In some situations, the prognosis of a particular condition is of fundamental importance, over and above its general significance in relation to specific interventions. Areas where this is particularly likely to occur relate to assessment of risk, for example in terms of behaviour modification or screening and early intervention. In addition, review questions related to issues of service delivery are occasionally specified in the remit from the Department of Health/Welsh Assembly Government. In these cases, appropriate review questions were developed to be clear and concise.

Although service user experience is a component of all review questions, specific questions concerning what the experience of care is like for adults 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 2. 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.

Deciding on the best design type to answer a specific review question does not mean that studies of different design types addressing the same question were discarded.

Table 2: Best study design to answer each type of question

Type of question	Best primary study design
Effectiveness or other impact of an intervention	Randomised controlled trial (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 randomised trial 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, thematic analysis)

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 (see Section 3.5.8) and the need for future research is specified.

3.5.1 Methodology

A stepwise, hierarchical approach was taken to locating and presenting evidence to the GDG. The NCCMH developed this process based on methods set out by NICE (*The Guidelines Manual* [NICE, 2009e]), and after considering recommendations from a range of other sources. These included:

- *British Medical Journal* (*BMJ*) Clinical Evidence
- Clinical Policy and Practice Program of the New South Wales Department of Health (Australia)
- The Cochrane Collaboration
- Grading of Recommendations: Assessment, Development and Evaluation (GRADE) Working Group
- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination
- Oxford Centre for Evidence-Based Medicine
- Oxford Systematic Review Development Programme
- Scottish Intercollegiate Guidelines Network (SIGN)
- United States Agency for Healthcare Research and Quality (AHRQ).

3.5.2 The review process

Scoping searches

A broad preliminary search of the literature was undertaken in January 2010 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 reports, key systematic reviews and randomised controlled trials (RCTs) and conducted in the following databases and websites:

- *BMJ* Clinical Evidence
- Canadian Medical Association (CMA) 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)
- EMBASE (Excerpta Medica database)
- Guidelines International Network (G-I-N)
- Health Evidence Bulletin Wales
- Health Management Information Consortium [HMIC]
- Health Technology Assessment (HTA) database (technology assessments)
- Medical Literature Analysis and Retrieval System Online MEDLINE/MEDLINE in Process
- National Health and Medical Research Council (NHMRC)
- National Library for Health (NLH) Guidelines Finder
- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination (CRD)
- Organizing Medical Networked Information (OMNI) Medical Search
- SIGN
- Turning Research Into Practice (TRIP)
- United States AHRQ
- Websites of NICE and the National Institute for Health Research (NIHR) HTA Programme for guidelines and HTAs in development.

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. Further information about this process can be found in *The Guidelines Manual (*NICE, 2009e).

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 systematic reviews, randomised controlled trials, observational studies, case-series,

quasi-experimental studies, qualitative and survey research, and conducted in the following databases:

- Allied and Complementary Medicine (AMED)
- Applied Social Services Index and Abstracts (ASSIA)
- Australian Education Index (AEI)
- British Education Index (BEI)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Excerpta Medica database (Embase)
- Education Resources in Curriculum (ERIC)
- Health Management Information Consortium (HMIC)
- Health Technology Assessment (HTA) database
- International Bibliography of Social Science (IBSS)
- Medline / Medline in-process
- PsycBOOKS
- PsycEXTRA
- Psychological Information Database (PsycINFO)
- Sociological Abstracts
- Social Services Abstracts

The search strategies were initially developed for Medline before being translated for use in other databases/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 spectrum conditions 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. In the absence of good quality evidence on autism, additional searching was conducted for wider literature on intellectual disabilities. The search terms for each search are set out in full in Appendix 9.

Reference Manager

Citations from each search were downloaded into the reference management software 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, randomised controlled trials, observational studies, case-series, quasi-experimental studies, qualitative and survey research. The search filters for

systematic reviews and randomised controlled trials are adaptations of filters designed by the Health Information Research Unit of McMaster University. The remaining filters used were developed in-house. Each filter comprises index terms relating to the study type(s) and associated textwords for the methodological description of the design(s).

Date and language restrictions

Systematic database searches were initially conducted in November 2010 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in September 2011 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.

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) sending lists of studies meeting the inclusion criteria to subject experts (identified through searches and the GDG) and asking them to check the lists for completeness, and to provide information of any published or unpublished research for consideration (see Appendix 6); (c) checking the tables of contents of key journals for studies that might have been missed by the database and reference list searches; (d) tracking key papers in the Science Citation Index (prospectively) over time for further useful references.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 9.

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 methodological quality (see Appendix 10 for methodology checklists). The eligibility of each study was confirmed by at least one member of the appropriate topic group.

For some review questions, it was necessary to prioritise the evidence with respect to the UK context (that is, external validity). To make this process explicit, the topic groups took into account the following factors when assessing the evidence:

- participant factors (for example, gender, age and ethnicity)
- provider factors (for example, model fidelity, the conditions under which the intervention was performed and the availability of experienced staff to undertake the procedure)
- cultural factors (for example, differences in standard care and differences in the welfare system).

It was the responsibility of each topic group to decide which prioritisation factors were relevant to each review question in light of the UK context and then decide how they should modify their recommendations.

Unpublished evidence

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.

3.5.3 Data extraction

Study characteristics and outcome data were extracted from all eligible studies that met the minimum quality criteria, using Review Manager 5.1 (The Cochrane Collaboration, 2011) (see Appendix 14).

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 was 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, we used outcome data from an intention-to-treat analysis (ITT) (that is, a 'once-randomised-always-analyse' basis). For dichotomous efficacy outcomes we re-calculated the effect size if ITT had not been used. When making the calculations if there was good evidence that those participants who ceased to engage in the study were likely to have an unfavourable outcome, early withdrawals were included in both the numerator and denominator. 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.

Where some of the studies failed to report standard deviations (for a continuous outcome), and where an estimate of the variance could not be computed from other reported data or obtained from the study author, the following approach was taken.[1]

When the number of studies with missing standard deviations was less than one-third and when the total number of studies was at least ten, the pooled standard deviation was imputed (calculated from all the other studies in the same meta-analysis that used the same version of the outcome measure). In this case, the appropriateness of the imputation was made by comparing the standardised mean differences (SMDs) of those trials that had reported standard deviations against the hypothetical SMDs of the same trials based on the imputed standard deviations. If they converged, the meta-analytical results were considered to be reliable.

When the conditions above could not be met, standard deviations were taken from another related systematic review (if available). In this case, the results were considered to be less reliable.

The meta-analysis of survival data, such as time to any mood episode, was based on log hazard ratios and standard errors. Since individual participant data were not available in included studies, hazard ratios and standard errors calculated from a Cox proportional hazard model were extracted. Where necessary, standard errors were calculated from confidence intervals or *p* value according to standard formulae (see the Cochrane Reviewers' Handbook 5.1.0; Higgins *et al.*, 2011). Data were summarised using the generic inverse variance method using Review Manager.

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 data set. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer was 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

A systematic search for published reviews of qualitative studies relevant to the experience of care review question was conducted. Reviews were sought of qualitative studies that used relevant first-hand experiences of service users and their families and/or carers. A particular outcome was not specified by the GDG. Instead, the review was concerned with narrative data that highlighted the experience of care. Where the search did not generate an adequate body of literature, a further search for primary qualitative studies was undertaken. Studies were excluded based on the criteria specified

[1] Based on the approach suggested by Furukawa and colleagues (2006).

in the protocol for the review question (see section 4.2.1), and if they did not provide a first-hand account of experience.

The purpose of the qualitative search was to identify qualitative evidence sources for which an analysis could be undertaken in order to identify themes relevant to the experience of the condition in question, and the experience of services and treatment from the point of view of the service user and/or their families and carers. The intention was that this thematic analysis would inform the development of recommendations about service users' experience of the disorder, of care and treatment and of the organisation and delivery of services.

For primary studies, a broad thematic analysis of individual patient data was undertaken by one reviewer; this was then discussed and developed with another reviewer. The evidence was then extracted and the themes coded independently by the two reviewers; finally the themes were checked to ensure all of the data were covered.

The results of this thematic analysis were used to develop:

- recommendations about service users' and carers' experience of care
- recommendations that were based on other evidence sources but where the data from the qualitative analysis could be used to provide a context for or inform the wording or focus of a recommendation.

3.5.4 Evaluating psychometric data

The psychometric properties of case identification and assessment instruments that met inclusion criteria were evaluated according to the following criteria:

Reliability[2]

- ≤.60 = unreliable; >.60 = marginally reliable; ≥.70 = relatively reliable
- Inter-rater reliability (r≥.70) = relatively reliable
- Test-retest reliability (r≥.70) = relatively reliable
- Internal consistency (r≥.70 or α≥.50; kappa ≥.40) = relatively reliable.

Validity

- Content validity
    - Content Validity Index (CVI) – where available – of ≥.78 for three or more experts[3]
    - Does a self-report scale have items that capture the components of the disorder? This is judged by evaluating evidence by referring to (a) established criteria for a particular construct; (b) other published rating scales; (c) characteristic behaviours reported in the literature[4]

[2] Sattler, J. M. (2001)
[3] Polit *et al*. (2007)
[4] Stoesz *et al.* (2011)

- Criterion validity - minimum .50[5] (or some suggest .30 to .40 is more reasonable[6]).
- Construct validity ≥.0.50
- Sensitivity/specificity (as previously used):- ≥.0.80

Clinical utility

The assessment instrument should be feasible and implementable in routine clinical care across a variety of assessment settings. The time and skills required to administer, score and interpret the instrument was also considered, as well as the cost and any copyright issues.

3.5.5 Synthesising the evidence from comparative effectiveness studies

Meta-analysis

Where possible, meta-analysis was used to synthesise evidence from comparative effectiveness studies 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 (RR) with the associated 95% CI (see Appendix 15 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. An RR of 1 indicates no difference between treatment and control. In the overall RR of 0.73 indicates that the event rate (that is, non-remission rate) associated with intervention A is about three-quarters of that with the control intervention or, in other words, the relative risk 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.

[5] Andrews *et al*. (1994); Burlingame *et al.* (1995)
[6] Nunnally & Bernstein (1994)

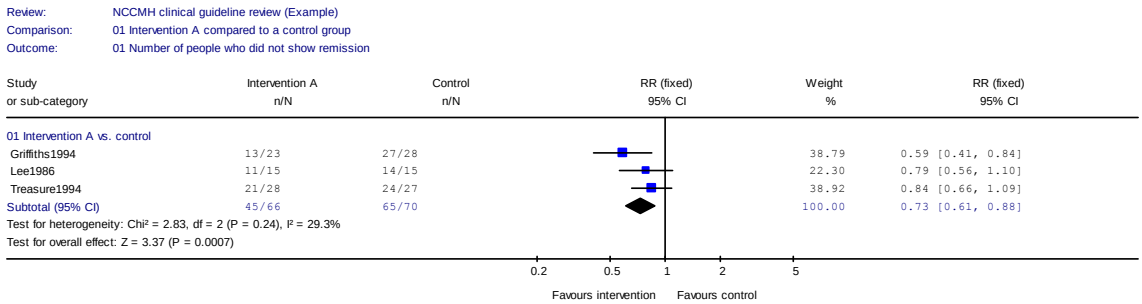

Figure 1: Example of a forest plot displaying dichotomous data

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, intention-to-treat data, using a valid method for imputation of missing data, were preferred over data only from people who completed the study.

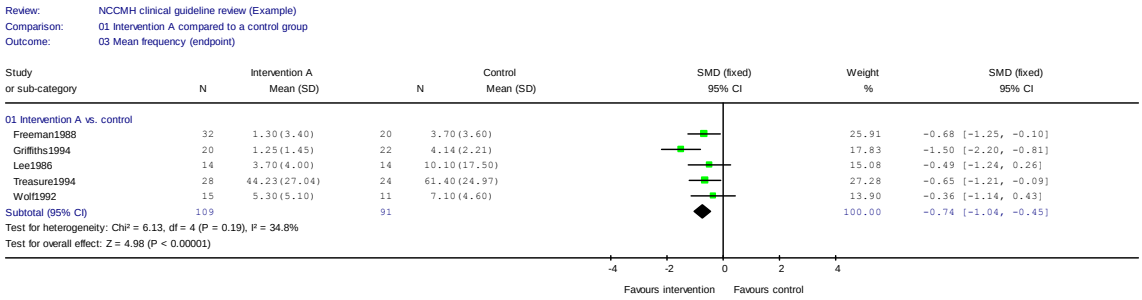

Figure 2: Example of a forest plot displaying continuous data

The number needed to treat for benefit (NNTB) or the number needed to treat for harm (NNTH) was reported for each outcome where the baseline risk (that is, the control group event rate) was similar across studies. In addition, NNTs calculated at follow-up were only reported where the length of follow-up was similar across studies. When the length of follow-up or baseline risk varies (especially with low risk), the NNT is a poor summary of the treatment effect (Deeks, 2002).

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 due to heterogeneity (Higgins & Thompson, 2002). For a meta-analysis of comparative effectiveness studies, the I^2 statistic was interpreted in the follow 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.

Two factors were used to make a judgement about the importance of the observed value of I^2: (1) the magnitude and direction of effects, and (2) the strength of evidence for heterogeneity (for example, *p* value from the chi-squared test, or a confidence interval for I^2).

3.5.6 Synthesising the evidence from test accuracy studies

Meta-analysis

Review Manager was used to summarise test accuracy data from each study using forest plots and summary ROC plots. Where more than two studies reported appropriate data, a bivariate test accuracy meta-analysis was conducted using Meta-DiSc (Zamora *et al.*, 2006) in order to obtain pooled estimates of sensitivity, specificity, and positive and negative likelihood ratios.

Sensitivity and specificity

The sensitivity of an instrument refers to the probability that it will produce a true positive result when given to a population with the target disorder (as compared to a reference or "gold standard"). An instrument that detects a low percentage of cases will not be very helpful in determining the numbers of service users who should receive further assessment or a known effective intervention, as many individuals who should receive the treatment will not do so. This would lead to an under-estimation of the prevalence of the disorder, contribute to inadequate care and make for poor planning and costing of the need for treatment. As the sensitivity of an instrument increases, the number of false negatives it detects will decrease.

The specificity of an instrument refers to the probability that a test will produce a true negative result when given to a population without the target disorder (as determined by a reference or "gold standard"). This is important so that people without the disorder are not offered further assessment or interventions they do not need. As the specificity of an instrument increases, the number of false positives will decrease.

To illustrate this: from a population in which the point prevalence rate of anxiety is 10% (that is, 10% of the population has anxiety at any one time), 1000 people are given a test which has 90% sensitivity and 85% specificity. It is known that 100 people in this population have anxiety, but the test detects only 90 (true positives), leaving 10 undetected (false negatives). It is also known that 900 people do not have anxiety, and the test correctly identifies 765 of these (true negatives), but classifies 135 incorrectly as having anxiety (false positives). The positive predictive value of the test (the number correctly identified as having anxiety as a proportion of positive tests) is 40%

(90/90+135), and the negative predictive value (the number correctly identified as not having anxiety as a proportion of negative tests) is 98% (765/765 +10). Therefore, in this example, a positive test result is correct in only 40% of cases, while a negative result can be relied upon in 98% of cases.

The example above illustrates some of the main differences between positive predictive values and negative predictive values in comparison with sensitivity and specificity. For both positive and negative predictive values, prevalence explicitly forms part of their calculation (see Altman & Bland, 1994a). When the prevalence of a disorder is low in a population this is generally associated with a higher negative predictive value and a lower positive predictive value. Therefore although these statistics are concerned with issues probably more directly applicable to clinical practice (for example, the probability that a person with a positive test result actually has anxiety) they are largely dependent on the characteristics of the population sampled and cannot be universally applied (Altman & Bland, 1994a).

On the other hand, sensitivity and specificity do not necessarily depend on prevalence of anxiety (Altman & Bland, 1994b). For example, sensitivity is concerned with the performance of an identification instrument conditional on a person having anxiety. Therefore the higher false positives often associated with samples of low prevalence will not affect such estimates. The advantage of this approach is that sensitivity and specificity can be applied across populations (Altman & Bland, 1994b). However, the main disadvantage is that clinicians tend to find such estimates more difficult to interpret.

When describing the sensitivity and specificity of the different instruments, the GDG defined values above 0.9 as 'excellent', 0.8 to 0.9 as 'good', 0.5 to 0.7 as 'moderate', 0.3 to 0.4 as 'low', and less than 0.3 as 'poor'.

Receiver operator characteristic curves

The qualities of a particular tool are summarised in a receiver operator characteristic (ROC) curve, which plots sensitivity (expressed as a per cent) against (100-specificity) (see Figure 3).

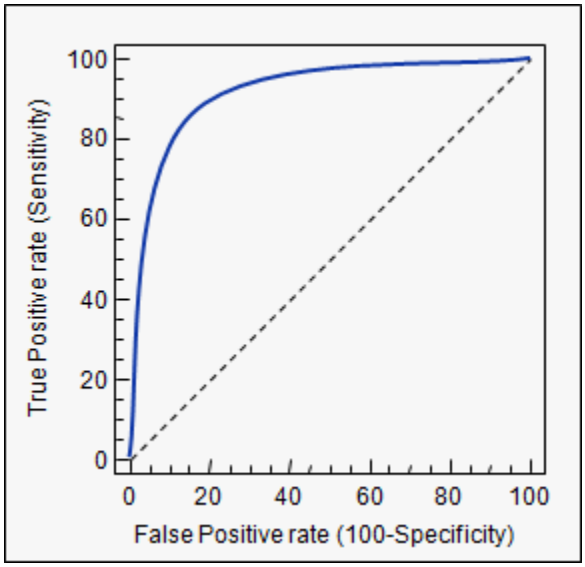

Figure 3: Receiver operator characteristic (ROC) curve

A test with perfect discrimination would have an ROC curve that passed through the top left hand corner; that is, it would have 100% specificity and pick up all true positives with no false positives. While this is never achieved in practice, the area under the curve (AUC) measures how close the tool gets to the theoretical ideal. A perfect test would have an AUC of 1, and a test with AUC above 0.5 is better than chance. As discussed above, because these measures are based on sensitivity and 100-specificity, theoretically these estimates are not affected by prevalence.

Negative and positive likelihood ratios

Positive (LR+) and negative (LR-) likelihood ratios are thought not to be dependent on prevalence. LR+ is calculated by sensitivity/(1-specificity) and LR- is (1-sensitivity)/specificity. A value of LR+ >5 and LR- <0.3 suggests the test is relatively accurate (Fischer *et al.*, 2003).

Heterogeneity

Heterogeneity is usually much greater, and is to be expected, in meta-analyses of test accuracy studies compared with meta-analyses of RCTs (Macaskill *et al.*, 2010). Therefore, a higher threshold for acceptable heterogeneity in such meta-analyses is required. However, when pooling studies resulted in $I^2 > 90\%$, meta-analyses were not conducted.

3.5.7 Presenting the data to the Guideline Development Group

Study characteristics tables and, where appropriate, forest plots generated with Review Manager were presented to the GDG. The GRADE approach[7] was used to grade the quality of evidence and strength of recommendations. The technical team produced

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

GRADE evidence profiles (see below) using the GRADE profiler software, and 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.

Evidence profile tables

A GRADE evidence profile was used to summarise both the quality of the evidence and the results of the evidence synthesis (see Table 3 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.

Within the GRADE approach to 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 the following factors:

- **limitations** in study design or execution (risk of bias)
- **inconsistency** (see section 3.5.5 for how consistency was assessed)
- **indirectness** (that is, how closely the outcome measures, interventions and participants match those of interest)
- **imprecision** (based on the confidence interval around the effect size)
- **publication bias.**

For observational studies, the quality may be up-graded 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 considerations column). Each evidence profile also included a summary of the 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.

Table 3: Example of a GRADE evidence profile

Quality assessment							Summary of findings				
							No. of participants		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Intervention	Control	Relative (95% CI)	Absolute	
Outcome 1											
6	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious1,2	None	8/191	7/150	RR 0.94 (0.39 to 2.23)	0 fewer per 100 (from 3 fewer to 6 more)	⊕⊕OO LOW
Outcome 2											
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	120/600	220/450	RR 0.39 (0.23 to 0.65)	30 fewer per 100 (from 17 fewer to 38 fewer)	⊕⊕⊕⊕ HIGH
Outcome 3											
3	Randomised trials	No serious limitations	Serious inconsistency3	No serious indirectness	Very serious1,2	None	83	81	-	MD -3.51 (-11.51 to 4.49)	⊕OOO VERY LOW
Outcome 4											
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious1	None	88	93	-	SMD -0.26 (-0.50 to -0.03)	⊕⊕⊕O MODERATE
Outcome 5											
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious1,2	None	109	114	-	SMD -0.13 (-0.6 to 0.34)	⊕⊕OO LOW

[1] Optimal information size not met.
[2] The CI includes both (1) no effect and (2) appreciable benefit or appreciable harm.
[3] Considerable heterogeneity.

Table 3: Example of a GRADE evidence profile

Quality assessment							Summary of findings				
							No. of participants		Effect		Quality
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Intervention	Control	Relative (95% CI)	Absolute	
Outcome 1											
6	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1,2]	None	8/191	7/150	RR 0.94 (0.39 to 2.23)	0 fewer per 100 (from 3 fewer to 6 more)	⊕⊕OO LOW
Outcome 2											
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	120/600	220/450	RR 0.39 (0.23 to 0.65)	30 fewer per 100 (from 17 fewer to 38 fewer)	⊕⊕⊕⊕ HIGH
Outcome 3											
3	Randomised trials	No serious limitations	Serious inconsistency[3]	No serious indirectness	Very serious[1,2]	None	83	81	-	MD -3.51 (-11.51 to 4.49)	⊕OOO VERY LOW
Outcome 4											
3	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Serious[1]	None	88	93	-	SMD -0.26 (-0.50 to -0.03)	⊕⊕⊕O MODERATE
Outcome 5											
4	Randomised trials	No serious limitations	No serious inconsistency	No serious indirectness	Very serious[1,2]	None	109	114	-	SMD -0.13 (-0.6 to 0.34)	⊕⊕OO LOW

[1] Optimal information size not met.
[2] The CI includes both (1) no effect and (2) appreciable benefit or appreciable harm.
[3] Considerable heterogeneity.

3.5.8 Method used to answer a review question in the absence of appropriately designed, high-quality research

In the absence of appropriately designed, high-quality research, or where the GDG were of the opinion (on the basis of previous searches or their knowledge of the literature) that there were unlikely to be such evidence, an informal consensus process was adopted.

Informal consensus

The starting point for the process of informal consensus was that a member of the topic group identified, with help from the systematic reviewer, a narrative review that most directly addressed the review question. Where this was not possible, a brief review of the recent literature was initiated.

This existing narrative review or new review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the review question and to lead to written statements for the guideline. The process involved a number of steps:

1. A description of what is known about the issues concerning the clinical question was written by one of the topic group members.
2. Evidence from the existing review or new review was then presented in narrative form to the GDG and further comments were sought about the evidence and its perceived relevance to the review question.
3. Based on the feedback from the GDG, additional information was sought and added to the information collected. This may include studies that did not directly address the review question but were thought to contain relevant data.
4. If, during the course of preparing the report, a significant body of primary-level studies (of appropriate design to answer the question) were identified, a full systematic review was done.
5. At this time, subject possibly to further reviews of the evidence, a series of statements that directly addressed the review question were developed.
6. Following this, on occasions and as deemed appropriate by the development group, the report was then sent to appointed experts outside of the GDG for peer review and comment. The information from this process was then fed back to the GDG for further discussion of the statements
7. Recommendations were then developed and could also be sent for further external peer review
8. After this final stage of comment, the statements and recommendations were again reviewed and agreed upon by the GDG.

3.5.9 Extrapolation

In this guideline extrapolation was undertaken where the review question was considered to be important by the GDG but where primary data on adults with autism were not available or were deemed to be insufficient. For the review of organisation and delivery of care the decision was taken to extrapolate from three broad evidence bases. First was the *Common Mental Health Disorders* guideline (NCCMH, 2011), which had recommendations on the organisation and delivery of care for people with depression and anxiety disorders based on an extensive review of: (a) mental health datasets including for local care pathways, and (b) the wider healthcare literature. Second, was the evidence base for the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming), which was used to inform the development of recommendations about the experience of care for both adults with autism and their families and carers. This evidence base supplemented that developed from the review of the qualitative literature in Chapter 4. Third, and in line with other evidence reviews within this guideline, the GDG made a decision to extrapolate from evidence from intellectual disability populations. The GDG was careful to ensure that the extrapolation population shared some common characteristics with the adult autism population, for example age, gender or severity of disorder, and that other aspects of the problem (for example, harms) and outcomes (for example, improved access to services) were similar. The GDG also extrapolated from evidence from populations of children with autism.

Extrapolation was only performed where the data quality was equivalent; the same standards were applied for assessing and evaluating the evidence from adults with intellectual disability and children with autism, as for the primary data from adults with autism. In the case of the organisation and delivery of care, the focus was not necessarily on common characteristics of the population; but as the recommendations from the *Common Mental Health Disorders* guideline provided principles for the organisation of local care pathways, the GDG's concern was whether or not those principles could be applied to people with autism. Extrapolated data was recognised as lower quality evidence than data from adults with autism and this is reflected within the GRADE system, with outcomes using extrapolated populations.

3.5.10 The adoption and adaptation of existing NICE guideline recommendations

The GDG employed the methods developed for adoption and adaptation of existing guideline recommendations in the *Common Mental Health Disorders* (NCCMH, 2011) guideline. The key principles underpinning this process are twofold: (1) adopting a recommendation involves a simple transfer of a recommendation from one guideline to another; no changes are made to the wording or structure; (2) adapting a recommendation involves making a number of changes to a recommendation but

preserving the meaning and intent of the original recommendations (this is to ensure a clear link to the underpinning evidence base) (NCCMH, 2011). Adaptations can take a number of forms under two broad headings:

- Changes in terminology: changing the original wording of a recommendation in order to facilitate understanding, for example using a term such as 'facilitative self-help' to replace 'guided self-help'; this may do nothing more that reflect changes in current usage in the NHS or in the particular services covered by the guideline.

- Changes in structure and wording in order to best preserve the meaning and intent of the original in a form that is compatible with a recommendation for the new guideline: for example, this may involve restructuring and recontextualising a treatment recommendation as a recommendation for referral for that treatment.

In deciding whether to adopt or adapt existing guideline recommendations, the GDG first considered whether the direct evidence obtained from the autism dataset was of sufficient quality to allow development of recommendations. It was only where such evidence was not available and drawing on the principles of extrapolation (see Section 3.5.9) that the GDG would move to the 'adopt and adapt' method.

This process of adoption and adaptation drew on the knowledge and expertise of the GDG and was guided by a number of considerations. A key concern was that the recommendations in an existing guideline might have been developed for populations not covered by the guideline under development and as such might not be relevant to the experience of those whose care and treatment is covered by this guideline. Nevertheless the principles underpinning the recommendations might have considerable relevance. When adopting or adapting recommendations from other guidelines the GDG identified those recommendations that might be relevant but might require some adaptation in order to be comprehensible and of value in providing a set of principles underpinning recommendations for the organisation and delivery of care for adults with autism. In identifying those recommendations the GDG was guided by four considerations:

- the recommendation should have real value in improving services
- the inclusion of the recommendation in the guideline should facilitate the understanding, uptake of integration of other recommendations in this guideline
- the inclusion of the recommendation in the guideline should only be necessary where recommendations based on more direct sources of evidence could not be made
- the inclusion of the recommendation in the guideline should not lead to misrepresentation of the original guideline(s) from which it was drawn, or other recommendations developed for this guideline.

The process of identifying the recommendations from an existing guideline followed five stages:

Stage 1 - Identification of any recommendations in an existing guideline that were deemed to be relevant to the care and treatment of the population in the current guideline.

Stage 2 - Identification of any recommendations in an existing guideline(s) that were relevant to the care and treatment of the population in the current guideline but which the GDG considered were of general applicability and would not therefore warrant inclusion in the guideline under development.

Stage 3 - Identification of any recommendations in an existing guideline that were relevant to the care and treatment of the population in the current guideline and which the GDG considered were of such importance in the care and treatment of the population in the current guideline that they needed to be included in this guideline.

Stage 4 - The identification of those recommendations that: (1) could be adopted for this guideline without adaptation, and (2) required adaptation to be included in this guideline.

Stage 5 - The adaptation of any recommendation is in the line with the methods set out in this guideline and based on the process developed for the *Common Mental Health Disorders* guideline (NCCMH, 2011).

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 adults with autism covered in the guideline. This was achieved by:

- systematic literature review 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, 2009e). 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. An economic model was therefore developed to address the cost effectiveness of an employment support programme versus usual standard service.

In addition, literature on the health-related quality of life of 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 January 2010 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 health technology assessment reports, and conducted in the following databases:

- EconLit (the American Economic Association's electronic bibliography)
- EMBASE (Excerpta Medica database)
- Health Technology Assessment (HTA) database
- MEDLINE / MEDLINE In-Process
- 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 health technology assessment reports, and conducted in the following databases:

- EconLit (the American Economic Association's electronic bibliography)
- Health Technology Assessment (HTA) database
- EMBASE
- MEDLINE / MEDLINE In-Process
- NHS Economic Evaluation Database (NHS EED)
- PsycINFO.

In addition, we also searched Google and Google Scholar for any research potentially missed by the electronic database searches.

A**n**y 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/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 spectrum conditions 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. In the absence of good quality evidence on autism, additional searching was conducted for wider literature on intellectual disabilities.

For standard mainstream bibliographic databases (EMBASE, MEDLINE and PsycINFO) search terms for autism spectrum conditions were combined with a search filter for health economic studies. For searches generated in topic-specific databases (EconLit, HTA, NHS EED) search terms for autism spectrum conditions were used without a filter. The sensitivity of this approach was aimed at minimising the risk of overlooking relevant publications, due to potential weaknesses resulting from more focused search strategies. A more focused approach was employed for searches on intellectual disabilities. The search terms are set out in full in Appendix 11.

Reference Manager

Citations from each search were downloaded into Reference Manager (a software product for managing references and formatting bibliographies) 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 re-analysis 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 Centre for Reviews and Dissemination (CRD) (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. Full detail of the filter is provided in Appendix 11.

Date and language restrictions

Systematic database searches were initially conducted in November 2010 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in September 2011. 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 1996 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 11.

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. Poster presentations of abstracts were excluded.
- Full economic evaluations that compared two or more relevant options and considered both costs and consequences, as well as simple cost analyses were included in the review.
- Economic studies were included if they used clinical effectiveness data from an RCT, a cohort study, or a systematic review and meta-analysis of clinical studies.

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, 2009e), which is shown in Appendix 17 of this guideline. The methodology checklist for economic evaluations was also applied to the economic model developed specifically for this guideline. 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 17.

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 reference to the included study and the respective evidence table with the study characteristics and results are provided in Appendix 18. 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 19.

3.6.5 Results of the systematic search of economic literature

The title of the study identified by the systematic search of the literature was screened for their relevance to the topic (that is, economic issues and information on health-related quality of life in people with autism). References that were clearly not relevant were excluded first. The abstracts of all potentially relevant studies (two; Clark *et al.,* 2009; MAWHOOD1999) 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 (one; MAWHOOD1999 reference) were then appraised for their applicability and quality using the methodology checklist for economic evaluations. Finally, one economic study that fully or partially met the applicability and quality criteria were 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/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[8], and the group's awareness of practical issues (Eccles *et al.,* 1998; NICE, 2009e).

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

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 would not choose an intervention whereas others would. This may happen, for example, if some service users are particularly averse to some side effect 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 13.

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 Healthcare 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
- highlighting factual errors in the pre-publication check.

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 others were responded to, and the guideline updated as appropriate. The GRP 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 the pre-publication check where stakeholders are given the opportunity to highlight factual errors. Any errors are corrected by the NCCMH, then the guideline is formally approved by NICE and issued as guidance to the NHS in England and Wales.

4 EXPERIENCE OF CARE

4.1 INTRODUCTION

This chapter provides an overview of the experience of adults with autism, and the experiences of their families and carers. The experience of the care and treatment of adults with autism has not been well described, with the limited work in the field focusing more on the experience of children and young people and their families and carers (Thomas *et al*., 2007). However, as the Autism Strategy (Department of Health, 2010) makes clear, adults with autism have considerable problems accessing care, they receive only limited services at best (particularly if they do not have significant coexisting conditions) and there is also considerable concern about the nature of the treatment provided. Understanding the experience of having autism, of services and of caring for a family member with autism is of central importance in developing this guideline.

This chapter centres on a thematic analysis of the qualitative literature, which was undertaken in order to identify themes relevant to the experience of autism, and the experience of services and treatment from the point of view of adults with autism and/or their families and carers. The intention is that this thematic analysis will directly inform the development of recommendations about service user care but will also inform the development and content of other recommendations in this guideline, in particular those recommendations for the principles of care and the organisation and delivery of services (see Chapter 6).

4.2 REVIEW OF THE QUALITATIVE LITERATURE

4.2.1 Clinical review protocol (experience 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 4 (further information about the search strategy can be found in Appendix 9). A systematic search for published reviews of relevant qualitative studies of people (including service users and families and carers) with autism was undertaken using standard NCCMH procedures as described in Chapter 3. Reviews were sought of qualitative studies that used relevant first-hand experiences of 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 people with autism and their families and carers and adopted the method described in Section 4.3.2 for the analysis of the studies.

Table 4: Databases searched and inclusion/exclusion criteria for clinical evidence

Component	Description
Review question(s)	For people with autism, what are their experiences of having autism, of access to services, and of treatment? (CQ-E1) For families, carers or significant others of people who have autism, what are their experiences of caring for people with autism, and what support is available for families, carers or significant others? (CQ-E2)
Objectives	To identify the emerging themes for the experiences of individuals with autism and their families/carers in terms of the experience of autism and in terms of experiences of accessing services and of treatment
Criteria for considering studies for the review	
• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental disorder), and their families and carers.
• Intervention	None
• Comparison	None
• Critical outcomes	None specified - any narrative description of service user or carer experience of autism
• Study design	Systematic reviews of qualitative studies, qualitative studies, surveys
• Include unpublished data?	No
• Restriction by date?	No
• Minimum sample size	No minimum sample size
• Study setting	Any setting
Electronic databases	ASSIA, CINAHL, Embase, HMIC, IBSS, Medline, PsycBOOKS, PsycEXTRA, PsycINFO, SSA, Sociological Abstracts
Date searched	CINAHL, Embase, HMIC, Medline, PsycBOOKS, PsycEXTRA, PsycINFO: 01.01.1996 - 09.09.2011; ASSIA, IBSS, SSA, Sociological Abstracts: 01.01.1996 - 10.10.2011
Searching other resources	Hand-reference searching of retrieved literature
The review strategy	Thematic analysis of primary qualitative studies and surveys reporting experiences of individuals with autism and/or their families and carers
Note: ASSIA = Applied Social Services Index and Abstracts; CINAHL = Cumulative Index to Nursing and Allied Health Literature; Embase = Excerpta Medica database; HMIC = Health Management Information Consortium; IBSS = International Bibliography of Social Sciences; Medline = Biomedical Information Database; PsycBOOKS = Psychological Information Database; PsycEXTRA = Grey literature database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

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4.3 THEMATIC ANALYSIS OF THE QUALITATIVE LITERATURE

4.3.1 Introduction

In line with the method normally adopted for this type of review a search for systematic reviews of the experience of care for individuals 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 adults with autism and their families and carers. The review question was concerned with exploring the experience of care for people with autism and their families and carers in terms of the broad topics of receiving a diagnosis, accessing services and treatment, and the experience of autism. The literature review supported a thematic analysis of the qualitative data reported in the primary studies and identified emergent themes relevant to the experience of care.

4.3.2 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 4 for details on inclusion criteria) were reviewed using thematic analytic techniques (Boyatzis, 1998; Braun & Clarke, 2006). Each included study was reviewed by members of the review team and broad themes were identified (see Section 4.3.4). Relevant sections of the text were then extracted and categorised under the different headings and themes were checked to ensure all of the data were covered.

4.3.3 Studies considered[9]

Studies were sought that used relevant first-hand experiences of adults with autism and their families and carers. For more information about the databases searched see Table 4.

The search found 27 studies (reported across 29 studies) that met the eligibility criteria and were included (Bemporad, 1979 [BEMPORAD1979]; Blacher *et al.,* 2010 [BLACHER2010]; Cederlund *et al.,* 2010 [CEDERLUND2010]; Cesaroni & Garber, 1991 [CESARONI1991]; Clarke & van Amerom, 2008 [CLARKE2008]; Graetz, 2010 [GRAETZ2010]; Hare *et al.,* 2004 [HARE2004]; Hurlbutt & Chalmers, 2002 [HURLBUTT2002]; Huws & Jones, 2008 [HUWS2008]; Jennes-Coussens *et al.,* 2006 [JENNESCOUSSENS2006]; Jones *et al.,* 2001 [JONES2001]; Kraus *et al.,* 2005 [KRAUSS2005]; Krausz & Meszaros, 2005 [KRAUSZ2005]; Lau & Peterson, 2011 [LAU2011]; MacLeod & Johnston, 2007 [MACLEOD2007]; Magana & Smith, 2006 [MAGANA2006]; Orsmond & Seltzer, 2007 [ORSMOND2007]; Orsmond *et al.,* 2009

[9] 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).

[ORSMOND2009]; Punshon *et al.,* 2009 [PUNSHON2009]; Robledo & Donnellan, 2008 [ROBLEDO2008]; Ryan & Cole, 2009 [RYAN2009]; Ryan, 2010 [RYAN2010]; Seltzer *et al.,* [SELTZER2001]; Shtayermman, 2007, Shtayermman, 2009 [SHTAYERMMAN2007/2009]; Shu *et al.,* 2006 [SHU2006]; Smith *et al.,* 2010 [SMITH2010]; Sperry & Mesibov, 2005 [SPERRY2005]). All of these studies were published in peer-reviewed journals between 1979 and 2011. In addition, 140 studies were considered for the thematic analysis but were excluded as they did not meet the eligibility criteria for inclusion in the review (see Appendix 14). The most common reason for exclusion was that the age of the person, or mean age of the sample, with autism was under 18 years old or the studies focused on the predictive value of participant characteristics rather than experience of care. The characteristics of all the studies included in this review have been summarised in Table 5 and Table 6. These have been categorised under two main headings: service user experience and family and carer experience.

Table 5: Summary study characteristics for included studies of the experience of care of adults with autism

	Experience of care of adults with autism
Study IDs	(1) BEMPORAD1979 (2) CEDERLUND2010 (3) CESARONI2010 (4) CLARKE2008 (5) HURLBUTT2002 (6) HUWS2008 (7) JENNESCOUSSENS2006 (8) JONES2001 (9) LAU11 (10) MACLEOD2007 (11) PUNSHON2009 (12) ROBLEDO2008 (13) SHTAYERMMAN2007/2009 (14) SPERRY2005
Autism population (Axis I/II disorders/ Mean age)	(1) 100% autism/31 (2) 100% asperger's syndrome/22 (3) 100% autism (high functioning)/27 (4) Self identified asperger's syndrome/Not specified (5) 100% autism (high functioning)/42 (6) 100% autism/Age range = 16-21 (7) 100% asperger's syndrome/20 (8) 60% autism (high functioning), 20% atypical autism/Not specified (9) 100% asperger's syndrome/Not specified (10) 100% asperger's syndrome/Not specified (11) 100% asperger's syndrome/Age range = 22-45 (12) 100% autism/27 (13) 100% asperger's syndrome/20 (14) 100% ASD/34
Focus of study	(1) Experience of autism (2) Assessment (3) – (6) Experience of autism (7) Quality of life (8) Experience of autism

	(9) Relationship satisfaction (10) Experience of support group (11) Experience of autism (12) Experience of relationships (13) Perception of stigma (14) Perception of social challenges
Data Collection Method	(1) Interview/Case history (2) Interview/Questionnaire (3) Interview/Content analysis of documents (4) Content analysis of websites (5) Interview/Content analysis of documents (6) Interview (7) Interview/Questionnaire (8) Content analysis of websites (9) Questionnaire (10) Written interview (11) Interview (12) Interview/Content analysis of documents (13) Questionnaire (14) Focus group
Setting	(1) – (2) Not reported (3) Multiple (conference, home, telephone) (4) Online (5) Multiple (conference, telephone, email) (6) Academic institution (7) Home (8) Online (9) Postal questionnaire (10) – (12) Not reported (13) Online and postal questionnaire (14) Social group meeting
Country	(1) USA (2) Sweden (3) – (4) Canada (5) USA (6) UK (7) Canada (8) UK (9) Australia (10) – (11) UK (12) – (14) USA

Table 6: Summary study characteristics for included studies of the experience of families and carers of adults with autism

	Family and carer experience
Study IDs	(1) BLACHER2010 (2) GRAETZ2010 (3) HARE2004 (4) KRAUSS2005 (5) KRAUSZ2005 (6) LAU2011 (7) MAGANA2006 (8) ORSMOND2007

	(9) ORSMOND2009 (10) RYAN2009 (11) RYAN2010 (12) SELTZER2001 (13) SHU2006 (14) SMITH2010
Autism population (Axis I/II disorders/ Mean age)	(1) 100% autism/23 (2) 100% ASD/22 (3) 100% ASD/27 (4) 100% ASD/32 (5) 100% autism/19 (6) 100% asperger's syndrome/Not specified (7) 100%ASD/18 (8) 100% ASD/35 (9) 100% ASD/19 & 29 (10) 100% ASD/ Range = 23-53 (11) 100% ASD/Range = 18-28 (12) 100% autism/39 (13) 100% autism/18 (14) 100% ASD/25
Focus of study	(1) Expectations of transition (2) Opportunities in autism (3) Health and social care needs (4) Residential arrangement satisfaction (5) Experience of autism (6) Relationship satisfaction (7) Residential arrangement satisfaction (8) – (9) Sibling relationship (10) – (12) Experience of autism (13) Self identity (14) Experience of autism
Data Collection Method	(1) Interview (2) Questionnaire (3) Interview (4) Questionnaire (5) Interview (6) Questionnaire (7) Interview/Questionnaire (8) Questionnaire (9) Questionnaire/Interview (10) – (14) Interview
Setting	(1) Home (2) Online and postal survey (3) Not reported (4) Home (5) Not reported (6) Postal questionnaire (7) Home (8) – (9) Postal questionnaire (10) Not reported (11) Home (N=2 office settings) (12) Not reported (13) Home (14) Telephone

Country	(1) – (2) USA (3) UK (4) USA (5) UK (6) Australia (7) – (9) USA (10) – (11) UK (12) USA (13) Taiwan (14) USA

4.3.4 Experience of care of adults with autism

As described in Section 4.3.2, the review team identified broad themes from the primary qualitative studies and survey data. Initially this thematic analysis of the data resulted in seven broad headings:

- the impact of autism
- relationships
- awareness of being different
- stigma and judgement by others
- reactions to diagnosis
- treatment and services
- being an expert by experience.

Under these broad headings specific emergent themes have been extracted and are discussed below. A summary of these themes can be found in Table 7.

Table 7: Summary of emergent themes for the experience of care of adults with autism

	BEMPORAD1979	CEDERLUND2010	CESARONI1991	CLARKE2008	HURLBUTT2002	HUWS2008	JENNESCOUSSENS2006	JONES2001	LAU2011	MACLEOD2007	PUNSHON2009	ROBLEDO2008	SHTAYERMMAN2007/2009	SPERRY2005
Impact of autism		x	X	x	x	X	x	x		x	X		x	
Relationships	X	x	X		x		x	x	x	x	X	x		x
Awareness of being different	X	x	X	x	x	X	x	x		x	X			
Stigma and judgement by others			X	x	x	X		x		x	X	x	x	x
Reactions to					x	X		x		x	X			x

diagnosis														
Treatment and services	X			x	x		x	x		x	X	x		
Being an expert by experience				x	x					x		x		

Impact of autism

Participants in the studies expressed a range of different views about the way autism had impacted on their lives. Some participants described feelings of high self-esteem, especially in relation to overcoming difficulties. In addition, autism was viewed by some participants as an advantage particularly in, some areas of cognitive functioning (CLARKE2008; PUNSHON2009). This was, however, coupled with awareness of a negative impact of autism on areas such as quality of life (JENNESCOUSSENS2006), experience of their environment (CESARONI1991; HURLBUTT2002), education (HURLBUTT2002; JENNESCOUSSENS2006) and employment (HURLBUTT2002; JENNESCOUSSENS2006; MACLEOD2007). Difficulties with employment extended beyond finding a job. Participants who were in paid employment also reported difficulties with jobs that were often below their ability and poorly paid (HURLBUTT2002; JENNESCOUSSENS2006):

> *'I worked as a caseworker and was asked to leave 5 months later. I could have used support in asking the proper questions. I started in the food industry after that, and the only job I could get was washing pots or doing dishes. I had odd jobs, working in the hospital in the stockroom, and working in department stores in the same capacity. In these jobs, I was fired because either I asked too many questions, or didn't ask enough, or bothered the women, whatever that meant. Since autism was barely heard of, I couldn't figure out why I was having such bad luck. There were no job coaches then.'* (HURLBUTT2002).

Increased psychological distress was reported in adults with autism, with anxiety and depression (CEDERLUND2010; HURLBUTT2002; JONES2001; PUNSHON2009; SHTAYERMMAN2007/2009), self-harm and suicidal ideation (MACLEOD2007; PUNSHON2009; SHTAYERMMAN2007/2009) all being experienced. There were also negative emotions around the enduring nature of autism, feelings of frustration and of being 'stuck like this' (HUWS2008; JONES2001; PUNSHON2009), and sadness that their diagnosis threatened their expectations (HUWS2008; PUNSHON2009):

> *There was this dip…I think because I felt like well, you know, I was feeling a bit hopeless, you know that maybe this wasn't something I could overcome…I am never going to be like one of these 'normal' people and you know…and I thought 'I am stuck being like this now'."* (PUNSHON2009).

Relationships

Adults with autism expressed a need for good interpersonal relationships (BEMPORAD1979; CESARONI1991; JONES2001) and intimate relationships (HURLBUTT2002; LAU2011; SPERRY2005) despite an awareness of being different from their peers (CEDERLUND2010; CESARONI1991; HURLBUTT2002; MACLEOD2007; PUNSHON2009) and a self-awareness regarding social difficulties (HURLBUTT2002; JENNESCOUSSENS2006; JONES2001). There was an indication that their social needs might not be recognised or might be underestimated by those around them (CEDERLUND2010), and this angered some participants (CESARONI1991; SPERRY2005). There was talk of the difficulties faced by individuals with autism when engaging in social interactions (CESARONI1991), and of the fact that such efforts to socialise were not always successful (BEMPORAD1979; HURLBUTT2002; JONES2001) or sustained (BEMPORAD1979), which could cause distress and frustration (BEMPORAD1979; HURLBUTT2002; JONES2001; MACLEOD2007). There was also discussion of positive relationships formed (CESARONI1991; HURLBUTT2002; SPERRY2005) and how such support was valued (HURLBUTT2002; JENNESCOUSSENS2006; ROBLEDO2008).

The most appreciated relationships were those formed with other people with autism (HURLBUTT2002; JONES2001; MACLEOD2007; PUNSHON2009), as there could be mutual understanding and a feeling of 'fitting in' (MACLEOD2007; PUNSHON2009), as well as an opportunity to socialise without feeling like 'getting it wrong' (MACLEOD2007; PUNSHON2009). A feeling of relief was discussed upon discovering these relationships (MACLEOD2007), often formed at support groups (HURLBUTT2002; MACLEOD2007; PUNSHON2009):

> *'I found it a relief to meet other people who had similar difficulties to myself. For example, I heard people tell anecdotes about times they had "said the wrong thing" and had accidentally insulted other people. As my mother had described it, in my case, "Paula tells the awful truth". When I had been attending the group for some time, I saw one of the members on the bus, and went up to say "hello". However, he looked at me blankly and said, "How do I know you?" which amazed me, as this is an expression I have often used myself. When I meet someone that I deal with quite often, like the doctor's receptionist, but they are in unfamiliar surroundings, like in the street, if they say "hello", I often can't place who they are, and may have to say, "How do I know you?" So, to be on the receiving end of this was an uncanny experience'.* (MACLEOD2007)

Adults with autism discussed their awareness of their difficulties in social interaction (HURLBUTT2002; JENNESCOUSSENS2006) and with communication (CESARONI1991; HURLBUTT2002; ROBLEDO2008), and their concerns and frustrations about these problems (HURLBUTT2002; JONES2001; MACLEOD2007). They described confusing social environments (BEMPORAD1979; CESARONI1991; JONES2001), sensory overload (BEMPORAD1979; HURLBUTT2002; JONES2001) and having to apologise for their behaviour (JONES2001; PUNSHON2009), which could leave them feeling isolated (BEMPORAD1979; HURLBUTT2002, JONES2001;

PUNSHON2009) and envious of 'neurotypicals'[10] (HURLBUTT2002; PUNSHON2009). However awareness was not always present and some participants spoke of growing up oblivious to social deficits (HURLBUTT2002; PUNSHON2009) and their inappropriate behaviour in certain situations (HURLBUTT2002). Participants also stressed the importance of not using autism as an excuse (SPERRY2005). There was discussion of strategies for approaching social situations that people with autism have developed (PUNSHON2009; SPERRY2005) and interventions to help with learning social skills (HURLBUTT2002):

> *'…I would say you have to figure out about your own personal space and your comfort. I give people 3 feet of space. With facial expressions you can look at eyebrows and whether they're smiling. It's experience. If they're staring or spaced out, that means they're not paying attention'.* (SPERRY2005)

Awareness of being different

As mentioned above, adults with autism described an awareness of being different from their peers (CEDERLUND2010; CESARONI1991; HURLBUTT2002; JENNESCOUSSENS2006; MACLEOD2007; PUNSHON2009). This was often associated with feelings of failure, alienation and not belonging (BEMPORAD1979; HURLBUTT2002; JONES2001; PUNSHON2009). Insight into these differences and the extent of these difficulties varied, especially when there was a delay in diagnosis (BEMPORAD1979; CEDERLUND2010; CLARKE2008; HURLBUTT2002; HUWS2008; PUNSHON2009):

> *'I do feel that if people had known then a lot of things could have been different. And, as well, that's perhaps a difficult thing to think about, just feeling that a lot of suffering might have been avoided. I wouldn't have blamed myself because I used to self-harm when I was younger and I don't think I would…if I had known I had Asperger's earlier. I would have been more aware of my problems…and better able to cope with them.'* (PUNSHON2009)

Adults with autism reported a conflict between the desire and effort expended to 'fit in' and be like others (CESARONI1991; HURLBUTT2002; PUNSHON2009) and the realisation that they could not or should not have to do so. Participants described how 'normalising' behaviour would mean they could not be themselves (BEMPORAD1979; CESARONI1991; HURLBUTT2002; PUNSHON2009). Attempts to 'fit in' were also linked with negative emotions such as anxiety and stress (BEMPORAD1979; CESARONI1991; PUNSHON2009). The knowledge that other people like them existed was a great help for many individuals with autism (CLARKE2008; HURLBUTT2002; JONES2001; MACLEOD2007; PUNSHON2009). Following on from this there was much talk of acceptance of their autism and any difficulties it presented (CLARKE2008; HURLBUTT2002), and frustration at the view

[10] A term used by some people with autism to refer to people without autism or another neurodevelopmental condition, the purpose being to emphasise the 'different' rather than the pathological nature of autism.

that they should desire to be 'neurotypical' (CLARKE2008; HURLBUTT2002), as they believed that it was society that needed to change:

> *'I have been told in the past that certain things I do are weird and unacceptable, but I am not going to change them now. Sometimes, people's reactions would teach me stuff, but not as much now, because I really don't care what other people think of me as much. Now I don't want to be like anyone else, period. I don't necessarily see the idea of NT [neurotypical] as perfection. Hey, regular people do stupid, mean, and often evil things that people with autism would never do. I am supposed to look up to that? I don't think so! I am tired of having to do 100% of the changing, and there is no change with most people without autism*'. (HURLBUTT2002).

Stigma and judgement by others

Many adults with autism reported victimisation by peers, especially in the workplace (CESARONI1991; HURLBUTT2002; HUWS2008; MACLEOD2007; PUNSHON2009; SHTAYERMMAN2007/2009), with high-functioning adults particularly at risk of this (JONES2001; PUNSHON2009; SHTAYERMMAN2007/2009). There were also reports of being stigmatised (CLARKE2008; HURLBUTT2002). Participants described worrying about what others thought of them (HURLBUTT2002; JONES2001) and the desire to be treated like a 'normal' person (ROBLEDO2008; SPERRY2005). However, as mentioned above, this contrasted with feelings of self-esteem about their autism and the view that the problem was the reactions of others, not the condition itself (CLARKE2008; HURLBUTT2002). Participants expressed anger that people with autism were viewed not to have empathy (CESARONI1991; HURLBUTT2002) and it was suggested that 'neurotypicals' may be the ones without empathy:

> *'Many NTs [neurotypicals] are very narrow in their view. I can look at different points of view. With me, my view is not the only way. Most people with autism get frustrated with NTs because very often, it's the so-called "normal" people who lack empathy because many of them don't want to listen to any point of view besides their own. Most people with autism I have spoken to are happy being who they are. They find most "normal" people narrow and biased.'* (HURLBUTT2002)

Participants expressed concern about being labelled as autistic as it could lead to people making assumptions about them on the basis of their diagnosis (HUWS2008; PUNSHON2009; ROBLEDO2008; SPERRY2005). The desire for people to get to know them and not the condition was described (ROBLEDO2008; SPERRY2005). However, participants did recognise that such labelling could be helpful in terms of receiving support (PUNSHON2009; SPERRY2005) and could reduce negative treatment from others (HUWS2008), although this was not always the case (ROBLEDO2008). Possible reasons for discrimination were perceived to be a lack of understanding of what autism is and how it affects the individual (HURLBUTT2002; PUNSHON2009), a lack of information available about autism (HURLBUTT2002; PUNSHON2009) and an incorrect portrayal of the condition in the media (CLARKE2008; PUNSHON2009):

> *'I have seen…people with Asperger's portrayed in dramas and plays and things and I cringe when I watch [laughs]. I suppose anyone who has got any problem who gets it shown on television goes, 'Oh God, it's not like that in real life'…people get the wrong reaction because someone has stereotyped it. It's quite annoying [laughs], just another one of those things that gets to you.'* (PUNSHON2009)

Reactions to diagnosis

Not all of the adults in the studies were diagnosed with autism as children—some received their diagnosis in adulthood (HURLBUTT2002; JONES2001; MACLEOD2007; PUNSHON2009). Mixed reactions to diagnosis were described by adults with autism, with some viewing their diagnosis as a positive thing (HURLBUTT2002; HUWS2008; PUNSHON2009; SPERRY2005), and others a negative (HUWS2008; MACLEOD2007; PUNSHON2009; SPERRY2005). Positive outcomes of diagnosis discussed were that it could open doors to support, both vocational and autism specific (HUWS2008; PUNSHON2009; SPERRY2005), make the person realise that they were not alone and there were other people like them (HURLBUTT2002; JONES2001), and finally, that they had answers (HURLBUTT2002; HUWS2008; MACLEOD2007; PUNSHON2009), which was especially true in cases of delayed or misdiagnosis (HURLBUTT2002; HUWS2008; JONES2001; PUNSHON2009):

> *'[It was] the missing piece of the jigsaw, it put everything into place for me and I got the bigger picture then. I knew why this had happened, this was happening and that was happening…it all just came together.'* (PUNSHON2009).

Negative reactions in response to a diagnosis included shock, disappointment, loss, anger and suicidal thoughts (HUWS2008; MACLEOD2007; PUNSHON2009; SPERRY2005), sometimes coupled with avoidance (HUWS2008; PUNSHON2009). Other negative feelings around diagnosis included concerns about stigma (HUWS2008; PUNSHON2009 SPERRY2005), negative reactions from others (PUNSHON2009) and mistrust of services after misdiagnoses (PUNSHON2009). However there was also talk amongst some participants of a gradual acceptance (HUWS2008):

> *'At first it was hard for me to accept it and then I sort of learnt to accept it a bit more, when I came here [college for young people with autism] I accepted it even more (…). I really find it annoying to have but it's something that you've got to accept and so, yeah."* (HUWS2008)

Treatment and services

There was relatively little discussion of treatment and services for autism, which is perhaps not surprising given the limited services available for adults with autism (GRAETZ2010; HARE2004). Interventions that were discussed included group support, which was an important means of help (HURLBUTT2002; MACLEOD2007; PUNSHON2009). Some settings were also talked about, with a dislike of institutionalisation (BEMPORAD1979; HURLBUTT2002), and preference for

community living (HURLBUTT2002) being expressed. Those that did discuss services were eager to make suggestions and participate in decisions about their care (HURLBUTT2002; ROBLEDO2008). There was some discussion of feeling let down by services, usually related to misdiagnosis or clinicians' lack of knowledge (PUNSHON2009), and examples of adults with autism being left with no follow-up support following diagnosis (MACLEOD2007; PUNSHON2009; ROBLEDO2008). This led some to seek out support groups (HURLBUTT2002; MACLEOD2007):

> *'…I was upset about my situation and, even before my diagnosis, I had been trying to get support. Now, at last, I had the opportunity to get some information about my condition and to meet some people who might turn out to be similar to myself. I had always felt so different from other people, which is OK, but I have been at the receiving end of such hostility, for example when I have tried to work. I suppose I was looking for something that might not throw me out!'* (MACLEOD2007).

Much discussion focused around the importance of support and how much this support was appreciated (HURLBUTT2002; JENNESCOUSSENS2006; ROBLEDO2008), with family (HURLBUTT2002), other people with autism (CLARKE2008; HURLBUTT2002; JONES2001; MACLEOD2007; PUNSHON2009), religion (HURLBUTT2002), and the internet (CLARKE2008) all being cited as valued sources of support. Supportive relationships were said to help with development of self-worth and social skills (HURLBUTT2002), and were associated with greater quality of life (JENNESCOUSSENS2006). That these relationships were based on trust and an assumption of competence, and allowed independence, was important to individuals (HURLBUTT2002; ROBLEDO2008):

> *'My staff push me to be able to do things with the least amount of support necessary. They are constantly teaching me that I must rely on myself first and then ask for aid if I am not able to accomplish something on my own. I find that I am happier being tested to see what my strengths and weaknesses actually are. I am not afraid at all to ask for help from my staff and friends because they are truly there for the purpose of aiding me in my times of need. I feel much more independent than I could have ever imagined, and that feeling alone is intensely gratifying.'* (ROBLEDO2008).

Being an expert by experience

Many adults with autism expressed a strong wish to be considered as an 'expert' (HURLBUTT2002) and to have the opportunity to educate others about autism (HURLBUTT2002), and also to be an advocate for other people with autism (CLARKE2008; HURLBUTT2002; MACLEOD2007; ROBLEDO2008). Participants stressed the importance of being consulted and feeling in control of their life choices (HURLBUTT2002; ROBLEDO2008):

> *'I am committed to the cause of autism. I want to see people who are proud to have autism and accept themselves for who they are and all that they are. Too often in the past, people didn't listen to people with autism. Most people do not know about autism, much less what a person deals with. So, educating people about autism is a key.'* (HURLBUTT2002)

4.3.5 Clinical summary – experience of care of adults with autism

A number of themes emerged from the literature that captured the experience of adults with autism. One clear theme that was identified and underpins much of what follows was that living with autism represents a considerable burden for most people characterised by limited or lost opportunities to live a fuller life. This was often accompanied by considerable psychological distress that had a further negative impact on peoples' lives. This distress was further exacerbated by the stigma and exclusion that many people reported as a result of having autism. A strong theme that emerged (and consistent with the core symptoms of autism) was the considerable difficulty people had in developing and sustaining relationships. Often these were best developed with other people with autism and linked to a shared understanding of the problems faced. There was a shared concern that the nature of autism was simply not understood by others and this added to the difficulties experienced by many people.

Receiving a diagnosis of autism was viewed positively because it offered an explanation and understanding of a person's experience and also increased access to a range of services that otherwise were denied to people. However, it also brought with it concerns about increased stigma and exclusion. There was relatively little qualitative evidence of people's experience of services (perhaps reflecting the limited availability of services for adults) but what was identified emphasised the importance of support and help in developing skills in social interactions with others. On a positive note, the developing voice of people with autism as experts by experience was identified as an increasingly positive aspect of living with autism.

4.3.6 From evidence to recommendations

The GDG carefully reviewed the themes summarised in Section 4.3.4 and considered the implications of these themes when drafting recommendations in the following areas:

a) Case identification, assessment and diagnosis (see Chapter 5): ensuring that the recommendations in these areas were drafted in such a way as to reflect the messages that emerged from the identified themes.

b) Principles of care: the clinical summary (Section 4.3.5) was used in conjunction with the evidence reviewed in the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming), to guide the development of the recommendations and to identify important areas where a recommendation needed to be developed for this guideline. A particular concern was to ensure that key aspects of the principles of care identified in the evidence review for the *Service User Experience in Adult Mental Health* draft NICE guidance, and which the GDG viewed as being important in the care of people with autism, were not omitted from this guideline. In both the evidence reviewed in this section and in the *Service User Experience in Adult Mental Health* draft NICE guidance the need for working in partnership with

people with autism and ensuring that systems are in place that support such processes came through very clearly and this is reflected in the recommendations, specifically in recommendations 4.3.7.2 and 4.3.7.3. In drawing on the evidence base for the *Service User Experience in Adult Mental Health* draft NICE guidance, the GDG was also mindful of the specific communication problems associated with autism and therefore placed a particular emphasis on the need for any information to be provided in various visual, verbal and aural, easy read, colour and font formats, given the GDG's opinion that this may facilitate the readability, understanding and comprehension of the information for people with autism.

c) Organisation of care (see Chapter 6): here the clinical summary (Section 4.3.5) was used to inform the selection of recommendations from *Common Mental Health Disorders* (NICE, 2011b) to identify important areas where a new recommendation needed to be developed for this guideline.

The GDG developed a number of recommendations for this guideline, which drew on the evidence referred to above and which were supported by the qualitative analysis. The GDG was concerned that some people with autism felt 'let down' by professionals' lack of knowledge of autism, and therefore made a recommendation that all staff working with adults with autism should have a basic understanding of autism, and that professionals providing care and treatment to adults with autism should have an extensive understanding of its nature, development and course. The GDG also wished to alert all health and social care professionals to the need to make modifications to their assessment procedures so that adults with autism could receive the most effective care. There was good evidence from the qualitative analysis that talking to other people with autism was felt to be beneficial and therefore the GDG drew on their expert knowledge and experience, along with the evidence in the *Service User Experience in Adult Mental Health* draft NICE guidance and other NICE guidelines for people with long-term disorders (for example, NCCMH 2010a, 2010c), and made a recommendation for the provision of information about organisations and websites that can provide support and the use of face-to-face self-help and support groups.

4.3.7 Recommendations

Principles for working with adults with autism and their families and carers

4.3.7.1 All staff working with adults with autism should have a basic understanding of the:

- nature, development and course of autism
- impact of autism on personal, social, educational and occupational functioning
- impact of the social and physical environment on autism.

4.3.7.2 All staff working with adults with autism should:

- work in partnership with adults with autism and their families or carers
- offer help, treatment and care respectfully
- take time to build a trusting, supportive, empathic and non-judgemental relationship as an essential part of care.

4.3.7.3 All health and social care professionals providing care and treatment to adults with autism should:

- aim to foster the person's autonomy, promote active participation in treatment decisions and support self-management
- maintain continuity of individual relationships wherever possible
- ensure that comprehensive information about the nature of, and treatments and services for, their problems is available in an appropriate language or format (including various visual, verbal and aural, easy read, colour and font formats)
- offer access to a trained advocate.

4.3.7.4 All health and social care professionals providing care and treatment to adults with autism and their families or carers should ensure that they are:

- familiar with local and national sources (organisations and websites) of information and/or support for people with autism
- able to discuss and advise how to access these resources
- able to discuss and provide support to people with autism to engage with these resources.

4.3.7.5 All staff working in services used by adults with autism should have a basic understanding of any modifications that need to be made to the method for delivery of the assessment, the setting in which assessment is delivered and the duration and pacing of the assessment.

4.3.7.6 All health and social care professionals providing care and treatment to adults with autism specifically for the autism or related conditions should have an extensive understanding of the nature, development and course of autism and:

- its impact on personal, social, educational and occupational functioning
- its interaction with the social and physical environment
- its impact on other coexisting mental and physical disorders and their management
- the potential discrepancy between intellectual functioning as measured by IQ and adaptive functioning as reflected, for example, by difficulties in planning and performing activities of daily living.

4.3.7.7 The specialist autism team should support access to services and increase the uptake of interventions by:

- delivering assessment and interventions in a physical environment that is appropriate for people with hyper- or hypo-sensory sensitivities
- changing the professional responsible for the person's care if an appropriate therapeutic relationship cannot be established.

4.3.7.8 If adults with autism need social support, provide information about, and consider facilitating the use of, self-help groups, support groups, one-to-one support and other local and national resources.

4.3.8 Experience of families and carers of adults with autism

As described in Section 4.3.2, the review team identified broad themes from the primary qualitative studies and survey data. Initially this thematic analysis of the data resulted in seven broad headings. The themes echo those explored for adults with autism:

- impact of autism
- relationships
- awareness of being different and judgement by others
- treatment and services
- having a role as advocate.

Under these broad headings specific emergent themes have been extracted and are discussed below. A summary of these themes can be found in Table 8.

Table 8: Summary of emergent themes – experience of families and carers of adults with autism

	BLACHER2010	GRAETZ2010	HARE2004	KRAUSS2005	KRAUSZ2005	LAU2011	MAGANA2006	ORSMOND2007	ORSMOND2009	RYAN2009	RYAN2010	SELTZER2001	SHU2006	SMITH2010
Impact of autism	X	x	x	x	x		x	x		X		x	x	x
Relationships	X	x	x	x	x	x	x	x	x			x	x	x
Awareness of being different and judgement by others		x	x	x	x		x			X	x		x	x
Treatment and services	X	x	x	x	x		x			X		x	x	
Role of advocate		x			x		x			X				

Impact of autism

Families and carers of adults with autism discussed the impact of the condition on various areas of their life. Views were varied, and although difficulties were experienced (BLACHER2010; GRAETZ2010; KRAUSZ2005; MAGANA2006; SHU2006; SMITH2010), there was a sense of acceptance (HARE2004; MAGANA2006). Parents discussed their accomplishments (KRAUSZ2005), personal growth (HARE2004; MAGANA2006) and their own happiness (HARE2004) and positive caregiving experiences (KRAUSZ2005):

> *'I think when you raise a child like Philip, he teaches me more than I will ever teach him. I'm not a very patient person but I learned how to be patient with Philip. I always wanted everything to happen instantly. But I've learned that some goals are long term and I've settled down and I've become less impatient, less frustrated. That's a good thing to learn. I'm surprised I ever did it. That is not the way I was. I'm just more comfortable and content and satisfied with my life and with the way things go, the speed at which things happen. That's good experience for me. Took a long time (chuckle) to learn.'* (KRAUSZ2005)

However families and carers also reported disruption to their work and financial strain (KRAUSS2005; MAGANA2006; SMITH2010), reduced free time and leisure activities and a limited social life (HARE2004; KRAUSS2005; MAGANA2006; SHU2006; SMITH2010), restricted choice of living location (HARE2004) and changes to family life (BLACHER2010; GRAETZ2010; HARE2004; KRAUSS2005; MAGANA2006): *'Life for the parent is like being a prisoner in one's own home.* (KRAUSS2005).

Psychological distress was reported by families and carers of adults with autism (HARE2004; KRAUSZ2005; SMITH2010), with stress and strain (KRAUSS2005; KRAUSZ2005; MAGANA2006; SELTZER2001; SMITH2010), worry (BLACHER2010; HARE2004; KRAUSS2005; KRAUSZ2005), frustration (KRAUSZ2005), guilt (KRAUSS2005), fatigue (GRAETZ2010; KRAUSS2005; SELTZER2001; SHU2006; SMITH2010) and feelings of being overwhelmed (GRAETZ2010; HARE2004) all experienced:

> *'You asked me a couple of times; How did I cope with that? How did I get through that? And I didn't even know what to say to you. Because nobody really ever asked me that before. Nobody seemed to care (chuckle) how I was coping as long as Philip was doing okay, you know. I never really thought about that, about how I coped with it. But it's interesting, that just… Everything seemed fine back then, you know, when the kids were little and Philip was going through all those bad things. But now, that Richard's [sibling] living with his dad, and he's like 24 and a half, and Philip's in the group home and I don't have a lot of stress in my life, and some quiet time for myself. And now my nerves are just a wreck. You know, I ended up going to a psychiatrist. And I just said: "You have to do something because I have to work and I'm a mess! I cannot work you know." He feels it's delayed stress syndrome. And I, I said: "But you know, I didn't have any stress. Everything was fine. I had my parents supporting me and the kids are fine. Everything worked out fine. And he said "You didn't feel it then, you're feeling it now. Because now everything is done and you have time to feel it." It's seems a little strange to me (chuckle), but that's what he said.'* (KRAUSZ2005).

There were also negative emotions about the enduring nature of autism, with worry for their sons' and daughters' future (GRAETZ2010; ORSMOND2007; SELTZER2001) after, they, the parents, had died (GRAETZ2010; HARE2004; KRAUSS2005; SHU2006): *'After we are gone, he will be hopelessly lost.'* (KRAUSS2005).

There were also positive views of the future (BLACHER2010), and reduced worries in some areas of life (HARE2004) compared with families and carers of people with other developmental conditions (BLACHER2010). Some families and carers reported a gradual change in future expectations and acceptance (KRAUSZ2005; MAGANA2006; RYAN2009; SHU2006):

> *'I would say that the impact is a total 100% turnaround in my life. Everything I had planned for being a mother has gone because that path, that path I saw around me everywhere just didn't happen and doesn't happen. So as a mother I have had to reassess who I am.'* (RYAN2009).

Relationships

Families and carers discussed the supportive relationships they have, and how they valued this support (GRAETZ2010; HARE2004; KRAUSZ2005; SHU2006; SMITH2010). However, others described a sense of isolation, usually due to reduced social opportunities and freedom (KRAUSS2005; SHU2006). Families reported positive relationships with their family member with autism (HARE2004; KRAUSS2005; LAU2011; MAGANA2006; SHU2006), and where the person with autism had left home, close relationships were still maintained (KRAUSS2005; ORMOND2009). However, these relationships were not always easy, and difficulties were discussed (KRAUSS2005; ORSMOND2007; ORSMOND2009; SELTZER2001; SMITH2010). The person's autism had an inevitable impact on family relationships, affecting parental relationships with other siblings (HARE2004; ORSMOND2007), marital relationships (HARE2004; KRAUSS2005; SHU2006), and general family life (BLACHER2010; GRAETZ2010; HARE2004; KRAUSS2005; MAGANA2006): *'My husband blames me that I over protect him, that he is spoiled.'* (SHU2006).

Awareness of being different and judgement by others

Some parents described how they had taken on different roles because of their sons' or daughters' autism, for example mothers felt that they had become 'carers' or 'teachers' (HARE2004; KRAUSS2005; KRAUSZ2005; MAGANA2006; SHU2006; SMITH2010) and had had to reassess their self-identity (RYAN2009; SHU2006); these self-perceptions changed over time (KRAUSS2005; KRAUSZ2005; SHU2006). Perceptions of others had also changed, and many families and carers expressed concern over how others viewed them and their family member with autism (GRAETZ2010; KRAUSZ2005; RYAN2010):

> *'When she is naughty, you look at Mandy when she is like now, when she is walking along, no one would think anything was wrong but all of a sudden in the supermarket she will just have a hissy fit and you get the dirty looks, and you get the 'tch haa' because these people don't know that that is what they are, that is what they do [um] and there is no way that you can stop that because it is just spontaneous, you just don't sort of really know…I sort of see a few signs, you might be able to predict it is going to happen, but not all the time.'* (RYAN2010).

Families and carers also reported that their autistic family member was not always accepted in their community (GRAETZ2010): *'Our son is social…but there is a lack of understanding and compassion from the non-disabled…for that reason we do not push socialization.'* (GRAETZ2010).

Treatment and services

There was some discussion of services for adults with autism, including day services such as colleges, day centres, respite care (HARE2004; SELTZER2001) and psychological services (SELTZER2001), and some therapies such as speech therapy (HARE2004) and occupational therapy (SELTZER2001), though uptake was low in some areas (HARE2004). However, there was much less discussion of services utilised by families and carers themselves (GRAETZ2010; HARE2004; RYAN2009; SHU2006). In some cases, knowledge of available autism-specific interventions such as social skills training was poor (HARE2004), though generally knowledge of services was good (BLACHER2010; GRAETZ2010; HARE2004). The living arrangements of adults with autism were also discussed, with feelings expressed about their family member continuing to live at home contrasted with those felt when the person moved to a residential setting (KRAUSS2005; KRAUSZ2005; MAGANA2006). Positive and negative emotions were associated with both options (BLACHER2010; GRAETZ2010; KRAUSS2005; MAGANA2006; SELTZER2001). For instance, benefits of the son or daughter with autism living at home were reported for the family (son/daughter '*keeps us company/is fun to be around*'), for the individual with autism (is getting good care at home/is secure) and for the parent (peace of mind). However, negative aspects of the son or daughter with autism living at home included problems for the family (dealing with son/daughter's behaviour), problems for the son/daughter (residing at home does not challenge son/daughter) and for the parent (constant caregiving/cannot leave son/daughter alone). Similarly, positive and negative aspects were reported for the son or daughter with autism living outside the home (predominantly in a community residential programme or in a semi-independent living setting), with benefits reported for the family (calmer, more typical family life), for the individual with autism (learning new skills/growing more independent/confident) and for the parent (more free time/freedom and less stress/fatigue). However, negative aspects included problems with the programme (staff not well trained), problems for the son or daughter (safety and grooming/personal appearance concerns) and problems for the parent (miss son/daughter and worried/guilt) (KRAUSS2005).

Opinions about services were mixed, with both praise and criticism reported (GRAETZ2010; HARE2004; SELTZER2001). This was coupled with much discussion of unmet needs by services (GRAETZ2010; HARE2004; KRAUSS2005; KRAUSZ2005; SELTZER2001). Families and carers expressed the need for more support in planning for the future and transition to adult services (BLACHER2010; GRAETZ2010; HARE2004), residential, recreation and employment opportunities for the person with autism (GRAETZ2010; MAGANA2006), and to enable breaks from caring (GRAETZ2010; HARE2004; KRAUSS2005): *'Hard to get respite care for a 28-year-old'* (KRAUSS2005) and *'I have no idea where to begin…we want to take a short vacation*

but there is no one to watch her…she functions at a 36 month level…who will watch her. (fGRAETZ2010).

More services specifically for autism and especially Asperger's syndrome (HARE2004), and improved staff training (GRAETZ2010; HARE2004; KRAUSS2005), were also requested: *'I feel that staff need more training than is provided to work with people with autism.'* (KRAUSS2005).

Role of advocate

Many families and carers of adults with autism found themselves in a new role of being an advocate for their family member and others with autism (GRAETZ2010; KRAUSZ2005; MAGANA2006; RYAN2009) and enjoyed having the opportunity to educate others about the condition (RYAN2009), a role that continued as their sons and daughters moved into adulthood (RYAN2009):

> *'We [support group] have run Asperger courses at our local community centre. I now go round to talk to mental health teams, schools, colleges, social care departments and give talks about Asperger's raising awareness and, of course, I have got a teaching qualification so I also have a job teaching Asperger youngsters.'* (RYAN2009)

4.3.9 Clinical summary – experience of families and carers of adults with autism

A number of themes emerged from the literature that captured the experience of families and carers of adults with autism. Although living with a person with autism could be challenging and could lead to reduced work, accommodation and leisure opportunities, and also financial strain, there was a recognition and sense of pride in their caregiving achievements. Psychological distress was common and often linked to coming to terms with the life-long impact of autism on their child as well as their own increased experience of stress and anxiety. The impact of autism was keenly felt on relationships within the family including the parental relationship, the impact on other siblings and spousal relationships. Advice and help from services and from other families and carers of individuals with autism was valued highly. Parents also reported a struggle to come to terms with a new identity as a carer of a person with autism and the sense of isolation or ostracism that came from this.

There was relatively little qualitative evidence of families and carers' experience of services either for themselves or for their son or daughter. No doubt this reflected the limited availability of services for adults. There was considerable concern about the availability of day, residential, employment and support services and the need for support from specialist services in accessing these services. There was little comment on services accessed by families and carers themselves, but there was recognition of the need for increased information about autism (coupled with better trained and informed staff). Some families reported gaining real benefit from involvement in advocating for services for their children and others with autism.

4.3.10 From evidence to recommendations

The clinical summary identified serious limitations in the services available for families and carers and services to facilitate and support their active involvement in the care of their child with autism. The GDG considered this evidence, along with the evidence base for the *Service User Experience in Adult Mental Health* draft NICE guidance, and their knowledge of, and expertise about, services for families and carers. This led the GDG to identify a number of issues, which in combination with the themes identified above, suggested some key areas for the development of recommendations. These included the involvement of families and carers in their family member's care (and how this may be approached if the person with autism does not wish for them to be involved); the assessment of families' and carers' own needs; information about and help in accessing support and treatment for their family member and a range of family and carer support groups, including specific support for families in their parenting role by experienced professionals. The GDG carefully considered these issues and the implications of the themes identified in Section 4.3.8 in the drafting of recommendations in the following areas:

a) The involvement of families and carers in the care and treatment of their family member and the information, assessment, care and interventions that families and carers might themselves need: the aim was to ensure that all recommendations in these areas (concerned with the family or carer directly or the care of their relative) were drafted in such a way as to reflect the issues and concerns that emerged from the thematic analysis and the GDG's knowledge and expertise.
b) Principles of care: the GDG's decision was informed by the clinical summary (Section 4.3.9) and the evidence base from the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming) to identify important areas where a new recommendation needed to be developed for this guideline.

4.3.11 Recommendations

Involving families and carers

4.3.11.1 Discuss with adults with autism if and how they want their families or carers to be involved in their care. During discussions, take into account any communication needs the person may have (see recommendation 6.3.5.1).

4.3.11.2 If the person with autism wants their family or carer(s) to be involved, encourage this involvement and:

- negotiate between the person with autism and their family or carer(s) about confidentiality and sharing of information on an ongoing basis
- explain how families or carers can help support the person with autism and help with treatment plans

- make sure that no services are withdrawn because of families' or carers' involvement, unless this has been clearly agreed with both the person with autism and their family or carer(s).

4.3.11.3 If the person with autism wants their family or carer(s) to be involved, give the family or carer(s) accessible information about:

- autism and its treatment
- statutory and third sector, including voluntary, local support groups and services specifically for families and carers, and how to access these
- their right to a formal carer's assessment of their own physical and mental health needs, and how to access this.

4.3.11.4 If a person with autism does not want their family or carer(s) to be involved in their care:

- give the family or carers verbal and written information about
- autism and its treatment
- statutory and third sector, including voluntary, local support groups and services specifically for families or carers, and how to access these
- who they can contact if they are concerned about the person's care and treatment
- tell the family or carers about their right to a formal carer's assessment of their own physical and mental health needs, and how to access this
- bear in mind that people with autism may be ambivalent or negative towards their family for many different reasons, including as a result of a coexisting mental health problem or prior experience of violence or abuse.

4.3.11.5 Ensure that adults with autism who have caring responsibilities receive support to access the full range of mental and physical health and social care services, including childcare to enable them to attend appointments, groups and therapy sessions.

5 CASE IDENTIFICATION AND ASSESSMENT

5.1 INTRODUCTION

Identification and recognition of autism in adults is challenging and the assessment and diagnosis of autism can also be problematic. This is due to a number of factors. Intellectual disability (an IQ below 70) is frequently observed and may affect up to 60% of people with autism (Baird *et al.,* 2006). Autism also coexists with a number of other disorders other than just intellectual disability. In childhood, attention deficit hyperactivity disorder (ADHD) is common, affecting 40 to 50% of children with autism (Gadow *et al.,* 2004; 2005) and the differential diagnosis from a range of other neurodevelopmental disorders can be challenging (see NICE, 2011a for a more detailed review of these issues). In adults, particularly where a diagnosis has not been established in childhood (this is the case for about 20% of adults with autism [see Chapter 2]), this can be complicated by coexisting mental disorders such as depression and schizophrenia. Finally, the interaction between autism and the person's social and physical environment can further complicate diagnosis.

In the last 30 years effort has been made to improve identification in children and refine the assessment process. This has led to the establishment of multidisciplinary assessment clinics and the development and validation of various screening tools and diagnostic instruments for children. However, few equivalent clinics, identification tools, diagnostic instruments or assessment systems have been developed for adults. This is not surprising, as in the NHS secondary care health services for children with neurodevelopmental disorders are relatively coherent and have well-established links to the wider health service. In contrast, services provided for adults are almost entirely limited to those who have intellectual disabilities. This means that not only are there poor services for the identification of adults with autism who have not been identified as children but there are also very limited specialist services available for people with autism unless they have a physical or intellectual disability, or become severely mentally or physically ill.

Inadequate identification and assessment of adults with autism not only leads to lack of adequate provision of care and treatment for the problems associated with autism but can also lead to inadequate recognition and assessment of coexisting mental and physical health problems with consequent sub-optimal treatment.

This under-recognition and inadequate treatment of adults with autism may lead to increased health and social care costs. For example, Knapp and colleagues (2007) estimated that the yearly cost to society of each adult with autism in the UK is £90,000 and with a cost to the economy of around £25.5 billion per year. Of the cost for adults, 59% is accounted for by services, 36% through lost employment and the remainder by family expenses. There is also an emotional cost not only for adults

with autism who have reported a high incidence of depression and attempted suicide (Stewart *et al.,* 2006) but also for their families and carers (Hare *et al.,* 2004).

The GDG recognised the limited provision of specialist assessment and treatment services for adults but in developing the review protocols set out in this chapter were mindful that some 20% of adults with autism have never received a formal diagnosis (see Chapter 2). The GDG also took into account that a number of these people have rewarding and successful lives (Baron-Cohen, 2000), and may require no intervention or would not wish to have a formal diagnosis. This meant that the issue of identification and recognition in non-specialist services such as primary care, social care and general medical settings was of particular importance and this is reflected in the review protocols set out below.

5.2 SIGNS AND SYMPTOMS THAT SHOULD PROMPT A FURTHER ASSESSMENT OF AUTISM IN ADULTS

5.2.1 Introduction

As described in Chapter 2 and Section 5.1, a significant number of adults with autism will have not had a diagnosis. Those who have previously received a diagnosis during childhood are also unlikely to be recognised as having autism as they do not often present to health or social care services with a complaint directly concerning the core symptoms of autism. Instead, they are much more likely to present with a coexisting mental or physical health problem or with a social problem arising from the autism or the coexisting condition, the course and presentation of which may well have been affected by the autism. In addition, a number of people who have autism and an intellectual disability may have an existing diagnosis of autism but not disclose the diagnosis and they or the services may not be aware of it due to unavailability or inadequacy of the records system. While people with more severe intellectual disabilities will be recognised as having a significant problem, the autism may go undetected. For individuals with autism who are not intellectually disabled but who have significant communication problems an incorrect assumption of intellectual disability may be made.

In contrast with some common mental health problems such as depression, the core symptoms of autism are often not well understood by health and social care professionals (Heidgerken *et al*., 2005). However, it should be noted that even in a disorder such as depression it is likely that only around 30% of people presenting with a depressive disorder are diagnosed and offered treatment (NCCMH, 2010a). The consequences of this under-recognition are not well described (see Chapter 2) but it is likely that they lead to a poor quality of life for the person with autism and inadequate care and treatment for both the autistic problems and the associated coexisting conditions. A good example of the impact of under-recognition and inadequate treatment is the 90% unemployment rate in adults with autism.

Although the focus of this section of the chapter is on the nature and content of case identification tools it should be noted that consultation skills of health and social

care professionals have been shown to be important in determining effective recognition of mental disorders (Gask *et al.*, 1998).

5.2.2 Strategies to improve the recognition of autism

A number of NICE mental health guidelines have considered the case for general population screening for some mental disorders and concluded that the case for general population screening is not appropriate and that approaches to case identification should focus on specific high-risk populations, such as people with a history of depression, significant physical illnesses causing disability or other mental health problems, such as dementia, where benefits of early identification outweigh the downsides (see for example, NICE, 2006). The criteria by which the GDGs judged the value of this approach were adapted from those developed for the assessment of screening instruments by the UK NHS National Screening Committee (available from www.screening.nhs.uk/criteria). That is the GDG looked for evidence that the instrument in question had appropriate sensitivity and specificity, that interventions for the disorder identified by the instrument were available or could be made available and that the interventions were likely to be of benefit.

An example of this approach can be seen in the updated edition of the *Depression* guideline (NICE, 2009a) and the guideline on *Depression in Adults with a Chronic Physical Health Problem* (NICE, 2009b) both of which reviewed available case identification instruments for depression. These guidelines recommended that healthcare professionals should be alert to possible depression (particularly in people with a past history of depression or a chronic physical health problem with associated functional impairment) and consider asking people who may have depression two questions, known as the 'Whooley questions' (NICE, 2009a):

1. During the last month, have you often been bothered by feeling down, depressed or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?

If a person answers 'yes' to either of these questions, then the guidelines recommend that a practitioner who is competent to perform a mental health assessment should review the person's mental state and associated functional, interpersonal and social difficulties. Furthermore, when assessing a person with suspected depression, the guidelines recommend that practitioners should consider using a validated measure (for example, for symptoms, functions and/or disability) to inform and evaluate treatment.

Compared with depression, routine identification of autism has received scant attention despite a demonstrable need for care and treatment. However, the GDG were mindful of the uptake of the case identification questions for depression in the Quality and Outcomes Framework (Department of Health, 2004) and the subsequent adoption of a similar approach to the case identification of anxiety disorders in the *Common Mental Health Disorders* guideline (NICE, 2011b). Following from this the

GDG decide to adopt a similar framework when approaching case identification in autism.

5.2.3 Aim of the review

This review aimed to identify the signs and symptoms that may provide an index of suspicion and prompt a healthcare professional to consider referral for further assessment or to undertake further assessment of possible autism.

5.2.4 Clinical review protocol (review of signs and symptoms that should prompt a referral for further assessment)

A summary of 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 9 (the full protocol can be found in Appendix 8 and further information about the search strategy can be found in Appendix 9).

5.2.5 Methodological approach

The review team conducted a systematic review of the literature (both primary studies and systematic reviews or published guidance) that evaluated the signs and symptoms, and other factors such as personal history that might raise suspicion about the possible presence of autism. The GDG aimed to critically evaluate the sensitivity and specificity of these signs and symptoms when compared with a DSM-IV (APA, 1994) or ICD-10 (WHO, 1992) diagnosis.

Table 9: Clinical review protocol for the review of signs and symptoms that should prompt a referral for further assessment

Component	Description
Review question (s)	What signs or symptoms should prompt any professional who comes into contact with an adult with possible autism to consider referral for further assessment? (CQ-A1)
Objectives	• To identify the signs and symptoms that would prompt referral for further diagnostic assessment. • To suggest how recognition of autism can be improved
Criteria for considering studies for the review	
• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental disorder) Consideration should be given to the specific needs of: • people with coexisting conditions • women • older people • people from black and minority ethnic groups transgender people
• Comparison	Individuals with or without diagnosed autism
• Critical outcomes	Sensitivity, specificity, positive predictive value, negative predictive value, area under the curve
• Study design	Cross-sectional, Systematic reviews
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, Medline, PsycINFO, Sociological Abstracts, SSA
Date searched	Systematic reviews: 1995 up to 09/09/2011. RCT, QE, OS, case-series: inception of database up to 09/09/2011.
The review strategy	To provide a GDG-consensus based narrative of signs and symptoms that should prompt a referral for specialist assessment as well as identify any amendments that need to be made to take into account individual variation
Note: autism = autism spectrum disorders; RCT = randomised controlled trial; QE = quasi-experimental; OS = observational study; AEI = Australian Education Index; ASSIA = Applied Social Services Index and Abstracts; BEI = British Education Index; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts and Reviews of Effectiveness; Embase = Excerpta Medica database; ERIC = Education Resources in Curriculum; HMIC = Health Management Information Consortium; Medline = Biomedical Information Database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

5.2.6 Studies considered

The literature search for studies resulted in 9,522 articles overall. Scanning titles/abstracts identified 99 potentially relevant studies that evaluated the recognition and case identification of autism. However, none of these studies met the inclusion criteria as outlined in Table 9. The GDG therefore utilised DSM-IV and ICD-10 criteria for autism as well GDG expert knowledge of the epidemiology, aetiology and presentation of autism to identify the signs and symptoms that may

prompt a healthcare professional to seek or conduct further assessment. This is summarised below.

5.2.7 Clinical evidence summary

In the absence of any good-quality evidence regarding the signs and symptoms that might prompt further assessment or inquiry, the GDG used both existing diagnostic systems and the expert knowledge of the group. In reviewing the diagnostic systems and weighing the various expert views the GDG agreed that the signs and symptoms would need to be identifiable in a range of different care settings and by health and social care professionals with varying knowledge and experience of autism. In a healthcare setting this might include a primary care professional such as a GP, practice nurse, a primary care mental health practitioner with limited experience of working with adults with autism or a doctor or nurse in an acute physical healthcare setting. Others working in social care or the housing sector providing support to people with a range of mental health problems may also have very limited knowledge of autism.

In developing the key criteria that would inform a selection of the signs and symptoms of autism that would need to be identifiable in the settings referred to above, the GDG decided on the following:

- The signs and symptoms[11] should be:
  - based on established and well-validated diagnostic systems
  - those that would provide the best balance between sensitivity and specificity
  - objective and where possible quantifiable against agreed norms
  - understandable by an individual without specialist knowledge of the condition
  - easily observed or inquired about in a brief encounter (of less than 10 minutes)
  - verifiable (where necessary) by an independent informant or review of easily available records

- The factors[12] concerning personal history should be:
  - based on evidence of an association between the factors and the development of the condition
  - objective and definable against agreed norms
  - understandable to the person with the possible condition or by an individual without specialist knowledge of the condition
  - easily inquired about or extracted from records in a brief encounter (of less than 10 minutes)

[11] In this case these can be taken to refer to an aspect of a person's personal or social functioning.
[12] These can include personal experience of care, diagnoses of other mental and physical health problems and social and occupational performance.

    - verifiable (where necessary) by an independent informant or review of easily available records

- The signs and symptoms and personal factors should be such that they would:
    - be easily assembled in a simple algorithm to support decision making
    - be understandable to the person with a suspected condition (or their carer)
    - facilitate communication about the need for further assessment to another professional.

Application of the above criteria led the GDG to identify two key diagnostic issues for autism, both of which the GDG judged needed to be present:

- persistent difficulties in social engagement or social communication
- repetitive or stereotypic behaviours or resistance to change.

The GDG considered the evidence for the association between a number of personal historical factors including service usage and, combined with the epidemiological evidence reviewed in Chapter 2 and their expert opinion, took the view that a number factors were associated with the presence of autism:

- problems in obtaining or sustaining employment or education
- initiating or sustaining social relationships
- previous or current contact with CAMHS or learning disability services
- history of a neurodevelopmental disorder.

The GDG also considered that the use of these signs, symptoms and factors should be part of a carefully constructed protocol for case identification and any subsequent assessment. The recommendations developed from this review and the reasoning behind their development are described in Section 5.3.12 and 5.3.11 respectively where the rationale for their integration into a coherent protocol is clearly set out.

5.3 REVIEW OF CASE IDENTIFICATION INSTRUMENTS

5.3.1 Introduction

Autism is under-recognised in adults in the UK (Brugha *et al.,* 2011). There are a number of reasons for this including: healthcare professionals' lack of knowledge and skill in the field of adult autism in non-specialist services; limited teaching about autism in the curricula of many health and social care professional training programmes; an absence of specialist practitioners to train and support non-specialists; a lack of services to which to refer when problems are identified; and the complexity of identifying autism in people with coexisting conditions that may mask the presence of autism. Given that health and social outcomes are poor for many people with autism and that the autism may complicate or impair effective treatment

of coexisting conditions, effective identification of autism may lead to better outcomes for individuals and more efficient use of healthcare resources.

Current practice

The majority of adults with autism who are receiving care in the UK are in specialist learning disability services. As at least 40% of adults with autism do not have an intellectual disability (Baird *et al.,* 2006), and a significant number of people with mild intellectual disability are not in regular contact with learning disability services, this means that the majority of people with autism are not in contact with health services. A very small number of special assessment and diagnosis teams for adults with autism exist in the country, such as the Cambridge Lifespan Asperger Syndrome Service (CLASS), which primarily offers diagnostic opinion. There are also a small number of services providing care and treatment, as well as assessment and diagnosis, such as the Nottingham City Asperger Service, which develops and delivers short-term coordinated packages of support including psychological interventions and specialist group work, for instance, in parenting skills. Of course an unknown number of adults with autism will be accessing services for mental health problems (often in relation to their autism), but it is probable that for many the autistic problems go unrecognised or may be misdiagnosed (Brugha *et al.,* 2011). In this context it is unsurprising that there has been little or no development of case identification tools for routine use, a major issue being the lack of options for referral especially in primary care but it can also be argued that better identification of autism in other specialist services would lead to improvements in care.

Definition

For the purposes of this review, case identification instruments were defined as validated psychometric measures used to identify people with autism. The review was limited to instruments likely to be used in UK clinical practice, that is, 'ultra-brief instruments' (defined as those with one to three items) or 'longer instruments' (four to 12 items). The identification instruments were assessed in consultation samples (including primary care and general medical services) and community populations. 'Gold standard' diagnoses were defined as a DSM or ICD diagnosis of autism (or their equivalent); studies were sought that compared case identification with an ultra-brief or longer instrument with a gold standard. Studies that did not clearly state the comparator to be diagnosis by DSM or ICD (or their equivalent) or did not provide sufficient data to be included in the review were excluded.

5.3.2 Methodological approach

The GDG considered the following criteria when evaluating case identification instruments for inclusion in the review.

Primary aim of the instrument: The identification of adults with possible autism but not the formal diagnosis or the assessment of a particular domain.

Clinical utility: This criterion required the use of the case identification instrument to be feasible and implementable in routine clinical care. The instrument may also contribute to the identification of further assessment needs and therefore be useful for care planning.

Tool characteristics and administrative properties: The case identification tool should have well-validated cut-offs in the patient population of interest. Furthermore, and dependent on the practitioners' skills and the setting, tools were evaluated for the time needed to administer and score them as well as the nature of the training (if any) required for administration or scoring. A case identification instrument should be brief, easy to administer, score and interpret without extensive and specialist training. Non-experts in a variety of care settings (for example, primary care and general medical services) should be able to complete the instrument with relative ease. The cost of the tool and copyright issues were also considered.

Population: The population being assessed reflects the scope of this guideline (see Table 10). The instrument should have been validated in a population >17 years of age. Tools that are designed for a child and adolescent population but were adequately validated in an adult sample were also considered. However, studies with a child and adolescent population (or where the population was mixed and the mean age was less than 17 years) were excluded

Psychometric Data: The instrument should have been validated against a gold standard diagnostic instrument (defined as a clinical diagnosis established based on a diagnostic manual such as DSM-IV or ICD-10) and have evidence of its sensitivity and specificity. Reported findings for sensitivity, specificity, area under the curve, positive predictive value, and negative predictive value were considered. See Chapter 3 for a description of diagnostic test accuracy terms. The tool should be applicable to a UK population, for example by being validated in a UK population, or a population that is similar to the UK demographic. It should also have established reliability and validity (although this was not evaluated for the purpose of this review).

5.3.3 Aim of the review

This review aims to identify and evaluate the most appropriate instruments to aid in the identification of adults with possible autism. The GDG did not consider screening tools for autism in adults as this was outside the scope of this guideline.

5.3.4 Clinical review protocol (case identification instruments)

A summary of 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 10 (the full protocol can be found in Appendix 8 and further information about the search strategy can be found in Appendix 9).

5.3.5 Studies considered[13]

The literature search for observational studies resulted in 9,522 articles. Scanning titles and/or abstracts initially identified 561 studies, which initial screening reduced to 93 potentially relevant studies; a further six studies were identified from hand-searches of relevant articles, giving 99 articles in total. Further inspection of the full texts identified using the criteria outline in sections 5.3.1 and 5.3.4, a number of studies did not meet one or more eligibility criteria. The reasons for exclusion were that: the study evaluated children or young people (81); the paper was outside the scope for another reason or not relevant to this guideline (1); the paper did not have sensitivity and specificity data that could be used in meta-analysis (1); or the paper provided a narrative review of issues around case identification (5). As a result of this, a total of 11 published studies met the eligibility criteria for this review: BARONCOHEN2001 (Baron-Cohen *et al.,* 2001); BERUMENT1999 (Berument *et al.,* 1999); FERRITER2001 (Ferriter *et al.,* 2001); GARFIN1988 (Garfin & McCallon, 1988); KRAIJER2005 (Kraijer & de Bildt, 2005); KURITA2005 (Kurita *et al.,* 2005); MESIBOV1989 (Mesibov *et al.,* 1989); NYLANDER2001 (Nylander & Gillberg, 2001); VOLKMAR1988 (Volkmar *et al.,* 1988); WAKABAYASHI2006 (Wakabayashi *et al.,* 2006); WOODBURYSMITH2005 (Woodbury-Smith *et al.,* 2005). One unpublished study that was obtained from the author was also included in the review: ALLISON (Allison *et al.,* in press), bringing the total number of studies to 12.

[13] 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).

Table 10: Clinical review protocol for the review of case identification tools

Component	Description
Review question (s)	What are the most effective methods/tools for case identification in autism in adults? (CQ-A2)
Sub-question	What amendments, if any, need to be made to the agreed methods for case identification to take into account individual variation (for example, gender, age, intellectual abilities, including cognitive strengths as well as difficulties, communication problems, developmental disorders, coexisting mental health problems, physical health problems including hyper/hyposensitivities, motor impairments, and visual and hearing impairments)? (CQ- A2a)
Objectives	• To identify and evaluate case identification tools used in the recognition of autism • To suggest how recognition of autism can be improved
Criteria for considering studies for the review	
• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental disorder). Consideration should be given to the specific needs of • people with coexisting conditions • women • older people • people from black and minority ethnic groups transgender people.
• Intervention	Case identification instruments (for example, the Autism-spectrum Quotient [AQ]; Social Communication Questionnaire [SCQ]; Autism Behaviour Checklist [ABC])
• Index test	Case identification instruments
• Comparison	DSM or ICD diagnosis of autism
• Critical outcomes	**Sensitivity**: the proportion of true positives of all cases diagnosed with autism in the population **Specificity**: the proportion of true negatives of all cases not-diagnosed with autism in the population.
• Important, but not critical outcomes	**Positive Predictive Value (PPV)**: the proportion of patients with positive test results who are correctly diagnosed. **Negative Predictive Value (NPV)**: the proportion of patients with negative test results who are correctly diagnosed. **Area under the Curve (AUC):** are constructed by plotting the true positive rate as a function of the false positive rate for each threshold.
• Other outcomes	**Reliability** (for example, inter-rater, test-retest) **Validity** (for example, construct, content) **Internal consistency**
• Study design	Cross-sectional
• Include unpublished data?	No
• Restriction by date?	No
• Minimum	N=10 per arm

sample size	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, tertiary, health and social care and healthcare settings (including prisons and forensic services) • Others in which NHS services are funded or provided, or NHS professionals are working in multi-agency teams
Electronic databases	AEI, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, Medline, PsycINFO, Sociological Abstracts, SSA
Date searched	Systematic reviews: 1995 up to 09/09/2011. RCT, QE, OS, case-series: inception of database up to 09/09/2011.
Searching other resources	Hand-reference searching of retrieved literature
The review strategy	To conduct pooled diagnostic accuracy meta-analyses on the sensitivity and specificity of case identification tools. This is dependent on available data from the literature. In the absence of this, a narrative review of case identification tools with be conducted and guided by a pre-defined list of consensus-based criteria (for example, the clinical utility of the tool, administrative characteristics, and psychometric data evaluating its sensitivity and specificity).
Note. autism = autism spectrum disorders; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; RCT = randomised controlled trial; QE = Quasi-experimental; OS = observational study; AEI = Australian Education Index; ASSIA = Applied Social Services Index and Abstracts; BEI = British Education Index; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts and Reviews of Effectiveness; Embase = Excerpta Medica database; ERIC = Education Resources in Curriculum; HMIC =Health Management Information Consortium; Medline = Biomedical Information Database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

Upon further inspection of the 12 studies, four were excluded due to lack of available data. Of the eight studies (N=5,603) included in the review, four were conducted using a sample of adults with high-functioning autism or Asperger's syndrome (ALLISON, BARONCOHEN2001; KURITA2005; WAKABAYASHI2006). Three studies included a mixed autism population consisting, for example, of autism, Asperger's syndrome, and pervasive developmental disorder (PDD) (BERUMENT1999; KRAIJER2005; WOODBURYSMITH2005). Three studies included populations with intellectual disability (BERUMENT1999; KRAIJER2005; VOLKMAR1988).

Further information about both included and excluded studies can be found in Appendix 14.

5.3.6 Case identification instruments included in the review

The instruments that meet the inclusion criteria and are included in the review are the Autism-Spectrum Quotient (AQ; Baron-Cohen *et al.*, 2001a); the Autism Screening Questionnaire (ASQ) now known as the Social Communication

Questionnaire (SCQ; Rutter *et al.,* 2003); the Autism Behavior Checklist (ABC; Krug *et al.,* 1979; 1980); and the Pervasive Developmental Disorder in Mentally Retarded Persons instrument (PDD-MRS; Kraijer, 1997a; 1997b). See Table 11 for the characteristics of these tools.

5.3.7 Clinical evidence

Review Manager 5 was used to summarise diagnostic accuracy data from each study using forest plots and summary ROC plots. Where more than two studies reported appropriate data, a bivariate diagnostic accuracy meta-analysis was used in order to obtain pooled estimates of sensitivity, specificity, likelihood ratios and diagnostic odds ratio (for further details, see Chapter 3). To maximise the available data, the most consistently reported and recommended cut-off points for each of the scales were extracted.

The only instrument evaluated by more than one study was the AQ (five studies). All other instruments were evaluated by single studies. The data below provides a summary of the evidence for all instruments (see Table 11) as well as a forest plot (see Figure 4) and ROC curve (see Figure 5) displaying the sensitivity and specificity of all instruments. In addition, the AQ was the only instrument to be evaluated for different number of items as well as at different cut-off points. Therefore, this data is extracted and displayed individually in a forest plot (see Figure 6) and ROC curve (see Figure 7).

Table 11: Characteristics of case identification tools included in the review

Instrument	Disorder Evaluated	Level of functioning	Domains Assessed	Number of Items, Scale, Cut-off	Completed by	Time to administer/score, Training required, Cost/copyright issues	Notes
ABC	Autism	Across the spectrum	Sensory, relating, body/object use, language, social and self-help	57 yes/no items (weighted from 1-4 points each), 54-67 = probable autism, >68 = positive case	Teacher or a parent	Estimated 15 minutes Free and available online	The cut-off suggested is 53. Part of the Autism Screening Instrument for Educational Planning (ASIEP)
ASQ/SCQ	Autism	>2 years mental age	Reciprocal social interaction, language and communication, repetitive and stereotyped patterns of behaviour, self-injurious behaviour, language functioning	40 yes/no items; Individuals with language = 0-39, without language 0-34, one item not included in total score, ≥15 positive case	Parent/primary caregiver	10 minutes, no training required Not free to use	Two versions – 'Lifetime Form' (covers entire developmental history), 'Current Form' (covers the last 3 months)
AQ - 50	HFA/AS	Normal to high functioning	Social skill, attention switching, attention to detail, communication, imagination	50 items on a likert scale, 0-50, ≥ 32 positive case	Self-report, 40/50 items can be parent/ carer reported (has been found to be reliable – Baron-Cohen *et al.*, 2001a)	10 minutes Free and available online	The cut-off suggested is 26 or 32
AQ - 21	HFA/AS	Normal to high functioning	Social skill, attention switching, attention to detail, communication, imagination	21 items on a likert scale, 0-50, ≥ 32 positive case	Self-report	5 minutes Free and available online	The cut-off suggested is 9

AQ - 10	HFA/AS	Normal to high functioning	Social skill, attention switching, attention to detail, communication, imagination	10 items on a likert scale, 0-50, ≥ 32 positive case	Self-report, Allison *et al.*, in press)	2 minutes Free and available online	The cut-off suggested is 6
PDD-MRS	PDD	Mild to profound intellectual disability	Social interaction with adults, social interaction with peers, language and speech, other behaviours	12 items, 0-19, score 0-5 = non-PDD, 6-9 = doubtful PDD, 10-19 = PDD	Practitioner with extensive experience in the field of autism and intellectual disabilities (observation)	10-20 minutes to administer and score, no training required Not free to use	Observation of current behaviour in last 2-6 months. Observation can be at home, school day-care centre etc.
Notes: ABC = Autism Behavior Checklist; ASQ = Autism Screening Questionnaire; autism = autism spectrum conditions; AQ = Autism-Spectrum Quotient; AS = Asperger's syndrome; HFA = high-functioning autism; SCQ = Social Communications Questionnaire; PDD = pervasive developmental disorder; PDD-MRS = Pervasive Developmental Disorder in Mentally Retarded Persons							

Table 12: Evidence summary table for all case identification instruments included in the review[14]

Instrument	Target condition	Cut-off	Included studies	Sensitivity Specificity	LR+ LR–	Diagnostic OR
ABC	Autism	57	1	0.75 0.81	3.95 0.31	12.79
ASQ	Autism	15	1	0.85 0.75	3.40 0.20	17.00
AQ – 50 item	HFA; Asperger's syndrome	32/33	3	0.77-0.88 0.74-0.98	2.96-34.48 0.31-0.21	9.53-232.69
AQ– 50 item	HFA; Asperger's syndrome	26	2	0.76-0.95 0.52-0.71	1.98-2.62 0.31-0.34	7.75-20.58
AQ-21 item	HFA; Asperger's syndrome	12	1	0.92 0.82	5.11 0.1	52.39
AQ– 10 item (Japanese version)	HFA; Asperger's syndrome	7	1	0.76 0.92	9.50 0.26	36.42
AQ-10 item	HFA; Asperger's syndrome	6	1	0.88 0.91	9.78 0.13	74.15
PDD-MRS	PDD with intellectual disability	10	1	0.92 0.92	12.16 0.08	147.81

Note. Autism Behavior Checklist (ABC); Autism Screening Questionnaire (ASQ); Autism-Spectrum Quotient (AQ); high-functioning autism (HFA) Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS)

[14] When data for an instrument is available from more than one study, a range of test data across the included studies is provided. See forest plots for individual data by study.

Figure 4: Forest plot of sensitivity and specificity for the ASQ, AQ (50, 21, and 10 item), PDD-MRS, and ABC

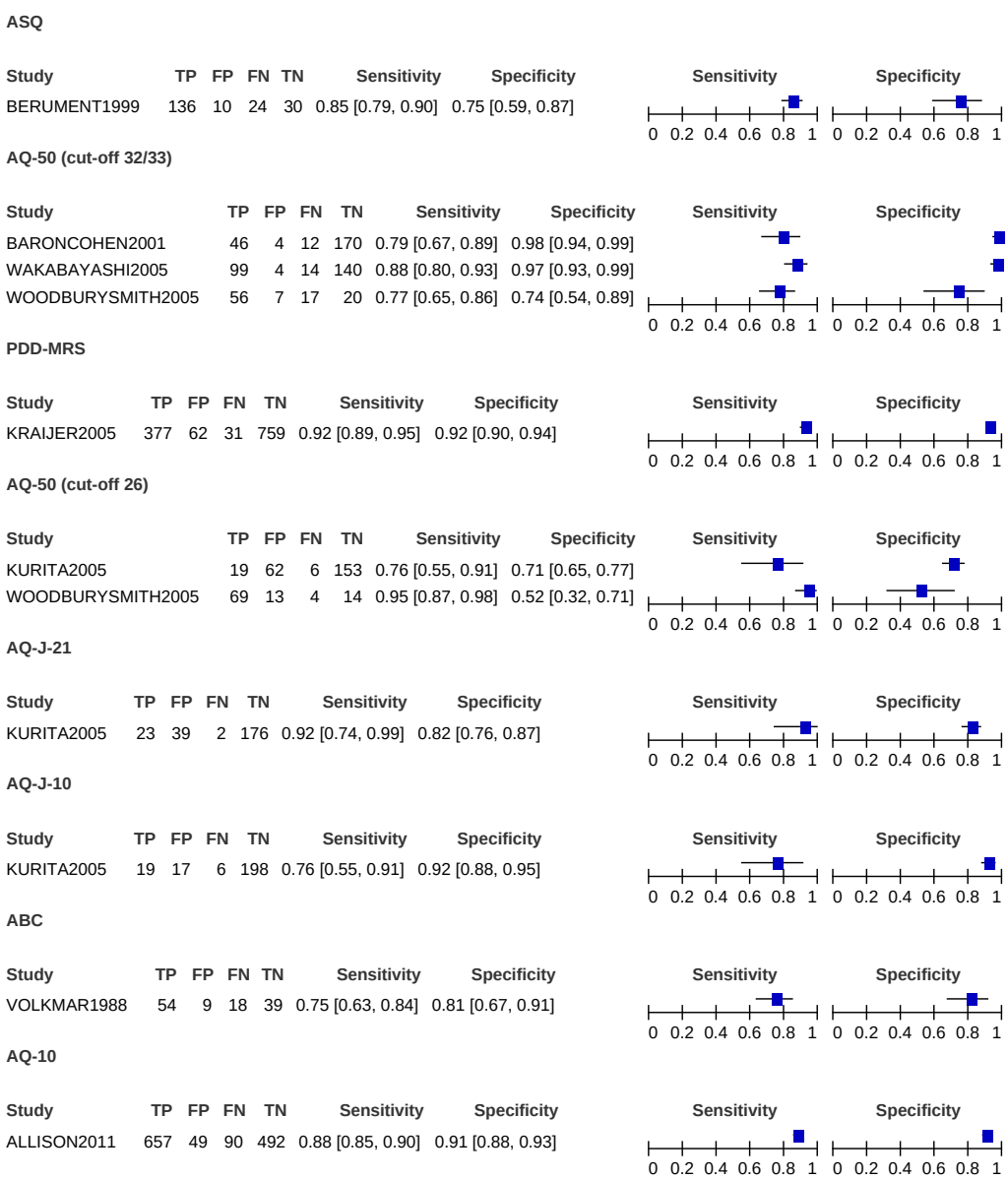


Figure 5: Summary ROC curve of all included instruments

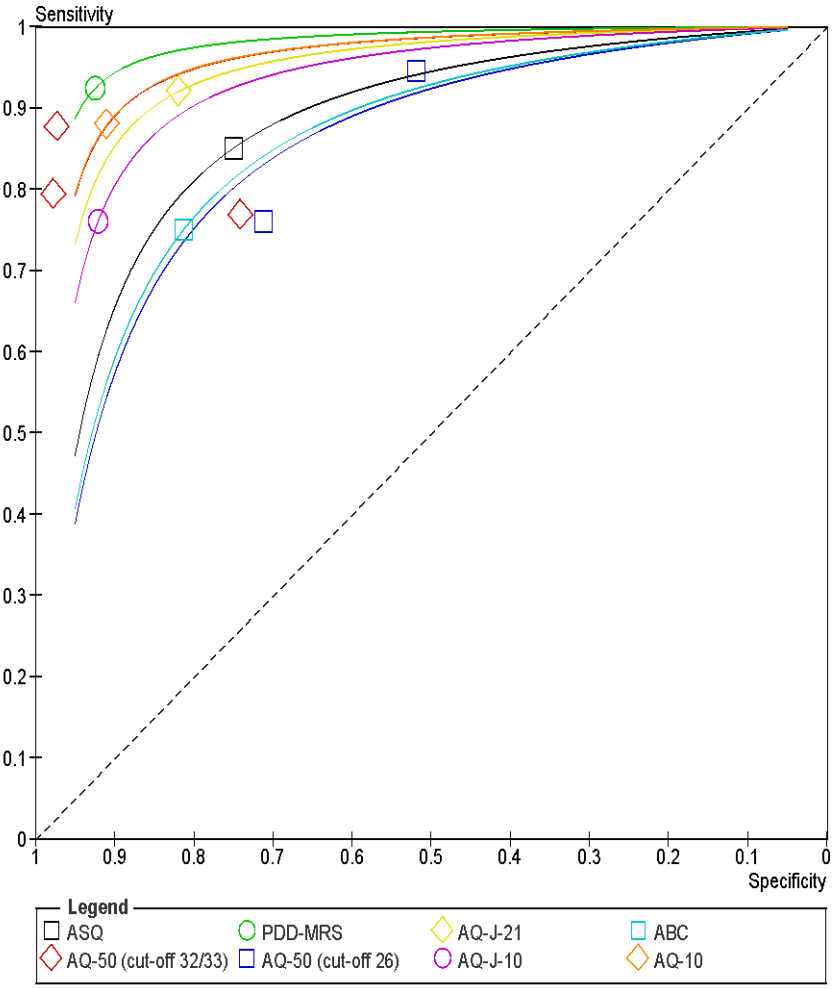


Figure 6: Forest plot of sensitivity and specificity for the AQ alone (50, 21 and 10 item versions) at different cut-offs

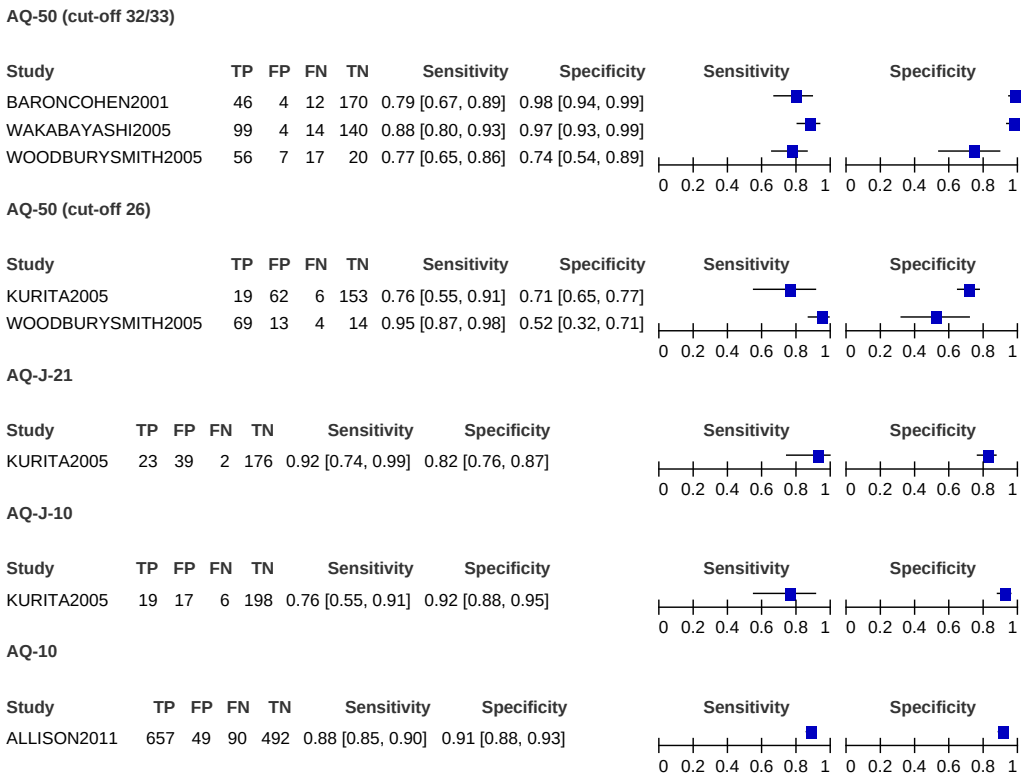
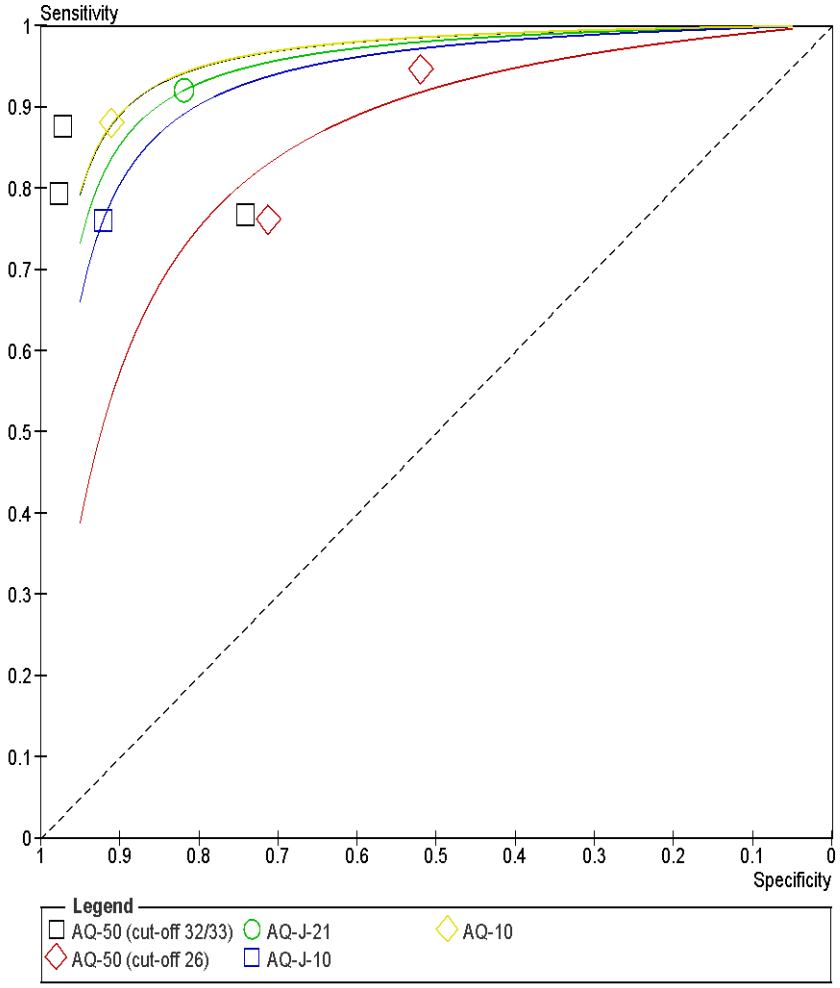


Figure 7: Summary of ROC curve of AQ alone



5.3.8 Clinical evidence summary

Identification of autism

The ASQ/SCQ and the ABC can be used to identify autism across a broad range of intellectual, social and personal functioning. The analysis showed that the sensitivity and specificity for both tests were 'good'. However, the evidence for this is weak and the results based on single studies, therefore it should be interpreted with some caution. The review did not show any noticeable difference in the psychometric properties of the ASQ/SCQ and the ABC. The ABC is not a self-report measure but completed by a parent or teacher and the ASQ is completed by a parent or carer. However, it should be noted that the ASQ/SCQ is not freely available and can only be used with permission from the developers.

Identification of normal/high-functioning autism

The AQ was the only instrument that met inclusion criteria for this population and had more than one study that could be synthesised in meta-analysis. The included

studies evaluated the original 50-item AQ at the cut-off score of 32/33 and 26. In addition, a single study also evaluated the sensitivity and specificity of a shorter 21-item and two studies of two different shorter 10 item versions of the AQ. At a cut-off of 32/33, the 50-item AQ had 'good' sensitivity and 'excellent' specificity. This result was based on meta-analysis of three studies. However, at a cut-off of 26 points, although the sensitivity was 'good' and 'excellent' in the two included studies, the specificity was very poor ('low' to 'moderate') reflecting the nature of the populations from which the data were collected.

The review of the AQ 21-item was based on a single study and the AQ 10-item was based on two studies each evaluating a different set of 10 items of the AQ in two different samples (Japanese and British). The specificity of the 21-item version was 'excellent' and the specificity 'good'. The 10-item Japanese version conversely had 'good' sensitivity' and excellent 'specificity'. The 10-item British version had 'good' sensitivity and 'excellent' sensitivity. This indicates that the 21-item version may be better at including true cases whereas the 10-item version may be better at excluding false cases. Furthermore, the 10 items identified in the British version was more accurate than the 10 items from the Japanese version for identifying true cases.

Identification of autism in an intellectual disability population

The PDD-MRS was the only instrument included in the review that was specifically designed for the identification of pervasive developmental disorders (including autism) in people with intellectual disability. On the basis of a single study, the PDD-MRS was found to have 'good' sensitivity and specificity. As can be seen from Figure 5, the PDD-MRS case identification accuracy is very similar to the AQ 50-item version (at a cut-off score of 32/33). However, this finding should be interpreted with caution due to the limited data for the PDD-MRS. In addition, the PDD-MRS has to be administered by a practitioner with considerable experience in the assessment of people with neurodevelopmental problems, which seriously limits its use in general healthcare settings.

As the review did not identify a tool for routine use for people with autism and intellectual disabilities, the GDG undertook a review of those studies identified in the original literature review that did not report on formal case identification tools and the GDG also reviewed the structure and content of the case identification tools identified in this review. Two studies, in particular, provided information that was used by the GDG in developing their recommendations. Bhaumik and colleagues (2010) in a study of carer-reported autistic traits in adults with autism and intellectual disability reported that the presence of two or more out of five autistic traits (minimal speech; poor social interaction; lack of empathy; presence of elaborate routines; and presence of stereotypies) gave the best sensitivity (63.2% - people with autism with two or more traits) and specificity (78.5% - people without autism with fewer than two traits). Those with two or more traits without a diagnosis of autism were likely to be aged over 50 years, have mobility problems, Down's syndrome, cerebral palsy or other significant mental health problems.

The autistic traits referred to above and their description drew on the work of Holmes and colleagues (1982) on the assessment of people with intellectual disability. The GDG reviewed this paper in order to inform the structure and content about possible areas for assessment in people with suspected autism and intellectual disabilities. Four areas identified by Holmes and colleagues (1982) were:

1. **Poor social interaction**
    - Does not interact – mainly aloof, indifferent or bizarre
    - Interacts to obtain needs only – otherwise indifferent
    - 'Unwarm' - does make social approaches, but these are peculiar, naive or even bizarre. The person does not modify behaviour in light of these responses, needs or interests of those whom s/he approaches. The interaction is one-sided and dominated by the person being rated
2. **Lack of empathy**
    - No or limited empathy
3. **Elaborate routines**
    - Marked repetitive activities (for example, rocking, hand or finger flapping or full body movements), especially when unoccupied, although may be controlled by close supervision or being kept fully occupied—often a constant feature, present each day
4. **Marked sterotypies**
    - Has elaborate routines of the kind and intensity found in early childhood autism

5.3.9 Case identification in special populations

The GDG had concerns that particular groups including people with coexisting conditions, women, older people, people from black and minority ethnic (BME) groups and transgender people were less likely to be identified by standard case identification tools. The review of the literature undertaken to address this question failed to find any tools that specifically addressed the needs of these groups. The GDG reviewed the literature identified in the searches undertaken for this guideline where it addressed the needs of the above groups and considered this alongside the expert knowledge of the GDG in developing the brief narrative summaries set out below.

Women

It has been suggested that there is a significant gender gap in the recognition and diagnosis of Asperger's syndrome and high-functioning autism (Wilkinson, 2008), with women being under-diagnosed (Attwood, 2006a; Ehlers & Gillberg, 1993). Some believe that the manifestation of symptoms may be more subtle in women than in men and hence are more difficult to recognise (Attwood, 2006a; Bashe & Kirby, 2005). For example, girls display better superficial social skills, better language and communication, less inappropriate special interests and activities, and less aggressive and hyperactive behaviour than boys (Gillberg & Coleman, 2000). Furthermore, it has also been suggested that girls who have difficulty maintaining

eye contact and seem to be socially withdrawn may be thought to be 'shy' rather than having a symptom of autism (Wagner, 2006). Hence the core symptoms of autism may not easily be recognised in girls. This gender issue may also interact with coexisting mental disorders and lead to further under-recognition of those disorders (see for example, Zucker and colleagues [2007] who highlight a particular problem in identifying autism in young women with anorexia nervosa).

Older adults

Autism was not included in psychiatric classification systems until DSM-III in 1980 and the diagnostic criteria for Asperger's syndrome was only established in 1994 with DSM-IV (APA, 1980, 1994). Therefore those who may meet these criteria and were children prior to this time are unlikely to have been identified and diagnosed with autism and, in particular, Asperger's syndrome. In addition, there is little research evaluating the recognition and diagnosis of autism in adults and even less in older adults.

Therefore, some people reach adulthood without ever having received a diagnosis of autism. This could be because they are able to make their way through life with relative success, that is they have finished schooling, married, had children and maintained jobs for most of their lives (James *et al.,* 2006). Such people are also likely to be of normal or above normal intelligence (see, for example, the case studies described in James *et al.,* 2006). Many also have a stable support network, for example still living with parents, and have not had contact with mental health or disability services where autism could potentially have been recognised. Conversely, the autism might have been missed in people who have severe cognitive impairments (such as Down's syndrome) or mental health problems. Key life events, such as the death of parents, can mean that a diagnosis of autism is made in later life, sometimes as late as retirement or following medical problems (James *et al.,* 2006). Some adults with unrecognised autism may also be identified after contact with the criminal justice system either as offenders, victims or witnesses (Hare *et al.,* 2000).

Although little is known about the healthcare needs and experiences of older people with autism, what is evident is that there is under-diagnosis in this demographic group (Brugha *et al.,* 2011) and that there are additional barriers to diagnosis such as behavioural or medical problems (Tsakanikos *et al.,* 2007). It is important for healthcare professionals to be aware of the signs and symptoms of autism and that they may be masked by coexisting conditions

Black and minority ethnic groups

The GDG found no relevant studies of the recognition of autism in adults from BME groups but there is a literature on children and young people that suggests recognition of autism in BME groups is limited. This is briefly summarised below.

Mandell and colleagues (2009) examined racial/ethnic disparities in a community sample of 2,568 children across 14 states of America. Experienced clinicians used

clinical and educational records to ascertain previous diagnosis of autism and identify undetected cases of autism. The study reported that black, Hispanic and other ethnic groups had lower odds of being identified than white children. For black children specifically, this was still the case across a range of intellectual ability levels. However, for Asian and Hispanic children, this was more likely the case for those with intellectual disability. Mandell and colleagues (2009) suggest that healthcare professionals screen for autism less often in children from BME groups. Begeer and colleagues (2009) have suggested that this might arise because healthcare professionals are more likely to attribute autistic features and symptoms such as communication and social deficits to culture or language in BME groups, resulting in under-diagnosis of autism. Cuccaro and colleagues (1996), who reported no significant difference in identification between different ethnic groups, and others have suggested any difference between different ethnic groups may be accounted for by socioeconomic status.

In a study of the prevalence of BME groups in Dutch institutions for people with autism, Begeer and colleagues (2009) reported a significant under-representation of Moroccan and Turkish children and young people. In a linked study they also reported that the ethnic background of the potential patient influenced paediatricians' diagnostic judgements on a series of clinical vignettes, with a diagnosis of autism more likely to be given to white Europeans compared with other ethnic groups.

Transgender people

There are two papers relating to transgender people with autism; one on autistic traits in transsexual people (Jones *et al.*, 2011) and one on prevalence of autism in children and young people with gender dysphoria (de Vries *et al.*, 2010). The latter suggests prevalence for autism of around 6% in children and young people with gender dysphoria, a rate significantly higher than in the general population. While this suggests the need for greater vigilance in this population, no specific data on case identification is provided.

5.3.10 Health economic evidence

No studies assessing the cost effectiveness of case identification tools 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.

5.3.11 From evidence to recommendations

The GDG was mindful of the practicalities of developing a measure to improve case identification and recognition of people with autism that would be of value in routine use in primary care and other settings. Initially, as in other NICE mental health guidelines, the GDG attempted to find very brief instruments composed of one to three questions that might have sufficient sensitivity and specificity to be of use in routine care. However, the search found no such measures. The GDG

therefore used their expert knowledge and judgement, together with the diagnostic criteria and related information contained in existing diagnostic manuals (principally DSM-IV), to identify the content for a number of questions that were in their view likely to have sufficient sensitivity and specificity to improve the identification of autism in adults and prompt further assessment were necessary. As is appropriate in such circumstances, the GDG favoured sensitivity over specificity.

The GDG did consider whether a formal questionnaire, if brief, might be of use as an alternative to the case identification questions. However, after reviewing a brief questionnaire (the AQ-10), the GDG judged it was not feasible for use as an initial case identification tool in primary care.

The review of existing case identification instruments considered the sensitivity and specificity of the four versions of the Autism Spectrum Questionnaires (AQ): the fifty item AQ-50; the twenty-one item AQ-21; and two versions of a ten item questionnaire, the AQ-10 (British) and the AQ-10 (Japanese). The GDG judged that there were no important differences between the AQ-50 (cut-off at 32), AQ-26 and AQ-10 (British) in terms of sensitivity and specificity in populations with normal intellectual ability. As a case identification instrument, the AQ-10 had the advantage of taking only a brief time to administer (2 minutes), and as a self-completion questionnaire it required no particular expertise in its administration or scoring. The GDG therefore decided that the AQ-10 (British) would be appropriate for use in primary care, social care and other non-specialist settings to support a referral for a specialist assessment in people of normal intellectual ability.

However, no such instruments were identified for people with suspected autism and an intellectual disability. Given that a significant proportion of adults with autism have an intellectual disability (perhaps 60%), it is important to provide advice in this area. The GDG took the view that a self-completion tool would not be feasible for a significant number of people with an intellectual disability and that a clinician-completed measure would be unlikely to be used routinely. Therefore, the GDG drew on a review of existing diagnostic manuals and assessment schedules designed specifically for use in people with autism and an intellectual disability, which enabled the GDG to identify a number of important indicators of autism including: social interaction problems; lack of responsiveness to others; little or no response to social situations; lack of demonstrable empathy; rigidity of routine; and marked indication of stereotypies. The GDG then formulated them in a questionnaire format for use by health and social care professionals to support them in determining whether or not to refer for a specialist assessment. Again, in developing this recommendation, the GDG adopted an approach that emphasised sensitivity over specificity.

5.3.12 Recommendations

Identification and initial assessment

5.3.12.1 Consider further assessment for possible autism when a person has:

- persistent difficulties in reciprocal (two-way) social engagement or social communication **and** stereotypic (rigid and repetitive) behaviours or resistance to change, and
- one or more of the following:
  - problems in obtaining or sustaining employment or education
  - difficulties in initiating or sustaining social relationships
  - previous, or current contact with CAMHS or learning disability services
  - history of a neurodevelopmental disorder.

5.3.12.2 For the further assessment of adults with possible autism who do not have a moderate or severe intellectual disability, use the Autism-Spectrum Quotient-10 items (AQ-10).[15] (If a person does not speak or read English, read out the AQ-10.) If a person scores above six on the AQ-10, or there is a high index of suspicion based on clinical judgement (including, where applicable, compelling evidence from an informant), offer a comprehensive assessment for autism.

5.3.12.3 For the further assessment of adults with possible autism who have a moderate or severe intellectual disability, consider a brief assessment to ascertain whether the following behaviours are present (if necessary using information from a family member or carer):

- poor reciprocal social interaction including:
  - limited interaction with others (for example, being aloof, indifferent or unusual)
  - interaction to fulfil needs only
  - social approaches that are naive or unusual
- lack of responsiveness to others and/or one-sided interaction
- little or no change in behaviour in response to different social situations
- no or limited social demonstration of empathy
- rigid routines and resistance to change
- marked repetitive activities (for example, rocking and hand or finger flapping), especially when under stress or expressing emotion.

If two or more of the above categories of behaviour are present, offer a comprehensive assessment for autism.

[15] Allison, C., Auyeung, B., Baron-Cohen, S. (in press) Towards brief 'red flags' for autism screening: the short AQ and the short Q-CHAT in 1000 cases and 3000 controls. *Journal of the American Academy of Child and Adolescent Psychiatry*.

5.4 ASSESSMENT AND DIAGNOSIS OF AUTISM IN ADULTS

5.4.1 Introduction

The purpose of this section is to identify best practice in the diagnosis and assessment of autism in adults across a range of clinical settings. A key aim of the assessment process should be to elicit information regarding the relevant characteristics of autism as outlined in the current diagnostic systems for autism, such as ICD–10 and DSM–IV. Although diagnosis is an important aspect of most assessments, the focus of assessment should not only be on diagnosis but should also consider the risks a person faces, as well as their physical, psychological and social functioning. The range and comprehensiveness of any assessment may vary depending on the setting in which it is undertaken and the particular purpose of the assessment, but in all cases the central aim is to identify need for treatment and care. The range and depth of the components of assessment should reflect the complexity of tasks to be addressed and the expertise required to carry out the assessment. Crucial to the effective delivery of any assessment is the competence of the staff who are delivering it, including the ability to conduct an assessment, interpret the findings of the assessment and use these finding to support the development of appropriate care plans and, where necessary, risk management plans.

Current practice

As was set out in Section 5.3, there is very limited access to services offering assessment for adults with autism outside specialist learning disability services. In services where specialist assessments are available the assessment will typically consist of a formal assessment of the core autistic symptoms, the nature and extent of any associated problems, the presence of any coexisting physical or mental disorders and an assessment of broader personal, social, educational and employment needs. In many specialist settings this will be undertaken by a multidisciplinary team, make use of structured instruments such as the Autism Diagnostic Observation Schedule (ADOS) (Lord *et al.,* 2001) or the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing *et al.,* 2002) and involve a family member or carer as a minimum as an informant.

Definition

For the purposes of this review, assessment and diagnostic instruments were defined as validated psychometric measures used to assess and diagnose people with autism. The review was limited to instruments likely to be used for adults with possible autism in UK clinical practice. 'Gold standard' diagnoses were defined as DSM or ICD (or equivalent) clinical diagnosis of autism.

5.4.2 Aim of the review

First, this section aims to identify and evaluate the diagnostic accuracy and usefulness of assessment instruments (including biological measures) that can aid in

a diagnosis of autism (see 5.4.4). The GDG used this review to then identify key components of an effective clinical interview to diagnose the presence and severity of autism in adults. Furthermore, this section aims to identify any amendments that may need to be made to take into account individual differences, identify the most effective methods for assessing an individual's needs and evaluate quality of life (see 5.4.5).

5.4.3 Clinical review protocol

A summary of 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 13 (the full protocol can be found in Appendix 8 and further information about the search strategy can be found in Appendix 9).

Table 13: Clinical review protocol for assessment and diagnosis

Component	Description
Review question (s)	In adults with possible autism, what are the key components of, and the most effective structure for, a diagnostic assessment? To answer this question, consideration should be given to: • the nature and content of the clinical interview and observation (including an early developmental history where possible) • formal diagnostic methods/ psychological instruments (including risk assessment) • biological measures • the setting(s) in which the assessment takes place • who the informant needs to be (to provide a developmental history). (CQ- B1) • What are the most effective methods for assessing an individual's needs (for example, their personal, social, occupational, educational, and housing needs) for adults with autism? (CQ – B3)
Sub-question	• When making a differential diagnosis of autism in adults, what amendments, if any, need to be made to the usual methods to make an assessment of autism itself in light of potential coexisting conditions (for example, common mental health disorders, ADHD, personality disorder, gender/identity disorders, eating disorder, Tourette's syndrome, and drug/alcohol misuse)? (CQ- B2)
Objectives	• To identify the key components of an effective clinical interview to diagnose the presence and severity of autism in adults. • To evaluate the diagnostic accuracy of assessment tools which aid the diagnosis of autism in adults. • To identify what amendments, if any, need to be made to take into account individual differences (for example, coexisting conditions). • To identify the most effective methods for assessing an individual's needs. • To evaluate an individual's quality of life • To suggest how diagnosis of autism in adults can be improved
Criteria for considering studies for the review	
• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental

	disorder) Consideration should be given to the specific needs of: • people with coexisting conditions • women • older people • people from black and minority ethnic groups • transgender people.
• Intervention	Formal assessments of the nature and severity of autism (including problem specification or diagnosis).
• Index Test	Formal assessments of the nature and severity of autism (including problem specification or diagnosis)
• Comparison	DSM or ICD clincial diagnosis of autism (or equivalent)
• Critical outcomes	**Reliability** (for example, inter-rater, test-retest) **Validity** (for example, construct, content) **Internal consistency** **Sensitivity**: the proportion of true positives of all cases diagnosed with autism in the population **Specificity**: the proportion of true negatives of all cases not-diagnosed with autism in the population. **Clinical utility outcomes**
• Important, but not critical outcomes	**Positive Predictive Value (PPV)**: the proportion of patients with positive test results who are correctly diagnosed. **Negative Predictive Value (NPV)**: the proportion of patients with negative test results who are correctly diagnosed. **Area under the Curve (AUC):** are constructed by plotting the true positive rate as a function of the false positive rate for each threshold.
• Study design	Cross-sectional
• Include unpublished data?	No
• Restriction by date?	No
• Minimum sample size	N=10 per arm 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, tertiary, health and social care and healthcare settings (including prisons and forensic services) • Others in which NHS services are funded or provided, or NHS professionals are working in multi-agency teams
Electronic databases	Australian Education Index, BIOSIS previews, British Education Index, CDSR, CINAHL, DARE, Embase, ERIC, HMIC, Medline, PsycINFO, Sociological Abstracts
Date searched	Generic, RCT, QE, OS. Inception of database up to 09/09/2011. Generic, systematic reviews. 1995 up to 09/09/2011.
Searching other resources	Hand-reference searching of retrieved literature
The review strategy	• To provide a GDG-consensus based narrative identifying the key components of an effective clinical diagnostic interview (considering possible amendments due to individual variation).

	• To conduct pooled diagnostic accuracy meta-analyses on the sensitivity and specificity, reliability and validity of assessment tools. This is dependent on available data from the literature. In the absence of this, a narrative review of assessment tools will be conducted and guided by a pre-defined list of consensus-based criteria (for example, the clinical utility of the tool, administrative characteristics, and psychometric data evaluating its sensitivity, specificity, reliability and validity).
Note. autism = autism spectrum disorders; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; RCT = randomised controlled trial; QE = Quasi-experimental; OS = observational study; AEI = Australian Education Index; ASSIA = Applied Social Services Index and Abstracts; BEI = British Education Index; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts and Reviews of Effectiveness; Embase = Excerpta Medica database; ERIC = Education Resources in Curriculum; HMIC =Health Management Information Consortium; Medline = Biomedical Information Database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

5.4.4 Review of autism assessment instruments

Inclusion criteria for autism assessment instruments

Instruments designed to structure and support clinical diagnosis and facilitate and structure direct observation were considered for the review. Instruments were included if they were:

- diagnostic instruments developed for the assessment of autism (but not generic assessment instruments developed to diagnose a range of disorders)
- structured, semi-structured or direct observation instruments
- validated in a sample aged over 17 years (even if developed for people aged under 17 years).

Biological measures

- No studies were identified that provided evidence on the use of biological measures in the routine assessment of autism in adults. A number of recently published studies of brain imaging (Bloeman *et al.,* 2010; Ecker *et al.,* 2010; Lange *et al.,* 2010) suggest that these techniques may have some value in the diagnosis of autism but the authors acknowledge that further development work is required before they could be considered for routine clinical use. The studies were therefore not considered further in this guideline.

Assessment instruments in the review

The GDG identified a list of possible instruments that could be used by clinicians in the diagnostic assessment of adults who are suspected of having autism. These instruments are for the assessment of autism only and intended to aid diagnosis. This list informed the development of the search terms and also provided useful markers for the searches. A number were excluded after a preliminary review of

their properties. (See footnotes for those that were excluded from further review or for other additional information).

- Adult Asperger Assessment (AAA)[16]
- Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)
- Asperger Syndrome Diagnostic Scale (ASDS)[17]
- Autism-Diagnostic Interview – Revised (ADI-R)
- Autism Diagnostic Observation Schedule (ADOS)
- Autism Spectrum Disorder – Diagnostic for Adults (ASD-DA)
- Children's Social Behavior Questionnaire (CSBQ)[18]
- Childhood Autism Rating Scale (CARS)
- Developmental, Dimensional and Diagnostic Interview (3di)
- Diagnostic Interview for Social and Communication Disorders (DISCO)
- Gilliam Asperger's Disorder Scale (GADS)[19]
- Gilliam Autistic Rating Scale (GARS)[20]
- Krug Asperger's Disorder Index (KADI)[21]
- Movie for the Assessment of Social Cognition (Mautism)
- Pervasive Developmental Disorders rating Scale (PDDRS)
- Revised Behavior Summarized Evaluation (BSE-R)
- Ritvo Autism and Asperger's Diagnostic Scale (RAADS)
- Ritvo Autism and Asperger's Diagnostic Scale-Revised (RAADS-R)
- Sensory Behavior Schedule (SBS)
- Short-Form Developmental Behaviour Checklist[22]
- Social Responsiveness Scale (SRS)
- Triple C: Checklist of Communicative Competencies[23].

Studies considered[24]

The literature was then scrutinised and studies considered for inclusion based on:

1. Agreed inclusion and exclusion criteria (see
2. Table 13)

[16] Includes the Autism-Spectrum Quotient (AQ) and the Empathy Quotient (EQ).
[17] Excluded from the review as designed for 5 to 18 year olds only.
[18] Excluded from the review as designed for 4 to 18 year olds only.
[19] Excluded from the review as designed for 3 to 22 year olds only.
[20] Excluded from the review as designed for 3 to 22 year olds and may also be more appropriate for screening.
[21] Excluded from the review as designed for 6 to 22 year olds and may also be more appropriate for screening.
[22] Excluded from review as not autism specific.
[23] Excluded from review as for intellectual disabilities (not autism specific)
[24] 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).

3. The availability of psychometric data evaluating the reliability and validity of the instrument (see Chapter 3 for a description of the types of reliability and validity).

The literature search for observational studies resulted in 21 articles which were evaluated by reading the full texts. Of these 21 articles, 10 were excluded because the mean age of the sample was too low, only a small proportion of the sample being evaluated had a diagnosis of autism, or no tangible psychometric data was provided.

Therefore, 11 articles met the eligibility criteria for inclusion in the review (Baron-Cohen *et al.,* 2005 [BARONCOHEN2005]; Dziobek *et al.,* 2006 [DZIOBEK2006]; Garfin & McCallon, 1988 [GARFIN1988]; Gillberg *et al.,* 2001 [GILLBERG2001]; Lord *et al.,* 1997 [LORD1997]; Lord *et al.,* 2000 [LORD2000]; Matson *et al.,* 2007a [MATSON2007A]; Matson *et al.,* 2007b [MATSON2007B]; Matson *et al.,* 2008 [MATSON2008]; Ritvo *et al.,* 2008 [RITVO2008]; Rivto *et al*, 2011 [RIVTO2011].

Of the 11 studies included in the review five were conducted using a sample of people with high- functioning autism or Asperger's syndrome (BARONCOHEN2005; DZIOBEK2006; GILLBERG2001; RITVO2008; RITVO2011), three included participants with an autism diagnosis across the spectrum (GARFIN1988; LORD1997; LORD2000), and five included participants with an autism diagnosis as well as an intellectual disability (GARFIN1988; LORD1997; MATSON2007A; MATSON2007B; MATSON2008).

Further information about both included and excluded studies can be found in Appendix 14.

Evaluating the psychometric data

The instruments that met inclusion criteria and were considered for review can be seen in Table 14. This table shows where data are available that assesses reliability and validity (including sensitivity and specificity) in an adult population with autism. All instruments were then evaluated according to criteria as set out in the methods chapter (section 3.5.4).

Table 14: Availability of reliability and validity data

Instrument	Reliability data	Validity data
Adult Asperger Assessment (AAA)	X	Sens/ spec/ PPV (Baron-Cohen *et al.*, 2005)
Autism Diagnostic Observation Schedule (ADOS)	Inter-rater reliability (Lord *et al.*, 2000); internal consistency (Lord *et al.*, 2000); test-retest reliability (Lord *et al.*, 2000)	Sens/spec (Lord *et al.*, 2000)
Autism Diagnostic Interview (ADI-R)	X	Sens/spec / PPV (Lord *et al.*, 1997)
Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)	Inter-rater reliability (Gillberg *et al.*, 2001); test-retest reliability (Gillberg *et al.*, 2001)	Criterion validity (Gillberg *et al.*,2001)
Autism Spectrum Disorder – Diagnostic for Adults (ASD-DA)	Inter-rater reliability (Matson *et al.*, 2007b); internal consistency (Matson *et al.*, 2007b); test-retest reliability (Matson *et al.*, 2007b)	Sens/spec / PPV (Matson *et al.*, 2007a); convergent and discriminant validity (Matson *et al.*, 2008)
Childhood Autism Rating Scale (CARS)	Inter-rater reliability (Garfin *et al.*, 1988); internal consistency (Garfin *et al.*, 1988)	Discriminant validity (Garfin *et al.*, 1988; Mesibov *et al.*, 1989)
Developmental, Dimensional and Diagnostic Interview (3di)	X	X
Diagnostic Interview for Social and Communication Disorders (DISCO)	X	X
Movie for the Assessment of Social Cognition (Mautism)	Inter-rater reliability (Dziobek *et al.*, 2006); internal consistency (Dziobek *et al.*, 2006); test-retest reliability (Dziobek *et al.*, 2006);	Concurrent validity (Dziobek *et al.*, 2006); AUROC (Dziobek *et al.*, 2006)
Pervasive Developmental Disorders Rating Scale (PDDRS)	X	X
Revised Behavior Summarized Evaluation (BSE-R)	X	X
Ritvo Autism and Asperger's Diagnostic Scale (RAADS)	Internal consistency (Ritvo *et al.*, 2008)	Sens/spec / PPV (Ritvo *et al.*, 2008)
Ritvo Autism and Asperger's Diagnostic Scale – Revised(RAADS-R)	Internal consistency (Ritvo *et al.*, 2011); Test-retest reliability (Ritvo *et al.*, 2011)	Criterion validity (Ritvo *et al.*, 2011); Sens/spec/ PPV (Ritvo *et al.*, 2011)
Social Responsiveness Scale (SRS)	X	X

Evidence summary

The following instruments used to support the diagnosis of autism in adults were not considered any further as no basic psychometric data was identified:

- the Developmental, Dimensional and Diagnostic Interview (3di)
- the Diagnostic Interview for Social and Communication Disorders (DISCO)
- the Pervasive Developmental Disorders Rating Scale (PDD-RS)
- the Revised Behavior Summarized Evaluation (BSE-R)
- the Social Responsiveness Scale (SRS).

All other instruments met all the basic inclusion criteria and did have available psychometric data. The properties of these instruments can be seen in Table 15. The psychometric data (see Table 16) and clinical utility for each instrument as well as if it met the criteria stipulated above is described below.

Adult Asperger Assessment (AAA)

There was no available evidence evaluating the reliability of the AAA. It was judged to capture the components of autism and hence have content validity, and was also found to have 'excellent' diagnostic validity. However, there was no available evidence assessing the construct and criterion validity of the AAA. The AAA can only be used with people with an IQ above 70, is lengthy to complete but is freely available. It does not require extensive training to administer, score or interpret.

Autism Diagnostic Interview - Revised (ADI-R)

There was no data evaluating the reliability of the ADI-R in an adult population. It was judged to have content validity and the data suggest 'excellent' diagnostic validity. However, no data evaluating the construct and criterion validity were available. The ADI-R can be used with people with a range of IQs, and is not excessively lengthy. However, it does require training to administer and is not free.

Autism Diagnostic Observation Schedule (ADOS-G) – module 4 (adults and high-functioning children)

The ADOS-G (module 4) was found to be 'relatively reliable' (inter-rater, test-retest and internal consistency). It was judged to have content validity and there is evidence that it has 'excellent' diagnostic validity. The ADOS-G can be used for those with varying intellectual ability as modules 1 to 2 can be used with adults with intellectual disabilities and module 4 for adults and high-functioning children. It is not lengthy to complete, no specific training is required for clinical use (although experience with autism is required to use it effectively) but is not free.

Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)

The ASDI was found to have 'relatively reliable' inter-rater reliability and internal consistency. No data were available evaluating its test-retest reliability. Although there is some evidence of criterion validity (the data suggest that the ASDI concurred with clinical diagnosis), this evidence was not found to be robust. The ASDI was judged to have adequate content validity. However, there is no data evaluating the diagnostic validity of the ASDI in the population of interest. The ASDI can only be used with individual with an IQ greater than 70 and is reliant on an informant. It is quick to administer, with no training available and is free to obtain. However, the developers state it should not be used as a stand-alone instrument for diagnosis but can be used as part of a diagnostic interview.

Autism Spectrum Disorder – Diagnostic for Adults (ASD-DA)

The ASD-DA was found to have 'unreliable' inter-rater and test-retest reliability and 'relatively reliable' internal consistency. The ASD-DA was judged to have content validity and 'moderate' diagnostic validity, but no evidence evaluating the construct and criterion validity of the ASD-DA was obtained. The ASD-DA was developed for use with an intellectual disabilities adult population and requires information from an informant. It is quick to administer, however the training and cost properties are unclear.

Childhood Autism Rating Scale (CARS)

The CARS was found to have 'relatively reliable' inter-rater reliability and internal consistency. There was no evidence evaluating its test-retest reliability. Additionally, the CARS was judged to have content validly and found to have acceptable construct validity. However, there was no data available evaluating its criterion and diagnostic validity. The CARS can be used across the range of intellectual ability and involves the use of an informant as well as direct observation. It is quick to use with minimal training and available from the developers (cost unclear). However, the CARS cannot be used alone to reach a diagnosis of autism.

Movie for the Assessment of Social Cognition (MASC)

The MASC was found to have 'relatively reliable' inter-rater reliability, test-retest reliability and internal consistency. Although there was no evidence of its construct validity, the MASC was found to have content validity, adequate criterion validity and 'excellent' diagnostic validity. The MASC only evaluates social cognition and can be used with adults across intellectual abilities (but has been validated in an Asperger's syndrome sample). Taking into consideration that it only evaluates a single aspect of autism, it is quite lengthy to complete. The MASC requires minimal training to use and is available from the developers upon request (cost unclear).

Ritvo Autism and Asperger's Diagnostic Scale (RAADS and RAADS-R)

The RAADS-R was found to be 'relatively reliable' for test-retest reliability and internal consistency. There was however, no evidence evaluating the inter-rater

reliability for the RAADS or RAADS-R. Both the RAADS and RAADS-R were judged to have adequate content validity, and 'excellent' diagnostic validity, and the RAADS-R had some evidence of criterion validity (concurrence with the Social Responsiveness Scale – Adult). The RAADS and RAADS-R have been developed for use in adults with an IQ greater than 70 as part of an assessment battery and not a stand-alone instrument for diagnosis of autism. The RAADS-R is intended to be completed by clinicians in conjunction with a clinical interview and takes approximately 45 minutes to complete.

Clinical evidence summary

The psychometric evidence evaluating the reliability and validity of diagnostic instruments in adults with autism is limited. For some measures, a number of which are in regular use in the UK, no basic psychometric evidence was available—this includes the DISCO, 3di, PDD-RS, SRS and BSE-R. In addition the evidence for the reliability and validity of the ASD-DA was poor and although the AAA and the ADI-R have some evidence of validity, there is no available reliability data. Given the quality of the evidence the GDG did not consider the above measures to have sufficient evidence to support their use.

The only instruments with adequate reliability and validity data are the ASDI, RAADS-R, MASC and the observational instruments the ADOS-G and CARS. However, the MASC, and the CARS should not be used as a stand-alone instrument for diagnosis and further work is underway to establish the validity of the instruments. This leaves the ASDI, the RAADS-R and the ADOS-G as possible instruments with reasonable psychometric properties. The ASDI and the RAADS-R are developed for use with people without intellectual disabilities whereas the ADOS-G (an observational measure) can be used across the whole autism spectrum. This leaves three measures (the ASDI, the RAADS-R and the ADOS-G) for use in supporting the diagnosis of autism.

Health economic evidence

No studies assessing the cost effectiveness of autism assessment instruments 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.

From evidence to recommendations

The rationale for the development of recommendations concerning autism assessment instruments is presented in Section 5.4.7, where the assessment of autism is considered by the GDG in an integrated manner. Recommendations regarding autism assessment instruments can be found in Section 5.4.8.

Table 15: Characteristics of assessment instruments

Instrument	Age range	Level of functioning	Domains assessed	Number of items, scale, cut-off	Completed by	Time to administer/score, training required, cost/copyright issues	Notes
Adult Asperger Assessment (AAA)	16 years and above	Higher functioning (IQ >70)	Social interaction, social skills, communication, cognitive empathy	AAA = 23 items; AQ= 50 items; EQ = 60 items; maximum score 18 Cut-off 10 for autism diagnosis	Two parts (AQ and EQ) are self-administered, diagnostic part is clinician-administered	3 hours (for AAA component) Freely available	Three-part instrument consisting of the Autism-Spectrum Quotient (AQ), Empathy Quotient (EQ) and a clinician-conducted diagnostic questionnaire – the AAA. No norms available for the AAA (sample size in Baron-Cohen 2005 study is small) . Not been validated by anyone other than primary authors/ developers.
Autism Diagnostic Interview – Revised (ADI-R)	18 months to adulthood	Mental age above 2 years	Language and communication; reciprocal social interactions; restricted, repetitive and stereotyped behaviours and interests	93 items, scale and cut-off unclear	Clinician administered interview of caregivers	1.5 to 2.5 hours, Training required Available to buy	Although good for varying levels of severity, is has not been designed to measure change. Can be used for diagnosis.
Autism Diagnostic Observation	2 years to adulthood; Module 4	Across spectrum (verbal	Social and communicative behaviours	15 items, unsure of scale or cut-	Clinician observation	30-40 minutes, training required for research but not clinical use	Originally developed as companion instrument for the ADI.

Schedule (ADOS) – G	for high-functioning young people and adults	adolescents/ adults only)		off		(although substantial experience with autism or PDD needed to use it effectively); available to buy	Not designed to measure change but can be used for response to treatment.
Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)	Children (6 years plus) and adults	Higher functioning (IQ >70)	Social interaction, interests, routine, speech and language peculiarities, non-verbal communication, motor clumsiness	20 items, 6 sub-scales; 2-point scale	Structured interview of person who knows subject well and has knowledge of his/her childhood	10 minutes, no training required, freely available	Instrument still in preliminary stages of validation. Not designed to be used with DSM-IV or ICD-10 criteria but designed to reflect criteria as described by Gillberg & Gillberg (1989), which are much broader and do not include the language delay component. Should not be used as a stand-alone instrument.
Autism Spectrum Disorder – Diagnostic for Adults (ASD-DA)	Adults	Intellectual disability	One measure for diagnosing autism and PDD-NOS, one measure for comorbid psychopathology, one measure for challenging behaviours	31 items, 0-1 points for each item, cut-off 19 points	Interview of third party informant	10 minutes, unclear about training, unclear about cost	Only validated by developers.
Childhood Autism Rating Scale (CARS)	2 to adulthood	Range (lower cut-off suggested for high functioning)	Relating to people, body use, object use, emotional response, verbal and nonverbal communication	15 items, 4-point scale, cut-off of 30	Parent, caregiver or teacher; direct observation by a clinician	30 minutes, minimal training; available on request (unsure of cost)	Cannot be used alone for diagnosis. Suggested that scores do not correspond to current DSM-IV/ICD-10.
Movie for the Assessment of Social Cognition (MASC)	Adults (lower end unclear)	Across spectrum	Social cognition	46 questions, 3- point scale; cut-off unknown	Tester	45 minutes, minimal training; available from the author by request (cost unclear)	Validated in an Asperger's syndrome sample because of evidence that social cognition presents with only subtle impairments.

Ritvo Autism and Asperger Diagnostic Scale (RAADS)	Adults	Higher functioning (IQ >70)	Social relatedness, language and communication; sensorimotor and sterotypies	78 items, 4-point scale	Clinician completed interview of individual	1 hour, minimal training, freely available	Superseded by RAADS-R
Ritvo Autism and Asperger Diagnostic Scale – Revised (RAADS-R)	18 – 65 years	Higher functioning (IQ >70)	Social relatedness, circumscribed interests, language, sensorimotor and stereotypies	80 items, 4-point likert scale ≥65 diagnosis of autism or AD	Self-rated	45 minutes, unclear about training, unclear about cost	This new version is based on the DSM-IV-TV and ICD-10 criteria. Authors recommend use as part of assessment battery not alone. RAADS-R is still in development and not be validated by anyone other than primary authors/ developers.

Table 16: Psychometric data for included instruments

	Reliability			**Validity**			
	Inter-rater	***Test-retest***	***Internal consistency***	***Evidence of content validity***	***Construct (convergent, discriminant) validity***	***Criterion (concurrent, predictive) validity***	***Diagnostic (SE, SP, PPV) validity***
Adult Asperger Assessment (AAA)	X	X	X	4	X	X	SE =.92; SP =1; PPV = 1
Autism Diagnostic Interview (ADI-R)	X	X	X	4	X	X	Mental age 3 to 11 years (SE = .86; SP= .91; PPV = .93); Mental age ≥12 years (SE = .86; SP = .93, PPV = .94)
Autism Diagnostic Observation	Social *r* = .93; communication *r* = .84; social	Social *r* = .78; communication *r* = .73; social	Social α = .86-.91; communication	4	X	X	SE= .90; SP = .93; PPV = .91

Schedule (ADOS-G) – Module 4 (adults & HF children)	communication *r* = .92; restricted repetitive *r* = .82	communication *r* = .82; restricted repetitive *r* = .59	α = .74-.84; social communication α = .91-.94; restricted repetitive α = .47-.56				
Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)	*r* = 0.91	*r* = 0.92	X	4	X	Concurred with clinical diagnosis (all participants met at least 5/6 criteria)	X
Autism Spectrum Disorder – Diagnostic for Adults (ASD-DA)	*r* = 0.295	*r* = 0.386	*r* = 0.94	4	X	X	SE = .86; SP = .62; PPV = .74
Childhood Autism Rating Scale (CARS)	*r* =0.98	X	α = .73	4	*r* =0.75	X	X
Movie for the Assessment of Social Cognition (MASC)	*r* =.99	*r* =0.97	α = 0.85	4	X	Concurrence with ADI-R social domain = -.533	AUROC = .98
Ritvo Autism and Asperger's Diagnostic Scale (RAADS)	X	X	Social relatedness α = 0.86; language and communication α = 0.65; sensorimotor and stereotypies α= 0.73	4	X	X	SE = 1; SP = 1; PPV = 1

Ritvo Autism and Asperger's Diagnostic Scale – Revised(RAADS-R)	X	*r* =0.987	Circumscribed interests α=.903; language α=.789; sensory motor α=.905; social relatedness α=.923	4		Concurrence with Social Responsiveness Scale – Adult (95.59%)	SE = .97; SP = 1, PPV = 1
X = no data available; 4 = adequately covers the different aspects of the construct that are specified in its definition							

5.4.5 The structure and content of the assessment process (including diagnosis)

In the review of the literature the GDG was unable to identify any formal evaluations of the structure and content of the overall clinical assessment process for adult autism other than the data on the various assessment scales described in the sections above. In light of this the GDG drew on their expert knowledge and experience regarding the structure and content of a clinical assessment for adults with autism. When considering this, the GDG assumed that any person referred for such an assessment would already have been identified as possibly having autism or there would have been concerns that they did.

Given the range of presentations covered within the autism spectrum and the extent and nature of the common coexisting conditions, the GDG was of the view that any assessment process should be undertaken by professionals who are trained and competent and have specific knowledge of autism and its assessment. The GDG also judged that assessment of people with autism required such a broad range of skills and knowledge that any specialist assessment should be team based and involve a range of professionals with the requisite skills to complete a comprehensive assessment. In addition, given the life-long course of autism, a family member or other informant with knowledge of the individual's personal history and development should be involved and where this was not possible, documentary evidence, such as school reports, should be obtained.

In considering the structure and content of a diagnostic assessment of autism the GDG was also mindful of the communication difficulties experienced by many people with autism and therefore thought considerable care and attention should be devoted to informing the person of the structure and content of the specialist assessment and ensuring its outcome is fed back to them in a way in which they would understand. The GDG considered that the involvement of a parent, carer or advocate to support the person during the assessment process and to facilitate the understanding of any feedback would also be very helpful.

The GDG identified a number of key components that should form the basis of any comprehensive assessment of autism, as follows:

- the core symptoms of autism including social interaction, communication and stereotypical behaviour
- a developmental history spanning childhood, adolescence and adult life
- the impact on current functioning including personal and social functioning, educational attainment and employment
- past and current history of mental and physical health problems, neurodevelopment disorders and the presence of any disability or hearing or visual problems.

Wherever possible this assessment should be supported by direct observation of the person's behaviour.

Having reviewed the formal assessment instruments the GDG did not judge that any one instrument had sufficient properties to recommend its routine use in the assessment of adults with autism. The GDG considered that a range of measures, including ADOS-G, ASDI and RAADS-R, could be used with people with normal intellectual ability, and for those with intellectual disabilities the use of ADOS –G should be considered.

The GDG also considered the use of a range of biological and neuroimaging tests for diagnostic purposes. In the review of the literature of diagnostic instruments no good-quality evidence for the use of these tests in routine care was found and therefore no recommendations were developed.

The GDG also recognised that for some individuals with suspected autism achieving a correct diagnosis can be difficult even for specialist teams (for example in the presence of coexisting conditions such as severe intellectual disability, hearing or motor problems or severe mental illness). With this in mind the GDG were of the view that an opportunity for further assessment ought to be considered in circumstances where: there is disagreement within the assessment team about the nature of diagnosis; disagreement from the family members about the diagnosis; and also in situations where the team judged themselves not to have the requisite skills and competencies to arrive at an accurate diagnosis. Although the GDG judged that biological tests should not form part of the routine diagnosis of autism they did accept that in particular circumstances biological tests could be important in the diagnostic process. This could include referral to a regional genetic testing centre if there are specific dimorphic or congenital anomalies or other evidence of intellectual disability. Similarly where epilepsy is suspected an EEG or a referral to a specialist epilepsy service may be considered. Similarly specialist testing of hearing and vision may be required.

Autism can have a profound effect on a person's ability to lead a normal life and the GDG's consideration was that a specialist diagnostic assessment must also address individual needs in relation to personal and social functioning and educational, housing and occupational needs. The assessment of these functions and needs may be provided from within a specialist autism team, but where this is not possible it should be the responsibility of the people within the team to obtain and coordinate these specific assessments by other competent individuals.

Assessment of coexisting conditions

The GDG recognised that significant coexisting physical or mental health conditions, communication problems or intellectual disabilities can make the diagnosis of autism complex and challenging. The GDG also considered to what extent an individual assessment might need to be adapted to take these difficulties into account. No evidence was identified that could inform such considerations, for example specific tools for the assessment of autism in people with schizophrenia,

except for the tools already reviewed concerning autism and intellectual disabilities. The GDG therefore took the view that specialist teams should have the skills and knowledge to adapt and develop assessments in relation to specific coexisting mental health disorders, for example schizophrenia, depression, obsessive-compulsive disorder (OCD) and neurodevelopmental disorders such as ADHD and intellectual disabilities. The GDG considered that the formal assessment of cognitive function may also be necessary.

The GDG was aware that that focus and orientation of many specialist autism teams will be primarily on mental health and neurodevelopmental disorders. It also recognised that in addition to a series of mental health problems significant physical health problems also exist in individuals with autism. The GDG considered that attention should also be paid to coexisting physical health problems (commonly occurring coexisting conditions include epilepsy and gastrointestinal problems) that may be unrecognised or not treated, in part because the person with autism had not complained of any such problems or had not been able to communicate their concerns in a way that had been understood. Up to one third of people with autism have a diagnosis of epilepsy with the highest rates in those with a severe intellectual disability (Danielsson *et al*., 2005), and achieving seizure control, for example, may require more specialist knowledge than a specialist autism team or local neurology service may possess. Other important issues relating to physical health problems in people with autism include compliance with medication and the recognition of side effects.

Clearly a number of the areas referred to above will be outside the expertise of a specialist autism team. Given this, the GDG wished to highlight that an important role of the specialist team is to advise, and to seek advice from, other health professionals on the management of coexisting mental and physical health conditions such as anxiety, depression, OCD and generalised anxiety disorder. This responsibility should sit alongside that of those health professionals working in primary care where the adoption of an annual physical health review for all people with autism might be considered.

Risk assessment and management

People with autism are often vulnerable and at risk because of the core autistic symptoms and coexisting mental health conditions, and for a significant number of autistic people, intellectual disabilities further increase their vulnerability. The GDG considered risk assessment and management to be an important area and in developing their recommendations drew on the advice developed for risk assessment in other relevant NICE guidelines (for example, NICE, 2009a). However, in addition to the risk of self-harm, the GDG considered the possibility of harms to others and the risk of exploitation and abuse by others. The GDG judged that any risk assessment of adults with autism should consider the risk of self-harm, in particular the risk of suicide in people who are also depressed or who have moderate or severe intellectual disabilities. Risk of harm to others also needs to be considered, particularly for family members and carers living at home where there

may be significant incidents of challenging behaviour. In addition many people with autism may be isolated from or have no identified family members or carers. This leaves a number of people at risk from self-neglect, exploitation or abuse (Fyson & Kitson, 2007). In developing an approach to risk assessment and management, the GDG was also mindful that it was important to be aware of the sensitivity of some people with autism to changes in their physical or social environment and the possibility of the very rapid escalation of problems including risk-related problems due to changes in the social or physical environment.

Assessing the needs of families and carers

The GDG recognised that given the life-long nature of autism and the significant impairment of personal and social functioning experienced by many people with autism across the range of intellectual ability, along with the fact that many adults with autism are not in contact with regular services there is a considerable burden of care that rests with relatives. There is limited evidence (see Chapter 4 on experience of care) for the burden on the family and the impact on their social functioning and mental health. In light of this it was felt that an assessment of families' and carers' needs should be considered.

Assessment of special populations

The GDG considered this issue in relation to assessment and found no new evidence other than that covered in the section on case identification (see Section 5.3).

Feedback following assessment

The GDG considered how the outcome of a comprehensive assessment should be fed back to the person with suspected autism and their family and carers. The view of the GDG was that there was a need for a comprehensive and informative profile of individual needs and risks and a care plan, which should include specification of:

- the nature and extent of core features of autism
- the nature and extent of any coexisting mental or physical health problems
- the nature and extent of behavioural problems
- the current speech, language, and communication skills
- the level of personal, social, occupational and educational functioning
- the risk to self and others including close family members and carers
- the problems faced and their impact on families' and carers' needs
- the impact of the social and physical environment.

The GDG took the view that these should be fed back in a manner adapted to a person's capacity to understand the problem and which also identified any unmet needs and specified the way in which those needs would be addressed.

5.4.6 Health economic evidence

No studies assessing the cost effectiveness of the structure and content of the assessment 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.

5.4.7 From evidence to recommendations

In developing the recommendation for the assessment instruments and for the structure and content of the assessment process for people with autism the GDG was conscious of the limited evidence base identified in the reviews above.

The GDG did not consider that any assessment tool had sufficiently good properties to warrant its recommendation for routine use in the assessment of all adults with autism. However, taking into account the complexity of autism and recognising that some measures had reasonable reliability and validity, it was the GDG's opinion that some measure may be of value in augmenting a clinically-led assessment. The review identified a number of instruments that had reasonable reliability and validity such that it would warrant their use in augmenting an assessment. The ADOS-G, ASDI and RAADS-R were identified as potentially of value in the diagnosis of autism in adults of normal ability and the ADOS-G as of value in supplementing the assessment process in adults with an intellectual disability.

In addition to the measures described above the GDG drew on their clinical knowledge and experience and developed recommendations for the structure, content and outcome of an assessment for adults with autism. In addition, the GDG felt that the complexity of autism meant that a team-based approach with a range of skills and, where appropriate, direct observation was required to ensure a comprehensive assessment. The opportunity for further assessment should be available where there were disagreements about the diagnosis.

The GDG also developed recommendations on assessment of coexisting conditions given the problems of diagnostic masking and the difficulties in assessing many of the common coexisting conditions.

The GDG recognised that the assessment of risk was important, and were particularly concerned about the risk of abuse and exploitation for vulnerable people with autism.

Given the failure to find any high-quality evidence for routine biological tests such as genetic testing or neuroimaging, the GDG did not make any specific recommendation, although it was recognised that in particular areas, such as dysmorphic facial features, genetic testing would be advised.

The GDG adapted an existing recommendation from *Autism: recognition, referral and diagnosis of children and young people on the autism spectrum* (NICE, 2001a) regarding

seeking a second opinion if there is uncertainty or disagreement about the diagnosis. For our methodology for adapting recommendations see Chapter 6.

As part of the comprehensive assessment for adults with autism there should be, where appropriate, an assessment of challenging behaviour.

Following assessment correct treatment and care options for adults with autism should be identified and discussed with the person. The GDG adapted existing recommendations from *Common Mental Health Disorders* (NICE, 2011b) (see sections 6.4.3 and 6.4.4 for methodology for adapting recommendations). In addition the GDG advised that any discussions should take into account any sensory sensitivities and a functional analysis of behaviour should be undertaken.

5.4.8 Recommendations

Comprehensive (diagnostic, needs and risks) assessment of suspected autism

5.4.8.1 A comprehensive assessment should:

- be undertaken by professionals who are trained and competent
- be team-based and draw on a range of professions and skills
- where possible involve a family member, carer or other informant or use documentary evidence (such as school reports) of current and past behaviour and early development.

5.4.8.2 At the beginning of a comprehensive assessment, discuss with the person how the outcome of the assessment will be fed back to them. Feedback should be individualised, and a family member, carer or advocate may be involved to support the person and help explain the feedback.

5.4.8.3 During a comprehensive assessment, enquire about and assess the following:

- core autism symptoms (social interaction, communication and stereotypic behaviour) that may have been present at any age
- early developmental history, where possible
- behavioural problems
- functioning at home, in education or in employment
- past and current physical and mental health problems
- other neurodevelopmental disorders, including intellectual disability
- hyper- and hypo-sensory sensitivities.

Carry out direct observation of core autism symptoms especially in social situations.

5.4.8.4 Consider using a formal assessment tool to aid the diagnosis and assessment, such as:

- the Autism Diagnostic Observation Schedule – Generic (ADOS-G) [25], the Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI)[26] or the Ritvo Autism Asperger Diagnostic Scale – Revised (RAADS-R)[27] for people with intellectual ability within the normal range
- the ADOS-G for people with intellectual disability.

5.4.8.5 During a comprehensive assessment, take into account and assess for possible differential diagnoses and coexisting conditions, such as:

- other neurodevelopmental disorders, including intellectual disability (use formal assessment tools) and attention deficit hyperactivity disorder
- mental health disorders (for example, schizophrenia, depression or other mood disorders, and anxiety disorders, in particular, social anxiety disorder and obsessive-compulsive disorder)
- neurological disorders (for example, epilepsy)
- physical health problems
- communication difficulties (for example, speech and language problems, and selective mutism)
- hyper- or hypo-sensory sensitivities.

5.4.8.6 Do not use biological tests, genetic tests or neuroimaging for diagnostic purposes routinely as part of a comprehensive assessment.

5.4.8.7 During a comprehensive assessment, assess the following risks:

- self-harm (in particular in people with depression or moderate or severe intellectual disability)
- rapid escalation of problems
- harm to others
- self-neglect
- breakdown of family or residential support
- exploitation or abuse by others.

Develop a risk management plan if needed.

[25] Lord C, Risi S, Lambrecht L, et al. The Autism Diagnostic Observation Schedule – Generic: a standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders, 2000;30:205-223.

[26] Gillberg C, Gillberg C, Rastam M, et al. The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. Autism, 2001;5:57-66.

[27] Ritvo RA, Ritvo ER, Guthrie D, et al. The Ritvo Autism Asperger Diagnostic Scale – Revised (RAADS-R): a scale used to assist the diagnosis of autism spectrum disorders in adults: an international validation study. Journal of Autism and Developmental Disorders, 2011;41:1076-1089.

5.4.8.8 Develop a care plan for adults with autism based on the comprehensive assessment, incorporating the risk management plan and including any particular needs (such as adaptations to the social or physical environment) and also taking into account the needs of families and carers.

5.4.8.9 As part of a comprehensive assessment (and in other settings, such as specialist mental health services), consider developing a 24-hour crisis management plan, which should detail:

- the likely trigger(s) for a crisis
- the nature and speed of the reaction to any trigger(s) including details about the way in which autism may impact on a person's behaviour leading up to and during a crisis
- the role of the specialist team and other services (including outreach services) in responding to a crisis
- advice to primary care professionals and other services on their responsibilities and appropriate management in a crisis
- advice for families or carers about their role in a crisis
- the nature of any changes to the environment needed to manage a crisis.

5.4.8.10 Consider obtaining a second opinion (including referral to another specialist autism team if necessary), where there is uncertainty about the diagnosis or if any of the following apply after diagnostic assessment:

- disagreement within the autism team about the diagnosis
- disagreement with the person, their family, carer(s) or advocate about the diagnosis
- a lack of local expertise in the skills and competencies needed to reach diagnosis in adults with autism
- the person has a complex coexisting condition, such as a severe intellectual, behavioural, visual, hearing or motor problem or a severe mental illness.[28]

5.4.8.11 On an individual basis, and using the comprehensive assessment, physical examination and clinical judgement, consider further investigations, including:

- genetic tests, as recommended by the regional genetics centre, if there are specific dysmorphic features, congenital anomalies and/or evidence of intellectual disability
- electroencephalography if there is suspicion of epilepsy
- hearing or sight tests
- other medical tests depending on individual symptoms (for example, sudden onset of challenging behaviours or change in usual patterns of behaviour).

[28] Adapted from the 'Autism: recognition, referral and diagnosis of children and young people on the autism spectrum' (NICE clinical guideline 128). Available from: www.nice.org.uk/guidance/CG128.

Identifying the correct treatment and care options for adults with autism

5.4.8.12 When deciding on treatment or care interventions with adults with autism, consider:

- experience of, and response to, previous interventions
- the nature, severity and duration of autism
- the extent of any associated functional impairment arising from the autism, any intellectual disability or physical health problem
- the presence of any social or personal factors that may have a role in the development or maintenance of any identified problem(s)
- the presence, and nature, severity and duration, of any coexisting conditions
- the identification of predisposing and possible precipitating factors that could lead to crises if not addressed.[29]

5.4.8.13 When discussing treatment and care interventions with adults with autism, take into account the:

- increased propensity for elevated anxiety about decision-making in people with autism
- greater risk of increased sensitivity to side effects of medications or other physical interventions
- environment, for example whether it is suitably adapted for people with autism, in particular those with hyper- or hypo-sensory sensitivities
- the presence and nature of hyper- or hypo-sensory sensitivities and how these might impact on the delivery of the intervention
- importance of clarity, structure and routine for people with autism
- nature of support needed to access interventions.

5.4.8.14 When discussing treatment or care interventions with adults with autism, provide information about:

- the nature, content and duration of any proposed intervention
- the acceptability and tolerability of any proposed intervention
- possible interactions with any current interventions and possible side effects
- the implications for the continuing provision of any current interventions.[29]

[29] Adapted from 'Common mental health disorders: identification and pathways to care' (NICE clinical guideline 123). Available from: www.nice.org.uk/guidance/CG123.

5.4.8.15 Provide a 'health passport' (for example, a laminated card) as part of any care and treatment plan. The health passport should be carried by the person with autism at all times and should provide information for all staff about the person's treatment and care needs.

5.4.8.16 When deciding on treatment and care interventions focused on a specific problem behaviour, perform a functional analysis of the behaviour, including:

- observation and description, in a range of environments, of:
  - the internal and external stimuli that appear to trigger the behaviour
  - the consequences of the behaviour (that is, the reinforcement received as a result of their behaviour[30])
- review of the observational data to identify trends in behaviour occurrence, stimuli that may be evoking that behaviour, and the needs that the person is attempting to meet by performing the behaviour.

Use the analysis to target interventions at addressing the causes and function(s) of problem behaviour(s).

Assessment of challenging behaviour

5.4.8.17 Assessment of challenging behaviour should be integrated into a comprehensive assessment for adults with autism (see recommendations 5.4.8.1-5.4.8.7). When assessing challenging behaviour undertake a functional analysis (see recommendation 5.4.8.16) and consider identifying and evaluating any factors that may trigger or maintain the behaviour, including:

- any physical health problems
- the social environment (including relationships with friends, families and carers)
- the physical environment, including sensory needs
- coexisting mental health disorders (including depression and anxiety disorders)
- communication problems
- changes to routines or personal circumstances.

5.4.8.18 Address any identified factors that may trigger or maintain challenging behaviour (see recommendation 5.4.8.17) before initiating any other intervention by offering:

- the appropriate care for physical health problems (for example, gastrointestinal problems or chronic pain)
- interventions aimed at changing the environment when problems related to the physical or social environment are identified; for example, advice to families or carers, changes to the physical

[30] Reinforcement may be by the person with autism or those working with or caring for them.

environment or accommodations such as wearing earplugs or dark glasses

- treatment for any coexisting mental health disorders informed by existing NICE guidance.

6 PRINCIPLES AND PRACTICE FOR THE EFFECTIVE ORGANISATION AND DELIVERY OF CARE

6.1 INTRODUCTION

The Department of Health's *Fulfilling and Rewarding Lives: the Strategy for Adults with Autism* (Department of Health, 2010) set out a number of aims to promote the development and improvement of services for people with autism. These include: increased understanding among the general population and health and social care professionals about autism; increased access to diagnostic services for autism; increased opportunities for people with autism to choose where they live; increased help for people with autism to find employment; and a requirement for both health services and local authorities to draw up joint plans to ensure people with autism receive the help they need. Implicit in this last aim is that services are organised in a way that facilitates the effective and efficient meeting of the needs of people with autism (the strategy was developed following the recognition that this was not the case for many people with autism). Such was the concern that these requirements were enshrined in the Autism Act (HMSO, 2009), the first ever disability-specific law in England. The impact of the act was to put a duty on the government to produce the strategy referred to above and to provide strategic guidance to local authorities and health bodies to implement the strategy by 2010. This guideline and the recommendations for the effective organisation and delivery of care are therefore developed in the context of the Department of Health's strategy (2010). A key purpose of this chapter is to provide the evidence base to underpin the most effective and efficient means to organise and deliver services for people with autism.

The effective organisation and delivery of services has to be built not only on an appropriate evidence base but also has to be guided by a number of key principles concerning the overall care and treatment, which are informed by a full understanding of the nature of autism and the impact that it has on people's lives. This approach has been developed in a number of related NICE mental health guidelines; for example, the recent guideline *Common Mental Health Disorders: Identification and Pathways to Care* (NICE, 2011b; NCCMH, 2011), which not only sets out recommendations on the efficient organisation and delivery of care for people with depression and anxiety disorders, but is based on a set of principles (which are set out in the relevant NICE guidelines from which the *Common Mental Health Disorders* guideline was developed) concerning the manner in which people with mental health problems are understood and treated by health services, which in turn has implications for the organisation and delivery of care. Other NICE guidance, in particular the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming) currently under development, provides further recommendations on the delivery of care from the perspective of service users of

adult mental health services. This is important for the development of recommendations for the organisation and delivery of care for adults with autism because if they are not situated within a set of overarching principles to promote further understanding of the needs of people with autism, the recommendations could fall short of their aim of improving the quality of care.

While there is no doubt that guidance on the development and organisation of care for people with autism is needed, it is nonetheless very challenging to develop. In significant part this relates to the very limited evidence base on the organisation and delivery of healthcare, a problem not limited to mental health (see NCCMH, 2011 for an overview). In addition the very wide range of problems in adults with autism, the different nature of the presentation of these problems and the needs for care that arise from them, adds considerably to the challenge. Guidance on the organisation and delivery of care has to encompass the needs of people with autism with moderate or severe intellectual disabilities (cared for mainly in the learning disability services), those with milder intellectual disabilities and those with normal intellectual ability. 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.

The approach taken in this chapter was first to attempt to identify high quality evidence drawn from studies of populations with autism, or the families and carers of people with autism, that could inform principles underlying the the care and treatment of adults with autism that were not covered in Chapter 4. As can be seen in Sections 6.2, 6.3 and **Error! Reference source not found.** very little direct evidence on these issues and on clinical care pathways was identified. However, evidence on the settings for care was available (see Section 6.5). In the absence of evidence to support the development of recommendations on the principles of care and the organisation of care, Section 6.3 reviewedthe evidence base for the *Service User Experience of Adult Mental Health* draft NICE guidance (NCCMH, forthcoming) and Section 6.4 reviewed the recommendations in the NICE guideline on *Common Mental Health Disorders* (NICE, 2011a). This use of the latter involves the process of adoption and adaptation developed for that guideline (see Chapter 3 and NCCMH, 2011, for a fuller account of the method).

6.2 REVIEW OF EVIDENCE FOR THE ORGANISATION AND DELIVERY OF CARE

6.2.1 Clinical review protocol (organisation and delivery of care)

A summary of 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 17(the full review protocol can be found in Appendix 8 and further information about the search strategy can be found in Appendix 9).

6.2.2 Extrapolation

The GDG took the view that with limited primary data of good quality (for example, RCTs and observational studies) for adults with autism, it might be necessary to extrapolate from other populations. Extrapolation was performed in cases where the review question was considered important to the GDG and where primary data for adults with autism was judged to be insufficient. For the organisation and delivery of care, the decision was made to extrapolate from an intellectual disabilities population. Extrapolation was performed on the basis that the extrapolated population shared common characteristics with the primary adult autism population (for example, age, gender, severity of disorder), where the harms were similar for the extrapolated dataset as for the primary dataset, and where the outcomes were similar across trials. Extrapolation was only performed where the data quality was equivalent and the same standards were applied for assessing and evaluating the evidence from adults with intellectual disabilities, as for the primary data from adults with autism. Extrapolated data were recognised as lower quality evidence than data from adults with autism and this is reflected within the GRADE system, with outcomes using extrapolated populations downgraded because of indirectness.

Table 17: Clinical review protocol for the review of organisation and delivery of care

Component	Description
Review question	What are the effective models for the delivery of care to people with autism including:- • the structure and design of care pathways? • systems for the delivery of care (for example, case management)? • advocacy services? (CQ – E1) For adults with autism, what are the essential elements in the effective provision of: • support services for the individual (including accessing and using services)? • day care? • residential care? (CQ – E2)
Sub-question	None
Objectives	To evaluate the components and effectiveness of different models for the delivery of care
Criteria for considering studies for the review	

• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental disorder). Consideration should be given to the specific needs of: • people with coexisting conditions • women • older people • people from black and minority ethnic groups • transgender people Excluded groups include: • children (< 18 years of age) Where data from adult autism populations was not sufficient, the GDG decided that extrapolating from an intellectual disabilities population was valid.
• Intervention(s)	• **Case co-ordination models** (for example, case management; collaborative care; key worker systems) • **Advocacy and support services** • **Multi-disciplinary team models (**for example, specialist assessment teams; specialist community teams; assertive community treatment teams) • **Models of care delivery** (for example, stepped care, clinical care pathways) • **Day care services (**including the model and content of services) • **Residential care** (including the model and content of services
• Comparison	Treatment as usual, standard care or other interventions
• Critical outcomes	Outcomes involving core features of autism (social interaction, communication, repetitive interests/activities); overall autistic behaviour; management of challenging behaviour; continuity of care, satisfaction with treatment, engagement, and healthcare utilisation (including access to treatment)
• Study design	• RCTs The GDG agreed by consensus that where there were no RCTs found in the evidence search, or the results from the RCTs were inconclusive, that the following studies would be included in the review of evidence: • observational • quasi-experimental • case series
• Minimum sample size	• RCT/observational/quasi-Experimental studies: N = 10 per arm (ITT) • Case series studies: N = 10 in total 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, tertiary, health and social care and healthcare settings (including prisons and forensic services) • Others in which NHS services are funded or provided, or NHS professionals are working in multi-agency teams
Electronic databases	AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, Medline, PsycINFO, Sociological Abstracts, SSA
Date searched	Systematic reviews: 1995 up to 09/09/2011.

	RCT, QE, OS, case-series: inception of database up to 09/09/2011.
Searching other resources	Hand-reference searching of retrieved literature

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.
	• Narratively review literature that takes into consideration any amendments due to common mental health disorders.
	• 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 co-existing conditions?
	  • age
	  • the presence of sensory sensitivities (including pain thresholds)
	  • IQ
	  • language level

Note. autism = autism spectrum disorders; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; RCT = Randomised Controlled Trial; QE = Quasi-Experiemental; OS = Observational Study; AEI = Australian Education Index; AMED = Allied and Complementary Medicine; ASSIA = Applied Social Services Index and Abstracts; BEI = British Education Index; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts and Reviews of Effectiveness; Embase = Excerpta Medica database; ERIC = Education Resources in Curriculum; Medline = Biomedical Information Database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

6.3 REVIEW OF PRINCIPLES UNDERPINNING EFFECTIVE ORGANISATION AND DELIVERY OF CARE FOR ADULTS WITH AUTISM

6.3.1 Methodological considerations

In reviewing the evidence in this section the GDG followed the methods outlined in Chapter 3 supplemented by the methodological considerations in Sections **Error! Reference source not found.** of this chapter. The GDG drew on three key sources of evidence:

- The experience of adults with autism and their families and carers as reviewed in Chapter 4.
- A review of the methods used and the evidence base in the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming).

When reviewing the *Service User Experience in Adult Mental Health* draft NICE guidance, a key consideration was that the evidence reviewed was for populations with mental health problems and as such were not directly relevant to the experience of many, if not all adults, with autism. In light of this the GDG considered that the

evidence was *potentially* relevant to autism and might be of value in providing a set of principles underpinning any recommendations for the organisation and delivery of care for adults with autism. In identifying those recommendations the GDG were guided by a further four considerations:

- the evidence should have real value in improving services for people with autism
- the development of any recommendation based on this evidence in the autism guideline should facilitate the understanding, uptake of integration of other recommendations in the guideline
- the inclusion of the recommendation based on this evidence in the autism guideline should only be necessary where recommendations based on more direct sources of evidence could not be made
- the inclusion of the recommendation based on this evidence in the autism guideline should not lead to misrepresentation of the original guideline(s) from which it was drawn, or other recommendations developed for this guideline.

As described above, the direct evidence that related to the principles of care was the review of the experience of adults with autism and their families and carers as set out in Chapter 4.

6.3.2 Review of the evidence

The GDG reviewed the evidence base from the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming). As described above a key consideration was whether or not the evidence allowed for the identification of an area of concern and the subsequent development of a recommendation.

6.3.3 Clinical summary of evidence

The GDG drew on two evidence sources in developing the recommendations in this section; the *Service User Experience in Adult Mental Health* draft NICE guidance (NCCMH, forthcoming) and the review of the evidence in Chapter 4 on experience of care of adults with autism and their families and carers. The underlying evidence is described fully in the *Service User Experience in Adult Mental Health* draft NICE guidance and Chapter 4. The GDG considered these two evidence sources and identified one area concerning the role and identification of health and social care staff that had been identified in the evidence base of the *Service User Experience in Adult Mental Health* draft NICE guidance but not in Chapter 4, and which the GDG considered to be of importance.

6.3.4 From evidence to recommendation

In developing the recommendation, the GDG recognised the importance of clarity around the identification of staff and the roles they perform. They were of the view that when considered alongside the nature of the communication problems associated with autism, this required staff to be clear about their role and the nature

of any interventions provided because this would help to facilitate the uptake of other recommendations in this guideline.

6.3.5 Recommendation

Principles for working with adults with autism and their families and carers

6.3.5.1 All health and social care professionals providing care and treatment to adults with autism and their families or carers should:

- ensure that they are easily identifiable (for example, by producing or displaying appropriate identification) and approachable
- clearly communicate their role and function
- address the person using the name and title they prefer
- clearly explain any clinical language and check that the person with autism understands what is being said
- take into account communication needs, including those of people with intellectual disability, sight or hearing problems or language difficulties and provide independent interpreters[31] or communication aids if required.

6.4 CLINICAL CARE PATHWAYS

6.4.1 Introduction

As set out in the introduction the Autism Strategy (Department of Health, 2010), which followed the Autism Act (HMSO, 2009), places a requirement on local health services and local authorities to develop systems for the efficient and effective delivery of care for people with autism. The commonly accepted way to do this is develop a set of services that meet the identified needs of people for autism. These services can be seen as the components of an overall system which when linked together in an effective manner provide something more than the sum of the individual parts.

It has long been argued that the effective and efficient organisation of healthcare systems is associated with better outcomes and much of the effort of managers and funders of healthcare is focused on the re-organisation of healthcare systems. Although there is considerable uncertainty about the best methods by which to organise healthcare systems, in recent years a consensus has emerged to support the development of clinical care pathways as one model for doing this (Whittle & Hewison, 2007; Vanhaecht *et al*., 2007), including interest in the field of mental health (Evans-Lacko *et al*., 2008).[32]

[31] Someone who does not have a personal relationship with the person with autism.

[32] This section draws on the description of the background to care pathways in the *Common Mental Health Disorders* guideline (NCCMH, 2011).

Recent developments in the NHS have supported the development of clinical care pathways for the organisation of care, and discussions are currently underway as to whether these may also form the basis for the future funding of mental healthcare (see HoNOS-PbR[33]). While there is general agreement about the potential advantages for clinical care, there is less evidence for benefits such as changes in professional practice, more efficient care, and more informed and empowered patients (Emmerson *et al*., 2006; Dy *et al*., 2005). Within specific areas of mental health there is emerging evidence, for example, in the area of collaborative care for depression (Bower *et al*., 2006; Gilbody *et al*., 2006), but precise methods for the organisation of care across the whole range of mental healthcare have not been well developed.

Historically, the development of care pathways has tended to focus more on the provision of specialist services and so uncertainty remains about the best way of structuring mental healthcare in primary or community care and the links between primary and secondary/specialist services. There is also some emerging evidence (NCCMH, 2010b) demonstrating that integration (for example, of physical and mental healthcare for people with depression) can bring real benefits.

Clinical care pathways (also referred to as 'critical pathways', 'integrated care pathways' or, simply, 'care pathways') are defined for the purpose of this guideline as systems that are designed to improve the overall quality of healthcare by standardising the care process. In doing so, they seek to promote organised, efficient patient care, based on best evidence, which is intended to optimise patient outcomes. Clinical care pathways are usually multidisciplinary in structure, and importantly, are focused on a specific group of service users. These service users have a broadly predictable clinical course in which different interventions provided are defined, optimised and sequenced in a manner appropriate to the needs of the service users and the setting in which they are provided.

A number of recent developments in the NHS in the UK have supported the development of clinical care pathways. Of particular note is the development of integrated care pathways in NHS Scotland (which has seen the development of locally agreed multidisciplinary and multi-agency practice, including pathways for mental health services[34]). In a recently proposed reorganisation of the NHS by Lord Darzi,[35] considerable emphasis was also placed on care pathways as a means to improve healthcare.

[33] http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Managingyourorganisation/Financeand planning/NHSFinancialReforms/DH_4137762

[34] http://www.nhshealthquality.org/mentalhealth/projects/4/Integrated_Care_Pathways.html

[35] http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/ DH_085825

However, the evidence for the effectiveness of care pathways remains uncertain (Emerson *et al*., 2006; Dy *et al*., 2005). This may be a particular problem in mental health where coexisting conditions (including mental and physical health problems), and considerable difference in severity and uncertainty about treatment options, mean that specifying interventions for defined patient groups can be challenging and with consequent uncertainty about the benefits (Wilson *et al*., 1997; Panella *et al*., 2006).

With the possible exception of the developments in Scotland (described above) there has been little systematic development of care pathways in the NHS, although it could be argued that the IAPT[36] (CSIP, 2007) stepped care model, with its clear focus on evidence-based psychological interventions, is a form of care pathway, albeit without an explicit claim to such. Outside the field of common mental disorders, the work of the National Treatment Agency on models of care for alcohol misuse has something in common with the care pathway model (Department of Health, 2006a). More recently, the development of care clusters in mental health, with the intention that such clusters form future funding schemes through Payment by Results suggest that care pathways will be an increasing aspect of care in the NHS (HoNOS-PbR[37]).

[36] http://www.iapt.nhs.uk/

[37] http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Managingyourorganisation/Financeandplanning/NHSFinancialReforms/DH_4137762

6.4.2 Studies considered

No studies on care pathways for people with autism were identified, therefore additional sources of evidence were required. The primary source of evidence for this guideline was the *Common Mental Health Disorders* guideline (NCCMH, 2011) supplemented by the evidence in Chapter 4 of this guideline.

6.4.3 Methodological considerations

In reviewing the evidence in this section the GDG followed the methods outlined in Chapter 3 supplemented by the methodological considerations in Sections **Error! Reference source not found.** and 6.3.1 of this chapter, adapted for the review of care pathways for people with autism.

6.4.4 Review of the evidence

The GDG reviewed recommendations from the *Common Mental Health Disorders* guideline (NICE, 2011). The GDG first compiled a list of recommendations from that guideline that could potentially be included in this current guideline – 23 in total (see Table 18). After further consideration, and based on a consideration of the principles set out in section 6.4.1 above,, the GDG decided on nine recommendations from this initial list that would be included in this guideline (see Table 19). The GDG then adapted the recommendations from the *Common Mental Health Disorders* guideline for final inclusion in this guideline (see Table 20). The rationale for why certain elements of the recommendations were adapted is explained in Section 6.4.6.

Table 18: Initial list of potential recommendations from the *Common Mental Health Disorders* guideline for inclusion

1. Primary and secondary care clinicians, managers and commissioners should collaborate to develop local care pathways (see also section 1.5) that promote access to services for people with common mental health disorders by: • supporting the integrated delivery of services across primary and secondary care • having clear and explicit criteria for entry to the service • focusing on entry and not exclusion criteria • having multiple means (including self-referral) to access the service • providing multiple points of access that facilitate links with the wider healthcare system and community in which the service is located.
2. Provide information about the services and interventions that constitute the local care pathway, including the: • range and nature of the interventions provided • settings in which services are delivered • processes by which a person moves through the pathway • means by which progress and outcomes are assessed • delivery of care in related health and social care services.
3. When providing information about local care pathways to people with common mental health disorders and their families and carers, all healthcare professionals should:

- take into account the person's knowledge and understanding of mental health disorders and their treatment
- ensure that such information is appropriate to the communities using the pathway.

4. Provide all information about services in a range of languages and formats (visual, verbal and aural) and ensure that it is available from a range of settings throughout the whole community to which the service is responsible.

5. Primary and secondary care clinicians, managers and commissioners should collaborate to develop care pathways (see also section 1.5) that promote access to services for people with common mental health disorders by:

- supporting the integrated delivery of services across primary and secondary care
- having clear and explicit criteria for entry to the service
- focusing on entry and not exclusion criteria
- having multiple means (including self-referral) to access the service
- providing multiple points of access that facilitate links with the wider healthcare system and community in which the service is located

6. Primary and secondary care clinicians, managers and commissioners should collaborate to develop local care pathways (see also section 1.5) that promote access to services for people with common mental health disorders from a range of socially excluded groups including:

- black and minority ethnic groups
- older people
- those in prison or in contact with the criminal justice system
- ex-service personnel.

7. Support access to services and increase the uptake of interventions by:

- ensuring systems are in place to provide for the overall coordination and continuity of care of people with common mental health disorders
- designating a healthcare professional to oversee the whole period of care (usually a GP in primary care settings).

8. Support access to services and increase the uptake of interventions by providing services for people with common mental health disorders in a variety of settings. Use an assessment of local needs as a basis for the structure and distribution of services, which should typically include delivery of:

- assessment and interventions outside normal working hours
- interventions in the person's home or other residential settings
- specialist assessment and interventions in non-traditional community-based settings (for example, community centres and social centres) and where appropriate, in conjunction with staff from those settings
- both generalist and specialist assessment and intervention services in primary care settings.

9. Primary and secondary care clinicians, managers and commissioners should consider a range of support services to facilitate access and uptake of services. These may include providing:

- crèche facilities
- assistance with travel
- advocacy services.

10. When discussing treatment options with a person with a common mental health disorder, consider:
- their past experience of the disorder
- their experience of, and response to, previous treatment
- the trajectory of symptoms
- the diagnosis or problem specification, severity and duration of the problem
- the extent of any associated functional impairment arising from the disorder itself or any chronic physical health problem
- the presence of any social or personal factors that may have a role in the development or maintenance of the disorder
- the presence of any comorbid disorders.

11. When discussing treatment options with a person with a common mental health disorder, provide information about:
- the nature, content and duration of any proposed intervention
- the acceptability and tolerability of any proposed intervention
- possible interactions with any current interventions
- the implications for the continuing provision of any current interventions.

12. When making a referral for the treatment of a common mental health disorder, take account of patient preference when choosing from a range of evidence-based treatments.

13. When offering treatment for a common mental health disorder or making a referral, follow the stepped-care approach, usually offering or referring for the least intrusive, most effective intervention first (see figure 1).

14. Local care pathways should be developed to promote implementation of key principles of good care. Pathways should be:
- negotiable, workable and understandable for people with common mental health disorders, their families and carers, and professionals
- accessible and acceptable to all people in need of the services served by the pathway
- responsive to the needs of people with common mental health disorders and their families and carers
- integrated so that there are no barriers to movement between different levels of the pathway
- outcomes focused (including measures of quality, service-user experience and harm).

15. Responsibility for the development, management and evaluation of local care pathways should lie with a designated leadership team, which should include primary and secondary care clinicians, managers and commissioners. The leadership team should have particular responsibility for:
- developing clear policy and protocols for the operation of the pathway
- providing training and support on the operation of the pathway
- auditing and reviewing the performance of the pathway.

16. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that promote a stepped-care model of service delivery that:
- provides the least intrusive, most effective intervention first
- has clear and explicit criteria for the thresholds determining access to and movement

between the different levels of the pathway
- does not use single criteria such as symptom severity to determine movement between steps
- monitors progress and outcomes to ensure the most effective interventions are delivered and the person moves to a higher step if needed.

17. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that promote a range of evidence-based interventions at each step in the pathway and support people with common mental health disorders in their choice of interventions.

18. All staff should ensure effective engagement with families and carers, where appropriate, to:
- inform and improve the care of the person with a common mental health disorder
- meet the identified needs of the families and carers.

19. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that promote the active engagement of all populations served by the pathway. Pathways should:
- offer prompt assessments and interventions that are appropriately adapted to the cultural, gender, age and communication needs of people with common mental health disorders
- keep to a minimum the number of assessments needed to access interventions.

21. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that provide an integrated programme of care across both primary and secondary care services. Pathways should:
- minimise the need for transition between different services or providers
- allow services to be built around the pathway and not the pathway around the services
- establish clear links (including access and entry points) to other care pathways (including those for physical healthcare needs)
- have designated staff who are responsible for the coordination of people's engagement with the pathway.

22. Primary and secondary care clinicians, managers and commissioners should work together to ensure effective communication about the functioning of the local care pathway. There should be protocols for:
- sharing and communicating information with people with common mental health disorders, and where appropriate families and carers, about their care
- sharing and communicating information about the care of services users with other professionals (including GPs)
- communicating information between the services provided within the pathway
- communicating information to services outside the pathway.

23. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that have robust systems for outcome measurement in place, which should be used to inform all involved in a pathway about its effectiveness. This should include providing:
- individual routine outcome measurement systems

• effective electronic systems for the routine reporting and aggregation of outcome measures • effective systems for the audit and review of the overall clinical and cost-effectiveness of the pathway.

Table 19: Revised list of recommendations from the *Common Mental Health Disorders* guideline to be included

3. When providing information about local care pathways to people with common mental health disorders and their families and carers, all healthcare professionals should: • take into account the person's knowledge and understanding of mental health disorders and their treatment • ensure that such information is appropriate to the communities using the pathway.
7. Support access to services and increase the uptake of interventions by: • ensuring systems are in place to provide for the overall coordination and continuity of care of people with common mental health disorders • designating a healthcare professional to oversee the whole period of care (usually a GP in primary care settings).
11. When discussing treatment options with a person with a common mental health disorder, provide information about: • the nature, content and duration of any proposed intervention • the acceptability and tolerability of any proposed intervention • possible interactions with any current interventions • the implications for the continuing provision of any current interventions.
14. Local care pathways should be developed to promote implementation of key principles of good care. Pathways should be: • negotiable, workable and understandable for people with common mental health disorders, their families and carers, and professionals • accessible and acceptable to all people in need of the services served by the pathway • responsive to the needs of people with common mental health disorders and their families and carers • integrated so that there are no barriers to movement between different levels of the pathway • outcomes focused (including measures of quality, service-user experience and harm).
15. Responsibility for the development, management and evaluation of local care pathways should lie with a designated leadership team, which should include primary and secondary care clinicians, managers and commissioners. The leadership team should have particular responsibility for: • developing clear policy and protocols for the operation of the pathway • providing training and support on the operation of the pathway • auditing and reviewing the performance of the pathway.
17. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that promote a range of evidence-based interventions

at each step in the pathway and support people with common mental health disorders in their choice of interventions.
18. All staff should ensure effective engagement with families and carers, where appropriate, to: • inform and improve the care of the person with a common mental health disorder • meet the identified needs of the families and carers.
20. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that respond promptly and effectively to the changing needs of all populations served by the pathways. Pathways should have in place: • clear and agreed goals for the services offered to a person with a common mental health disorder • robust and effective means for measuring and evaluating the outcomes associated with the agreed goals • clear and agreed mechanisms for responding promptly to identified changes to the person's needs.
21. Primary and secondary care clinicians, managers and commissioners should work together to design local care pathways that provide an integrated programme of care across both primary and secondary care services. Pathways should: • minimise the need for transition between different services or providers • allow services to be built around the pathway and not the pathway around the services • establish clear links (including access and entry points) to other care pathways (including those for physical healthcare needs) • have designated staff who are responsible for the coordination of people's engagement with the pathway.

Table 20: Final list of recommendations from the *Common Mental Health Disorders* guideline after adaptation

3. When providing information about local care pathways to adults with autism and their families and carers, all professionals should: • take into account the person's knowledge and understanding of autism and its care and treatment • ensure that such information is appropriate to the communities using the pathway. **(Adapted)**
7. Support access to services and increase the uptake of interventions by: • ensuring systems (for example, care coordination or case management) are in place to provide for the overall coordination and continuity of care for adults with autism • designating a professional to oversee the whole period of care (usually a member of the primary healthcare team for those not in the care of a specialist autism team or mental health or learning disability service). **(Adapted)**
11. When discussing treatment or care interventions with adults with autism, provide information about:

- the nature, content and duration of any proposed intervention
- the acceptability and tolerability of any proposed intervention
- possible interactions with any current interventions and possible side effects
- the implications for the continuing provision of any current interventions

(Adapted)

14. Local care pathways should be developed to promote implementation of key principles of good care. Pathways should be:

- negotiable, workable and understandable for adults with autism, their families and carers, and professionals
- accessible and acceptable to all people in need of the services served by the pathway
- responsive to the needs of adults with autism and their families and carers
- integrated so that there are no barriers to movement between different levels of the pathway
- outcome focused (including measures of quality, service user experience and harm)

(Adapted)

15. Autism strategy groups should be responsible for developing, managing and evaluating local care pathways. The group should appoint a lead professional responsible for the local autism care pathway. The aims of the strategy group should include:

- developing clear policy and protocols for the operation of the pathway
- ensuring the provision of multi-agency training about signs and symptoms of autism and training and support on the operation of the pathway
- making sure the relevant professionals (health care, social care, housing, employment and the third sector) are aware of the local autism pathway and how to access services
- supporting the integrated delivery of services across all care settings
- supporting the smooth transition to adult services for young people going through the pathway
- auditing and reviewing the performance of the pathway

(Adapted)

17. The autism strategy group should design local care pathways that promote a range of evidence-based interventions at each step in the pathway and support adults with autism in their choice of interventions.

(Adapted)

20. The autism strategy group should design local care pathways that respond promptly and effectively to the changing needs of all populations served by the pathways. Pathways should have in place:

- clear and agreed goals for the services offered to adults with autism
- robust and effective means for measuring and evaluating the outcomes associated with the agreed goals
- clear and agreed mechanisms for responding promptly to identified changes to people's needs.

(Adapted)

21. The autism strategy group should design local care pathways that provide an integrated programme of care across all care settings. Pathways should:

- minimise the need for transition between different services or providers
- allow services to be built around the pathway and not the pathway around the services
- establish clear links (including access and entry points) to other care pathways (including those for physical healthcare needs)
- have designated staff who are responsible for the coordination of people's engagement with the pathway.

6.4.5 Clinical summary of evidence

The GDG drew from two evidence sources in developing the recommendations in this section; the *Common Mental Health Disorders* guideline and the review of the evidence in Chapter 4 on experience of care for people with autism and their families and carers. The underlying evidence is described fully in *Common Mental Health Disorders* (NCCMH, 2011) guideline and Chapter 4. The GDG considered these two evidence sources and identified a number of recommendations (see Table 19) that in the view of the GDG were of importance in improving the care of people with autism and their families and carers. The GDG then reviewed the recommendations and made a decision on whether to adapt or adopt the recommendations based on methodological principles as developed in the *Common Mental Health Disorders* guideline (NCCMH, 2011) (see Table 20). The detail of the adaptations and the rationale for their development are given below in Section 6.5.6.

6.4.6 From evidence to recommendations

The process of moving from evidence to recommendations was based on a consideration as to whether a recommendation drawn from the *Common Mental Health Disorders* guideline would add value to the overall guideline in line with the key considerations set out in Section 6.2.1 of this chapter.

Only minor adaptations were made to recommendations 3, 11, 14, 17 and 20 (the numbers refer to Table 19 and Table 20) in terms of terminology more suitable to the context of this guideline and minor changes in style.

The GDG made some more extensive adaptations to recommendations 7 and 15. For recommendation 7, the GDG made adaptations that made the recommendation more suitable to the context of autism, for example by specifying that the professional overseeing the whole period of care should be a member of the primary care team for those not in the care of a specialist autism team or mental health or learning disability service.

For recommendation 15, the GDG wished to make a number of additions that were specific to developing local care pathways for adults with autism, including

appointing a lead professional responsible for the pathway, providing training about signs and symptoms of autism, making all professionals aware of the pathway and how to access services, supporting the integrated delivery of services across all care settings, and facilitating a seamless transition for people moving from child and adolescent services to adult services.

In addition, when considering the evidence in Chapter 4 on the experience of care for both adults with autism and their families and carers and the need to provide prompt and efficient access to services, the GDG drew on their expert knowledge and experience to develop two further recommendations to directly address the problems of access to services. This included a recommendation on a single point of referral and one on improving access for a range of groups such as people with coexisting mental and physical problem (including substance misuse), women, people with intellectual disabilities, older people, people from black and minority ethnic groups, transgender people, homeless people, the traveller community, those in the criminal justice system and parents with autism.

The GDG also made recommendations on the need for a local autism multi-agency strategy group, and the structure and function of multidisciplinary teams for the care of adults with autism based on their evaluation of the complexity of the tasks and poor access to specialist assessment services described in Chapter 4 of this guideline. The recommendation on the multi-agency strategy group was adopted from the *Autism: recognition, referral and diagnosis of children and young people on the autism spectrum* (NICE, 2011a), and a new recommendation made regarding how this team could be adapted for adults with autism.

6.4.7 Recommendations

Structures for the organisation and delivery of treatment and care

6.4.7.1 A local autism multi-agency strategy group should be set up, with managerial, commissioner and clinical representation from child health and mental health services, education, social care, parent and carer service users and the voluntary sector.[38]

6.4.7.2 The local autism multi-agency strategy group should have representation from the following services in addition to those specified in recommendation 6.4.7.1: primary healthcare, learning disabilities services, the criminal justice system, housing and, employment. There should be meaningful representation from people with autism and their families or carers.

6.4.7.3 In each area a specialist community-based multidisciplinary autism team should be established. The core membership should include:

- clinical psychologists

[38] Adopted from 'Autism: recognition, referral and diagnosis of children and young people on the autism spectrum' (NICE clinical guideline 128). Available from www.nice.org.uk/guidance/CG128

- nurses
- occupational therapists
- psychiatrists
- social workers
- speech and language therapists
- support workers (focused on providing employment, further education, residential advocacy, social inclusion interventions and personal and community safety skills).

6.4.7.4 The multidisciplinary autism team should have a key role in providing:

- specialist diagnostic and assessment services
- specialist care and treatment services
- coordination of specialist care and treatment while in the service
- advice and training to other health and social care professionals on the diagnosis, assessment, care and treatment of adults with autism
- support in accessing and maintaining housing, educational and employment services
- support to families and carers
- support, treatment and care for adults with autism living in specialist residential accommodation
- training, support and consultation for staff who care for adults with autism in residential and community settings.

Developing local care pathways

6.4.7.5 Local care pathways should be developed to promote implementation of key principles of good care. Pathways should be:

- negotiable, workable and understandable for adults with autism, their families and carers, and professionals
- accessible and acceptable to all people in need of the services served by the pathway
- responsive to the needs of adults with autism and their families and carers
- integrated so that there are no barriers to movement between different levels of the pathway
- outcome focused (including measures of quality, service user experience and harm). [39]

[39] Adapted from 'Common mental health disorders: identification and pathways to care' (NICE clinical guideline 123). Available from: www.nice.org.uk/guidance/CG123.

6.4.7.6 Autism strategy groups should be responsible for developing, managing and evaluating local care pathways. The group should appoint a lead professional responsible for the local autism care pathway. The aims of the strategy group should include:

- developing clear policy and protocols for the operation of the pathway
- ensuring the provision of multi-agency training about signs and symptoms of autism and training and support on the operation of the pathway
- making sure the relevant professionals (health and social care, housing, employment and the third sector) are aware of the local autism pathway and how to access services
- supporting the integrated delivery of services across all care settings
- supporting the smooth transition to adult services for young people going through the pathway
- auditing and reviewing the performance of the pathway.[47]

6.4.7.7 The autism strategy group should develop local care pathways that promote access to services for all adults with autism, including for people from certain groups such as:

- people with coexisting mental and physical conditions (including substance misuse)
- women
- people with intellectual disabilities
- older people
- people from black and minority ethnic groups
- transgender people
- homeless people
- people from the traveller community
- people in the criminal justice system
- parents with autism.

6.4.7.8 There should be a single point of referral (including self-referral) to specialist services for adults with autism.

6.4.7.9 When providing information about local care pathways to adults with autism and their families and carers, all professionals should:

- take into account the person's knowledge and understanding of autism and its care and treatment
- ensure that such information is appropriate to the communities using the pathway.[40]

[40] Adapted from 'Common mental health disorders: identification and pathways to care' (NICE clinical guideline 123). Available from: www.nice.org.uk/guidance/CG123.

6.4.7.10 The autism strategy group should design local care pathways that promote a range of evidence-based interventions at each step in the pathway and support adults with autism in their choice of interventions.[48]

6.4.7.11 The autism strategy group should design local care pathways that respond promptly and effectively to the changing needs of all populations served by the pathways. Pathways should have in place:

- clear and agreed goals for the services offered to adults with autism
- robust and effective means for measuring and evaluating the outcomes associated with the agreed goals
- clear and agreed mechanisms for responding promptly to identified changes to people's needs.[48]

6.4.7.12 The autism strategy group should design local care pathways that provide an integrated programme of care across all care settings. Pathways should:

- minimise the need for transition between different services or providers
- allow services to be built around the pathway and not the pathway around the services
- establish clear links (including access and entry points) to other care pathways (including those for physical healthcare needs)
- have designated staff who are responsible for the coordination of people's engagement with the pathway.[41]

6.4.7.13 Support access to services and increase the uptake of interventions by:

- ensuring systems (for example, care coordination or case management) are in place to provide for the overall coordination and continuity of care for adults with autism
- designating a professional to oversee the whole period of care (usually a member of the primary healthcare team for those not in the care of a specialist autism team or mental health or learning disability service).[48]

6.4.8 Research recommendation

6.4.8.1 What structure and organisation of specialist autism teams are associated with improvements in care for people with autism?

Why this is important

The Department of Health's autism strategy (2010)[42] proposes the introduction of a range of specialist services for people with autism; these will

[41]Adapted from 'Common mental health disorders: identification and pathways to care' (NICE clinical guideline 123). Available from: www.nice.org.uk/guidance/CG123.

[42] Department of Health (2010) Fulfilling and rewarding lives: the strategy for adults with autism. Available from: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_113369

usually be built around specialist autism teams. However, there is little evidence to guide the establishment and development of these teams. There is uncertainty about the precise nature of the population to be served (all people with autism or only those who are 'high functioning'), the composition of the team, the extent of the team's role (for example, diagnosis and assessment only, a primarily advisory role or a substantial care coordination role), the interventions provided by the team and the team's role and relationship with regard to non-statutory care providers. Therefore it is likely that in the near future a number of different models will be developed, which are likely to have varying degrees of success in meeting the needs of people with autism. Given the significant expansion of services, this presents an opportunity for a large-scale observational study, which should provide important information on the characteristics of teams associated with positive outcomes for people with autism in terms of access to services, effective coordination of care and outcomes for service users and their families.

6.5 SETTINGS FOR CARE

6.5.1 Introduction

Care for people with autism in England and Wales is delivered in a number of different settings. For some people, particularly those with more severe disabilities, a range of residential services provided 24-hour care, often integrated with services for people with intellectual disabilities. The precise numbers are not known and systems for supporting these individuals vary considerably. In some few cases there are residential services for people with autism. For this group of individuals with severe disabilities there has been a move over the last 20 to 30 years away from care in large institutions to care in smaller community-based settings. Some settings may have an explicit educational function. However, for the majority of people with autism they live in unsupported residential accommodation either with their family or friends but often alone and potentially socially isolated. This can place a large burden on care on families and carers. A limited range of day facilities and employment services for people with autism are offered, again often integrated with those for people with intellectual disabilities. For people with autism of normal intelligence there is often very limited access to specialist services such a diagnostic or community support services. Care pathways, as noted above, are not well developed. This review attempts to address the a number of question about the nature of the settings of care for people with autism, including the nature of the environment and what support services might be provided to services users, carers and staff in order to ensure good outcomes.

6.5.2 Outcomes

A large number of outcomes were reported by the settings for care studies. Those that reported sufficient data to be extractable and were not excluded (see Appendix 14) are in Table 21.

Table 21: Outcomes extracted from settings for care studies

Category	Sub-category	Scale
Core symptoms of autism	Communication	• Vineland Adaptive Behaviour Scale (VABS)
	Social interaction	• Staff-rated social skills • VABS
Challenging behaviour	Total score	• Part 2 of the AAMD Adaptive Behavior Scale (ABS) • Problems Questionnaire (PQ)
	Irritability	• Aberrant Behaviour Checklist (ABC) Irritability subscale
	Aggression	• Modified Overt Aggression Scale (MOAS)
	Hyperactivity	• Aberrant Behaviour Checklist (ABC) Irritability subscale
	Lethargy	• Aberrant Behaviour Checklist (ABC) Irritability subscale
Adaptive behaviour		• Adaptive Behaviour Scale (ABS) • Behaviour Development Survey (modified version) • VABS

Community living skills		• Average number of skills gained across community living skills behavioural domains
Access to services		• Number of contacts with services
Satisfaction		• Lifestyle satisfaction scale (LSS) • Satisfaction Questionnaire of Seltzer and Seltzer's (1978) Community Adjustment Scale
Social inclusion		• Diary self-report on the number of trips outside the home • Number of community amenities used in past months
Family contact		• Developmental Disabilities Quality Assurance Questionnaire (DDQAQ)
Quality of life		• Behavioural observations of quality of life • Quality of Life Questionnaire (QoL-Q) • The Questionnaire on Quality of Life

6.5.3 Studies considered

No RCTs in adults with autism were found that met the eligibility criteria for this review. However, one observational study (N = 12) was found (Siaperas & Beadle-Brown, 2006 [SIAPERAS2006]). Based on GDG expert judgement and extrapolation rules data from an intellectual disabilities population was considered. Two RCTs (N= 89) were found for adults with intellectual disability (Hassiotis *et al*., 2009 [HASSIOTIS2009}; Raghavan *et al*., 2009 [RAGHAVAN2009]). One quasi-experimental parallel group controlled study (N = 20) (Schalock *et al*., 1984 [SCHALOCK1984]), ten observational parallel group studies (N1514) (Barlow & Kirby, 1991; Chou *et al*., 2008 [CHOU2008]; Cullen *et al*., 1995 [CULLEN1995]; Dagnan *et al*., 1994 [DAGNAN1994A]; Holburn *et al*., 2004 [HOLBURN2004]; Kearney *et al*., 1995 [KEARNEY1995]; McConkey *et al*., 2007 [MCCONKEY2007]; Molony & Taplin, 1990 [MOLONY1990]; Schwartz, 2003 [SCHWARTZ2003]; Spreat *et al*., 1998 [SPREAT1998]) , and nine observational before-and-after studies (N = 704) were also found (Bhaumik *et al*., 2009 [BHAUMIK2009]; Bouras *et al*., 1993 [BOURAS1993]; Chou *et al*., 2011 [CHOU2011]; Dagnan *et al*., 1998 [DAGNAN1998]; Donnelly *et al*., 1996 [DONNELLY1996]; Gaskell *et al*., 1995 [GASKELL1995]; Hemming, 1983 [HEMMING1983]; Spreat & Conroy, 2002 [SPREAT2002]; Wehmeyer & Bolding, 2001 [WEHMEYER2001]. All of these studies were published in peer-reviewed journals between 1984 and 2011. In addition, 61 studies were excluded as they did not meet eligibility criteria. The most common reasons for exclusion were that the mean age of the sample was below 15 years old, the sample size was less than ten participants per arm, or data could not be extracted. Further information about included and excluded studies can be found in Appendix 14.

The before-and-after observational study in adults with autism involved an examination of the Treatment and Education of Autistic and related Communication Handicapped Children (TEACCH) approach in a residential setting (see Table 22).

Of the two RCTs in an intellectual disability population, one involved a comparison of a specialist behaviour therapy team with treatment as usual and one involved a

comparison of a liaison worker in helping to access relevant services with normal service interventions (see Table 23).

The one quasi-experimental study in adults with intellectual disabilities involved a comparison of community living skills (CLS) training within the participants' current living environment (group home or staffed apartment) with CLS training within a centre-based training environment (see Table 24).

Of the ten observational parallel group studies in an intellectual disability population, five compared residential institutions with community housing, one compared dispersed supported housing with residential homes, one compared group home with independent apartments, one compared small residential homes with institution, one compared an intermediate care placement between institution and community with direct community placement and one compared a comparison of person-centred with system-centred planning for the move from an institution into the community for adults with intellectual disability (see Table 25).

Finally, of the nine observational before-and-after studies, one reported change from baseline scores for a specialist assessment and treatment unit for challenging behaviour, six reported change from baseline scores for participants moving from an institution into the community, one compared pre-move to post-move scores for individuals placed in small scale community housing, and one compared change from baseline scores for participants who moved from more restrictive to less restrictive work or living environments (see Table 26)**.**

Table 22: Summary study characteristics for included observational studies in adults with autism

	TEACCH
No. trials (total participants)	1 (12)
Study ID	SIAPERAS2006
N/% female	4/33
Mean age	21
IQ	Not reported (all participants had mild to severe intellectual disability)
Axis I/II disorders	100% autism; 100% intellectual disability
Comparator	No comparator
Length of follow-up	6 months

Table 23: Summary study characteristics for included RCTs in adults with intellectual disabilities

	Specialist behaviour therapy team	**Liaison worker**
No. trials (Total participants)	1 (63)	1 (26)
Study Ids	HASSIOTIS2009*	RAGHAVAN2009*
N/% female	23/37	Not reported
Mean age	40 & 41	17 & 19
IQ	Not reported (N=42 with mild/moderate and N=21 with	Not reported (N=10 with mild, N=8 with moderate, and N=8

	severe/profound intellectual disability)	with severe intellectual disability)
Axis I/II disorders	100% intellectual disability	4% autism, 8% Down's syndrome, 4% cerebral palsy, 4% Joubert's syndrome and 15% epilepsy; 100% intellectual disability
Comparator	Treatment as usual	Treatment as usual
Length of follow-up	Mean of 6 months	9 months

*Efficacy data not extractable.

Table 24: Summary study characteristics for included quasi-experimental parallel group trials in adults with intellectual disabilities

	Current-living environment for community living skills training
No. trials (Total participants)	1 (20)
Study ID	SCHALOCK1984
N/% female	10/50
Mean age	31
IQ	Range not reported (mean 51)
Axis I/II disorders	100% intellectual disability
Comparator	Alternative treatment (centre-based training environment)
Length of follow-up	1 year

Table 25: Summary study characteristics for included observational parallel group studies in adults with intellectual disabilities

	Community housing	Small residential home	Dispersed supported housing	Semi-independent apartments	Intermediate care placement	Person-centred planning
No. trials (Total participants)	5 (304)	1 (248)	1 (620)	1 (247)	1 (57)	1 (38)
Study IDs	(1) BARLOW1991 (2) CULLEN1995 (3) DAGNAN1994A (4) MOLONY1990 (5) SPREAT1998	CHOU2008B	MCCONKEY2007	SCHWARTZ2003	KEARNEY1995	HOLBURN2004
N/% female	(1) 15/48 (2) Not reported (3) Not reported (4) 26/46 (5) 22/28	71/29	289/47	125/51	27/47	9/23
Mean age	(1) 29 & 33 (2) Not reported (majority 31-50) (3) 41 & 42 (4) 44 & 46 (5) 40	29-31	Not reported (61% aged under 50 years)	34	35	39
IQ	(1) Not reported (2) Not reported (more than 70% moderately or severely intellectually disabled) (3) Not reported (4) Untestable-80 (medians 45-54) (5) Not reported	Not reported (majority moderate to severe intellectual disability)	Not reported	Not reported (N=131 mild and N=116 moderate or above intellectual disability)	Not reported (3.5 % severe LD and 96.5% profound intellectual disability)	Not reported (68.4% severe/profound intellectual disability)
Axis I/II	(1)- (5) 100% intellectual	100% intellectual	100% intellectual	100% intellectual	100% intellectual	53% psychiatric

disorders	disability	disability	disability	disability	disability	diagnosis; 100% intellectual disability
Comparator	Residential institution	Institution	Residential homes	Group home	Direct community placement	System-centred planning
Length of follow-up	(1) Mean 1 and 3.5 years (time spent living in relevant setting) (2) 30 months (3) 18 months (4) 1 year (5) 4 years	Not reported	Not reported	1 year	1 year	3 years

Table 26: Summary study characteristics for included before-and-after observational studies in adults with intellectual disabilities

	Specialist assessment and treatment unit	Move from institution into community	Small scale community housing	Move from more restrictive to less restrictive work or living environment
No. trials (Total participants)	1 (34)	6 (590)	1 (49)	1 (31)
Study IDs	GASKELL1995*	(1) BHAUMIK2009* (2) BOURAS1993* (3) DAGNAN1998* (4) DONNELLY1996* (5) HEMMING1983* (6) SPREAT2002*	CHOU2011*	WEHMEYER2001*
N/% female	10/29	(1) 13/27 (2) 25/35 (3)-(5) Not reported (6) 71/40	16/33	14/45
Mean age	29	(1) 49 & 51	27	41

		(2) 46 (3) 61 (4)-(5) Not reported (6) 26-27		
IQ	Not reported	(1) Not reported (69% profound, 22% severe, 6% moderate and 2%mild intellectual disability) (2) Not reported (46% severe, 24% moderate and 30% mild intellectual disability) (3)-(5) Not reported (6) Not reported (majority have profound intellectual disability)	Not reported (31-33% severe/profound intellectual disability)	Range not reported (mean 60.25)
Axis I/II disorders	100% intellectual disability	(1) -(6) 100% intellectual disability	100% intellectual disability	100% intellectual disability
Comparator	No comparator	(1)-(6) No comparator	No comparator	No comparator
Length of follow-up	Not reported	(1) 18 months (2) 1 year (3) 53 months (4) 2 years (5) 5.5 years (6) Over 5 years	2 years	1 year

*Efficacy data not extractable.

6.5.4 Clinical evidence for community-based teams

The TEACCH approach in a residential setting

The only included study in adults with autism was an observational before-and-after study which examined the effects of the TEACCH approach in a residential setting (SIAPERAS2006). The TEACCH approach is individualised, but some common features include: strong cooperation between staff and parents; different areas designated for each activity; daily visual schedules; strong work rules, for example, 'first work then play'; a transition area; structured activities; and visual prompts. Efficacy data could not be extracted for this study. However, the authors report significant change-from-baseline score treatment effects for social abilities ($z = 3.063$; $p = 0.002$) and functional communication ($z = 3.062$; $p = 0.002$) as measured by staff-report questionnaire (based on VABS) and an observation checklist. Thus, the findings from this study are suggestive of significant positive treatment effects for the TEACCH approach (implemented in a residential setting) on core autism symptoms. However, efficacy data could not be extracted for this study and the GRADE quality rating is very low.

Specialist behaviour therapy teams

Based on the very limited evidence for settings of care for adults with autism, the GDG agreed to extrapolate from data for adults with intellectual disability. Two RCTs were included from this extrapolation population. One of which, HASSIOTIS2009, compared a specialist behaviour therapy team with treatment as usual for adults with intellectual disability and severe challenging behaviour. Unfortunately, median values and interquartile ranges were reported—this does not allow for the extraction of efficacy data and may also imply that the data were skewed. The analysis of the results is therefore by narrative review. The authors reported a significant group difference in mean transformed scores (square root of raw scores) for the Aberrant Behaviour Checklist (ABC) hyperactivity and lethargy subscales ($p = 0.008$ for both), with more adaptive scores found for participants in the specialist behaviour therapy team group. However, the ABC irritability subscale, which is the more commonly reported outcome measure for challenging behaviour, did not reveal a significant difference between participants who were treated by a specialist behaviour therapy team and participants who received treatment as usual ($p = 0.162$).

There was also one included observational (before-and-after) study, which examined the effects of a specialist assessment and treatment unit for adults with intellectual disability. GASKELL1995 examined the change-from-baseline adaptive behaviour scores following admission to the Mental Impairment Evaluation and Treatment Service (MIETS). This was a hospital-based unit that sought to prepare clients with mild intellectual disabilities and challenging behaviours for resettlement in the community. Three broad categories of interventions were used: medication, behavioural techniques (including anger management, graded exposure to stimuli

and reinforcement), and skills training (including social skills, sex education, and daily living skills). Efficacy data could not be extracted for this study. However, the authors report statistically significant change from baseline scores on the violent behaviour subscale of the ABS (II) ($Z = -3.05$; $p<0.002$).

Current living training environment compared with developmental centre group home training environment

The only included quasi-experimental study in adults with intellectual disability examined the impact of the training environment (in the participants' current living environment compared with in a developmental centre-based environment) on the acquisition of community living skills. Data were extracted from SCHALOCK1984 for the average number of skills gained across community living skills behavioural domains. Significant effects of the training environment on the number of community living skills acquired were observed (test for overall effect: $Z = 20.69$, $p<0.00001$), with participants who were trained in their current living environment acquiring a greater number of skills than participants who were trained in the developmental centre environment. The evidence from this single trial suggests that community living skills training will be more effective if delivered in the context of the participants' current living environment than if the training environment is centre-based (see Table 27). However, this evidence is indirect as it is an extrapolation from adults with intellectual disabilities, and the sample size is very small.

Table 27: Summary evidence profile for current living training environment versus centre-based training environment for teaching community living skills to adults with intellectual disabilities

Outcome	**Community living skills**
Study ID	SCHALOCK1984
Effect size	MD = 8.90 (8.06, 9.74)
Quality of evidence (GRADE)	Very low[1,2,3]
Number of studies/participants	(K = 1; N = 20)
Forest plot	1.3.1, Appendix 15

[1]Downgraded for risk of bias as the non-randomised allocation and non-blind assessment of outcome increases the risk of selection and detection bias

[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

[3]Downgraded for imprecision as the reliability and validity of the outcome measure is unclear and under-specified and the sample size is small

Liaison worker compared with normal service interventions

The second of the two included RCTs in adults with intellectual disability compared the additional help provided by a liaison worker in accessing services with normal service interventions for young people with intellectual disabilities and mental health/challenging behaviour needs and for their families. Unfortunately the data reported in this study did not allow for the extraction of efficacy data. However, the authors reported a significant group difference ($Z = -3.620$; $p = 0.001$), with the group who received the additional help of the liaison worker showing a greater number of contacts with services compared with the treatment as usual group. The group who received the additional help provided by the liaison worker also showed contact with a greater number of different services ($Z = -3.335$, $p = 0.001$) and more outcomes achieved from such contacts ($Z = -3.579$, $p = 0.001$). This single trial suggests that a liaison worker may help individuals with an intellectual disability and their families gain greater access to services. This finding is particularly interesting as the participants were all from Pakistani and Bangladeshi communities and people with intellectual disabilities and mental health needs from black and minority ethnic communities face additional problems in accessing services.

6.5.5 Clinical evidence summary for community-based teams

There was limited evidence on the effective operation of specialist community teams predominantly in the area of intellectual disability. The GDG took the view that this evidence was applicable to autism and there was evidence to support a range of functions including assessment, treatment and consultation/liaison roles.

6.5.6 From evidence to recommendations

The GDG did not find evidence to support the development of a particular model for the structure of community-based teams. However, the need for assessment and diagnostic services, to provide a focus for the coordination of care and to advise other professionals, people with autism and their families and carers, all supported the view of the GDG that community teams for autism should be developed. This was also supported by the review of experience of care in Chapter 4.

6.5.7 Clinical evidence for residential accommodation and related services

Residential institution compared with community housing

Five of the included observational (parallel group) studies in adults with intellectual disability compared outcomes for participants living in residential institutions compared to participants living in community housing.

Three studies compared adults with intellectual disability who were living in residential institutions with participants who were living in community housing on adaptive behaviour outcomes (CULLEN1995; MOLONY1990; SPREAT1998).

Consistent and statistically significant group differences were found with participants who were living in community housing showing superior scores on measures of adaptive behaviour (test for overall effect: Z=3.45, p=0.0006).

CULLEN1995 also examined the effects of accommodation on social skills and quality of life as measured by staff ratings and behavioural observations. This study failed to find evidence for a statistically significant group difference in social skills (test for overall effect: Z=1.09, p=0.28). However, limited evidence for statistically significant group differences was found on the quality of life outcome (test for overall effect: Z=8.02, p<0.00001), with participants in the community group showing superior scores.

BARLOW1991 examined the impact of accommodation on resident satisfaction as assessed with interview by the investigator, which was based on the Satisfaction Questionnaire of Seltzer and Seltzer's (1978) Community Adjustment Scale. Significant differences between the groups were found for residents' satisfaction with their social life (test for overall effect: Z = 4.27, p <0.0001) and total score for resident satisfaction (test for overall effect: Z = 2.44, p = 0.01) with the individuals living in the residential institution showing superior scores. However, for residents' satisfaction with autonomy, significant differences lay in the opposite direction with the residents in community housing showing greater satisfaction than the residents living in the institution (test for overall effect: Z = 2.18, p = 0.03).

Finally, DAGNAN1994A examined the effects of accommodation on social inclusion as measured by diary self-report on the number and features of trips outside the home. This study failed to find evidence for statistically significant group difference (test for overall effect: Z=1.48, p=0.14).

To sum up, these observational parallel group studies provide evidence for the superiority of community housing compared with residential institutions for resident satisfaction with autonomy, quality of life and adaptive behaviour outcomes (see Table 28). However, for residents' satisfaction with their social life and total satisfaction, scores were higher for participants living in a residential institution compared with participants who had moved into the community. Thus, although community living may offer beneficial effects on some measures it is not universally superior. However, it should be noted that this evidence is of a very low quality (it is indirect and the non-randomised allocation and non-blind assessment of outcome increases the risk of selection and detection bias).

Table 28: Summary evidence profile for residential institution versus community housing for adults with intellectual disabilities

Outcome	Adaptive behaviour	Satisfaction (total)	Satisfaction with social life	Satisfaction with autonomy	Social skills	Social inclusion	Quality of life
Study ID	CULLEN1995 MOLONY1990 SPREAT1998	BARLOW1991	BARLOW1991	BARLOW1991	CULLEN1995	DAGNAN1994A	CULLEN1995
Effect size	SMD = -0.48 (-0.75, -0.20)	MD = 5.60 (1.10, 10.10)	MD = 5.80 (3.14, 8.46)	MD = -1.20 (-2.28, -0.12)	MD = -5.10 (-14.31, 4.11)	MD = -3.00 (-6.99, 0.99)	MD = -12.90 (-16.05, -9.75)
Quality of evidence (GRADE)	Very low[1,2]	Very low[1,2,3]	Very low[1,2,3]	Very low[1,2,3]	Very low[1,2]	Very low[1,2,3]	Very low[1,2]
Number of studies/ participants	(K = 3; N = 224)	(K = 1; N = 29)	(K = 1; N = 29)	(K = 1; N = 29)	(K = 1; N = 100)	(K = 1; N = 36)	(K = 1; N = 100)
Forest plot	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15

[1]Downgraded for risk of bias as non-randomised allocation and non-blind assessment of outcome increases the risk of selection and detection bias
[2]Downgraded for indirectness as extrapolating from adults with intellectual disability.
[3]Downgraded for imprecision as the sample size is small.

Small residential homes compared with an institution

One of the included observational (parallel group) studies in adults with intellectual disability, CHOU2008B, compared people living in small residential homes (N = 103) to individuals living in an institution (N = 76). Data were also reported for group/community home residents (N = 69). However, those data are not extracted here as the authors' statistical analysis (which controlled for group differences in adaptive/maladaptive behaviour) suggested that the largest group differences lay with the groups selected. Limited evidence was found for significant group differences in quality of life (test for overall effect: Z = 8.57, p<0.00001), choice making (test for overall effect: Z = 12.57, p<0.00001), community inclusion (test for overall effect: Z = 5.71, p<0.00001), and family contact (test for overall effect: Z = 4.96, p<0.00001), with the residents of the small residential homes showing superior scores for all outcomes relative to the residents living in an institution (see Table 29). It is important to note that significant group differences were found in adaptive/maladaptive behavior, with the residents of the small residential homes showing more adaptive and less maladaptive behaviour and this may act as a confounding factor. However, the authors controlled for these group differences in their statistical analysis and found that small homes were still shown to provide better subjective and objective quality of life than traditional institutions.

Table 29: Summary evidence profile for small residential homes versus institution for adults with intellectual disabilities

Outcome	Quality of life	Choice making	Community inclusion	Family contact
Study ID	CHOU2008B	CHOU2008B	CHOU2008B	CHOU2008B
Effect size	MD = 11.40 (8.79, 14.01)	MD = 36.60 (30.89, 42.31)	MD = 7.40 (4.86, 9.94)	MD = 0.60 (0.36, 0.84)
Quality of evidence (GRADE)	Very low[1,2]	Very low[1,2]	Very low[1,2]	Very low[1,2]
Number of studies/participants	(K = 1; N = 179)	(K = 1; N = 179)	(K = 1; N = 179)	(K = 1; N = 179)
Forest plot	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15	1.3.2, Appendix 15

[1]Downgraded for risk of bias due to the non-randomised allocation of participants and significant group differences in adaptive/maladaptive behaviour
[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

Dispersed supported living compared with residential homes

One of the included observational (parallel groups) studies in adults with intellectual disability, MCCONKEY2007, compared participants living in dispersed supported housing (N = 103) with participants living in residential homes (N = 138). Data were also reported for clustered supported living (N = 132), small group homes (N = 152), and campus settings (N = 95). However, that data is not extracted here. For the dispersed supported living group the participant holds the tenancy

agreement for an ordinary house or apartment which is dispersed among other properties, and support staff are provided according to assessed needs and visit on a regular basis. Residential homes were group homes where an average of 19 people lived together. This study found a statistically significant difference between the groups for social inclusion (test for overall effect: Z = 3.75, p = 0.0002) with participants living in dispersed supported housing using significantly more community amenities than participants living in residential group homes (see Table 30).

Table 30: Summary evidence profile for dispersed supported housing versus residential group homes for adults with intellectual disabilities

Outcome	**Social inclusion**
Study ID	MCCONKEY2007
Effect size	MD = 0.90 (0.43, 1.37)
Quality of evidence (GRADE)	Very low[1,2]
Number of studies/participants	(K = 1; N = 241)
Forest plot	1.3.2, Appendix 15

[1]Downgraded for risk of bias as limited data could be extracted from the study because a measure of variation (SD) was only reported for one scale item. Non-randomised allocation and non-blind assessment of outcome also increases the risk of selection and detection bias.
[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

Group homes compared with semi-independent apartments

One of the included observational (parallel groups) studies in adults with intellectual disability, SCHWARTZ2003, compared residents of group homes (N = 147) with residents of semi-independent apartments (N = 57). Data were also reported for an independent apartment (N = 43) group. However, those data are not extracted here. This study found evidence for a statistically significant difference between settings (test for overall effect: Z = 4.39, p<0.0001) with participants living in group homes showing significantly higher levels of satisfaction than participants living in semi-independent apartments (see Table 31). However, differences in sample sizes across groups, and significant differences in demographic factors found between groups, for example, participants living in group home were older and this was not controlled for in the statistical analysis. These considerations limit the conclusions which can be drawn from this study.

Table 31: Summary evidence profile for group homes versus semi-independent apartments for adults with intellectual disabilities

Outcome	**Resident satisfaction**
Study ID	SCHWARTZ2003
Effect size	MD = -8.72 (-12.61, -4.83)
Quality of evidence (GRADE)	Very low[1,2]
Number of studies/participants	(K = 1; N = 204)
Forest plot	1.3.2, Appendix 15

[1]Downgraded for risk of bias due to differences in sample sizes across groups, and significant differences in demographic factors found between which were not controlled for in statistical analysis. Non-randomisation and non-blind assessment of outcome also increases the risk of selection and detection bias.
[2]Downgraded due to indirectness as extrapolating from adults with intellectual disability.

Intermediate care placement compared with direct community placement

One of the included observational (parallel group) studies in adults with intellectual disability compared the effects of placement into a transitional developmental centre before placement into intermediate care facilities with direct placement into an intermediate care facility (see Table 32). KEARNEY1995 failed to find evidence for a significant difference between groups in adaptive behaviour (test for overall effect: z = 0.64, p = 0.52).

Table 32: Summary evidence profile for placement into a transitional developmental centre before placement into intermediate care facilities versus direct placement into intermediate care facilities for adults with intellectual disabilities

Outcome	**Adaptive behaviour**
Study ID	KEARNEY1995
Effect size	MD = 5.89 (-12.24, 24.02)
Quality of evidence (GRADE)	Very low[1,2]
Number of studies/participants	(K = 1; N = 57)
Forest plot	1.3.2, Appendix 15

[1]Downgraded due to risk of bias as there is a discrepancy in sample size between groups. Also non-randomised allocation and non-blind assessment of outcomes increases the risk of selection and detection bias.
[2]Downgraded for indirectness as extrapolating from adults with intellectual disability.

Person-centred compared with system-centred planning

Finally, one of the included observational (parallel group) studies in adults with intellectual disabilities, HOLBURN2004, compared the effects of person-centred planning versus traditional interdisciplinary service planning (or 'system-centered' planning) on movement into the community for residents at four developmental centres. Person-centered planning involved four phases: introduction; development of a personal profile; creation of a vision of the future; and follow-along. The intervention was a slight modification of Mount's (1992, 1994) Personal Futures Planning. Person-centred planning meetings were held approximately once per month at the residence of the focus person and team composition varied but often consisted of a facilitator, co-facilitator, service user, family member, behaviour specialist, service coordinator or social worker, bridge-builder, direct-support staff, and unit or house manager. The control group consisted of matched peers who lived in the same developmental centres and received the type of individual habilitation planning typically provided to residents of large intermediate care facilities. The interdisciplinary service planning teams typically met quarterly in the developmental centre and the teams were interdisciplinary and largely composed of

professional staff (for example, client coordinator, nurse, psychologist, speech therapist, and teacher). The meetings involved discussion of assessments, review progress toward service plan goals, and the development of new written habilitative goals and methodologies to be pursued. This study found evidence for a significant group difference (test for overall effect: Z = 3.20, p = 0.001), with the risk ratio indicating that participants in the person-centered planning group were over three times more likely to move into the community than participants who received traditional interdisciplinary service planning (or 'system-centered' planning) (see Table 33). However, an important potential limitation of this study is that bridge building funds were only available to person-centred planning participants. Nevertheless, only half of the experimental group who moved into the community used such resources which might suggest that this fund did not create an advantage favouring the person-centred planning group. The evidence from this study suggests that person-centred planning can produce an improvement (even as an adjunctive process) over more conventional interdisciplinary treatment team planning procedures typical of intermediate care facilities serving people with developmental disabilities even after potential confounds have been removed.

Table 33: Summary evidence profile for person-centred versus system-centred planning for adults with intellectual disabilities

Outcome	**Movement into community**
Study ID	HOLBURN2004
Effect size	RR = 3.41 (1.61, 7.24)
Quality of evidence (GRADE)	Very low[1,2,3]
Number of studies/participants	(K = 1; N = 37)
Forest plot	1.3.2, Appendix 15

[1]Downgraded due to risk of bias because the allocation was not randomised and this increases the risk of selection bias

[2]Downgraded due to indirectness as extrapolating from adults with intellectual disability

[3]Downgraded due to imprecision as the sample size is small

Observational before-and-after studies for moving from residential institutions into the community

Of the nine included observational before-and-after studies in adults with intellectual disability, six examined change-from-baseline scores after moving into the community from residential institutions. Three of these studies examined the effects of the move on challenging behaviour (BHAUMIK2009; BOURAS1993; DONNELLY1996). Efficacy data could not be extracted for these studies. However, the authors report data suggestive of positive effects. BHAUMIK2009 report significant change from 6 months' pre-discharge to 6 months' post-discharge in aggression ($p<0.001$) as measured by the Modified Overt Aggression Scale (MOAS). However, this study reports median scores, which may indicate skewed data. BOURAS1993 report no significant change from pre- to post-move in total numbers of behavioural problems ($\chi^2 = 0.13$, $p>0.05$), but significant post-move improvements

were observed for frequencies of absconding behavioural problems ($\chi^2 = 8.5$, $p<0.05$) and disturbance at night ($\chi^2 = 8.2$, $p<0.05$). DONNELLY1996 also reported positive effects of the move with a statistically significant change from pre-discharge to 12 months' post-discharge in challenging behaviour ($U = -0.502$; $p<0.05$) as measured by the Problems Questionnaire (PQ; Clifford, 1987), which assesses dangerousness, psychological impairment, management problems, socially unacceptable behaviour, and problems relating to attitudes and relationships.

The effects of moving from an institution into the community were also examined for quality of life, family contact and adaptive behaviour outcomes.

DAGNAN1998 reported a statistically significant change from 5 months' pre-move to 30 months' post-move on all six subscales of the quality of life questionnaire: choice ($t = 6.38$, $p<0.001$); dignity ($t = 5.26$, $p<0.001$); relationships ($t = 5.72$, $p<0.001$); activity ($t = 5.37$, $p<0.001$); community ($t = 3.84$, $p<0.01$); and individuality ($t = 9.51$, $p<0.001$).

SPREAT2002 reported statistically significant increases in family contact over time for all four of the cohorts ($F = 209.68$, $p<0.01$ for $N = 24$ participants discharged in 1992; $F = 534.98$, $p<0.01$ for $N = 46$ participants discharged in 1993; $F = 338.37$, $p<0.01$ for $N = 36$ participants discharged in 1994; and $F = 334.05$, $p<0.01$ for $N = 45$ participants discharged in 1995).

Finally, HEMMING1983 reported statistically significant improvements from pre-move to post-move (at 5.5- year follow-up) in adapted behaviour, as reflected by significant changes in total ABS Part I scores ($p<0.01$), and more specifically for the subscales of independent functioning ($p<0.01$), domestic activity ($p<0.01$), self-direction ($p<0.02$), responsibility ($p<0.02$), and socialisation ($p<0.01$).

To sum up, these observational studies suggest beneficial effects for resettlement from a residential institution into the community on challenging behaviour, quality of life and family contact. However, this evidence is of very low quality, indirect, and the lack of control groups means that efficacy data cannot be extracted.

Observational before-and-after studies for moving into small scale group homes

One of the included observational before-and-after studies in adults with intellectual disability, CHOU2011, compared change-from-baseline scores for adults with intellectual disabilities who moved into small-scale residential homes from their family home or from institutions and remained in the same residential home 2 years later. This residential scheme provided accommodation in ordinary housing in established residential areas and all houses were a few minutes' walk from the town/city centre. Each home was limited to six or fewer residents and was staffed by support services 24 hours a day. Efficacy data could not be extracted for this study. However, the authors report statistically significant change-from-baseline

scores for quality of life as measured by the Quality of Life Questionnaire (QoL-Q; Schalock & Keith, 1993) ($p<0.01$) and family contact ($p<0.01$).

Observational before-and-after studies for moving from more restrictive to less restrictive work or living environments

Finally, the remaining included observational before-and-after study in adults with intellectual disability, WEHMEYER2001, compared change-from-baseline scores for individuals who moved from more restrictive to less restrictive work or living environments (N = 8 moved from more to less restrictive living environment, for example, institution/nursing home to group home or community, or group home to community living; and N = 21 moved from more to less restrictive work setting, for example, day programme to sheltered workshop or competitive employment, or sheltered workshop to competitive employment). Efficacy data could not be extracted for this study. However, the authors report statistically significant pre-move to post-move differences in self-determination as measured by the Arcs' Self-Determination Scale (SDS) ($p = 0.017$) and autonomous functioning as measured by the Adult Version and the Autonomous Functioning Checklist (AFC) ($p = 0.041$).

6.5.8 Clinical evidence summary for residential accommodation and related services

The evidence reviewed for residential accommodation, and related services, was based exclusively on populations with intellectual disabilities. This limits the generalisabilty to adults with autism although it should be noted that a significant proportion, if not the majority, of individuals with autism who live in residential accommodation will have intellectual disabilities. With this significant caveat in mind the evidence suggests that small group living situations have better outcomes than larger institutional settings and that planning to support transition from residential accommodation is also associated with improved outcomes. Enabling but structured environments appear to be associated with better outcomes, as does the provision of support from external agencies.

6.5.9 From evidence to recommendations

The GDG recognised the limitations of the evidence but felt that where residential care was needed small group living situations should be preferred over larger settings. The GDG also took the view that the presence of community support teams to enable transition and support people in residential care should be provided. Based on GDG expert knowledge and judgement, and in the absence of evidence pertaining to this issue, the GDG also concluded that certain environments were more conducive to the effective provision of care to adults with autism and these environments share common features such as a structured environment in terms of schedule and activities but also in terms of the physical environment.

6.5.10 Recommendations

6.5.10.1 If residential care is needed for adults with autism it should usually be provided in a small community-based unit. The environment should be structured to support and maintain a collaborative approach between the person with autism and their family or carer(s) for the development and maintenance of interpersonal and community living skills.

6.5.10.2 Residential care environments should include activities that are:

- structured and purposeful
- clearly timetabled with daily, weekly and sequential programmes that promote choice and autonomous action.

6.5.10.3 Residential care environments should have:

- designated areas for different activities in order to provide visual cues about expected behaviour
- adaptations made to the physical environment (especially lighting, sound insulation and furnishings) to accommodate people with hyper- and hypo-sensory sensitivities
- inside and outside spaces where the person with autism can be alone (for example if they are over-stimulated).

6.5.10.4 Staff in residential care environments should:

- be trained in assessing and supporting the needs of adults with autism
- demonstrate high levels of consistency and predictability, but with some flexibility to allow change and choice
- have a positive commitment to involving families and carers.

7 PSYCHOSOCIAL INTERVENTIONS

7.1 INTRODUCTION

Psychosocial interventions, in particular, those based on behavioural and educational approaches, have been a mainstay of treatment for individuals with autism. Much of the development in this area has focused on interventions in children, in part based on the premise that early diagnosis followed by appropriate treatment may improve outcomes in later life for most individuals. Over the past 30 years a variety of psychosocial interventions have been developed aimed at improving outcomes for people with autism, including: behavioural therapies; social skills training; sensory integration therapy; facilitated communication, and art, drama and music therapies. A problem in evaluating the efficacy of psychosocial interventions for adults with autism is the availability of evidence given that much of the research comes from children with autism. However, even where an adult with autism has been diagnosed and treated in childhood there is a need for ongoing support and intervention as there is no evidence to suggest that long-term outcomes for people with autism are significantly improved following intervention programmes in childhood (Howlin, 1998). This scarcity of evidence is particularly problematic because anecdotal reports and case studies suggest that many individuals with autism may face the greatest challenges during adolescence and adulthood when problems with social relationships can impact significantly upon education, employment, housing, and community inclusion (Barnhill, 2007).

Examples of psychosocial interventions based on the principles of applied behavioural analysis and operant conditioning theory have been used to modify challenging or aggressive behaviour or teach adaptive behaviours, such as activities of daily living. Alternatively, social skills groups attempt to target the core autistic symptom of problems with social interaction through the application of some behavioural therapy techniques within a social learning framework, for instance using video modelling, imitation and reinforcement to teach 'rules' of social engagement.

Many people with autism also suffer from a number of coexisting mental and physical health disorders, the treatment of which may be complicated in people with autism. A number of psychosocial interventions have targeted these conditions, for instance, cognitive behavioural therapies have been used to treat depression or anxiety disorders or the symptoms of OCD in individuals with autism (Russell *et al.*, 2009). This review will also consider psychosocial interventions, which provide support to the families and carers of individuals with autism, for instance, through psychoeducation and/or support groups.

During the 1980s and through the 1990s the psychosocial interventions for individuals with autism tended to be based on behavioural principles and targeted at learning new skills or increasing adaptive behaviour skills (García-Villamisar *et*

al., 2002). However, there have been recent calls for a different approach that places quality of life at the forefront of all interventions for people with autism (Wehman *et al*., 2005) and consequently, it has been regarded as crucial that efficacy studies of therapeutic interventions evaluate potential improvements to the quality of life for individuals with autism, by analysing subjective outcomes including well-being, satisfaction with lifestyle, community involvement, personal control, and social interpersonal relationships.

Interventions which focus more on quality of life rather than explicitly targeting core autism symptoms or coexisting behavioural problems include leisure programmes and supported employment programmes (García-Villamisar & Dattilo, 2010; García-Villamisar *et al*., 2002). Both interventions place an important focus on individual strengths and interests. Leisure programmes provide a structured group recreational context for individuals with autism to engage in leisure activities in an attempt to improve wellbeing, and indirectly intend to impact on social skills and community involvement. Supported employment programmes seek to assist individuals with autism in finding and retaining jobs in order to increase independence and improve self-esteem; evaluation of such schemes has also suggested indirect beneficial effects that extend beyond employment and impact upon core autism symptoms and quality of life.

7.1.1 Clinical review protocol (psychosocial 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 34 (further information about the search strategy can be found in Appendix 9).

7.1.2 Extrapolation

The Guideline Development Group (GDG) took the view that with limited primary data of good quality (RCTs and observational studies) for adults with autism, it might be necessary to extrapolate from other populations (the method for extrapolation was based on the method developed for the *Common Mental Health Disorders* guideline (NCCMH, 2011) and see section 3.5.8 in Chapter 3 of this guideline for further details on extrapolation). Extrapolation was performed in cases where the review question was considered important to the GDG and where primary data for adults with autism was insufficient. For psychosocial interventions, the decision was made to extrapolate from an intellectual disability population for psychosocial interventions aimed at behaviour management. In addition, for other psychosocial interventions where primary data was insufficient and according to GDG expert judgement decided on an intervention-by-intervention basis extrapolation from an autism population with a mean age of 15 years or above was considered. Extrapolation was performed on the basis that the extrapolated population shares common characteristics with the primary autism adult population (e.g. age, gender, severity of disorder), where the harms were similar for the

extrapolated data set as for the primary data set, and where the outcomes were similar across trials. Extrapolation was only performed where the data quality was equivalent and the same standards were applied for assessing and evaluating the evidence from adults with intellectual disability, as for the primary data from adults with autism. Extrapolated data was recognised as lower quality evidence than data from adults with autism and this is reflected within the GRADE system (see Appendix 19), with outcomes using extrapolated populations downgraded on the basis of indirectness.

Table 34: Clinical review protocol for the review of psychosocial interventions

Component	Description
Review questions	For adults with autism, what are the benefits and/or potential harms associated with different psychosocial interventions (for example, applied behavioural analysis, cognitive behavioural therapy, mentoring, social groups, and befriending schemes)? (CQ – C1) For adults with autism, what is the effectiveness of vocational and supported employment programmes? (CQ – C2) For adults with autism, what is the effectiveness of educational interventions (including specialist programmes, or support within mainstream education, or educational software, etc.)? (CQ – C3) What information and day-to-day support do families and carers need:- • during the initial period of assessment and diagnosis? • when treatment and care is provided (for example, telephone helpline, information packs, advocates or respite care, interpreters and other language tools)? • during periods of crisis? (CQ – D1) What role can families and carers play in supporting the delivery of interventions for people with autism? (CQ – D2)
Sub-question	For adults with autism, is the effectiveness of interventions moderated by: • the nature and severity of the condition? • the presence of coexisting conditions? • age? • the presence of sensory sensitivities (including pain thresholds)? • IQ? • language level? (CQ – C5) For adults with autism, what amendments, if any, need to be made to the current recommendations for psychosocial and pharmacological treatment (including the nature of drug interactions and side effects) for coexisting common mental health disorders? (CQ-C6)
Objectives	To evaluate the clinical effectiveness of psychosocial interventions for autism.
Criteria for considering studies for the review	
• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental disorder). Consideration should be given to the specific needs of: • people with coexisting conditions

	• women • older people • people from black and minority ethnic groups • transgender people Excluded groups include: • children (< 18 years of age) HOWEVER it was decided based on GDG consensus that where primary data from an adult population was absent it may be valid to extrapolate from an autism population with a mean age of 15 years or above. For interventions concerned with the management of behaviour, and where data from adult autism populations was not sufficient, the GDG decided that extrapolating from an intellectual disabilities population was valid.
• Intervention(s)	• **Psychosocial interventions aimed at behaviour management** (for example, applied behaviour analysis, behavioural therapies, cognitive behavioural therapy, social learning) • **Communication** (for example, augmentative and alternative communication, facilitated communication, picture exchange system) • **Vocational/employment interventions** (for example, vocational rehabilitation programmes, individual supported employment)
• Comparison	Treatment as usual, waitlist control, other active interventions
• Critical outcomes	Outcomes involving core features of autism (social interaction, communication, repetitive interests/activities); overall autistic behaviour; management of challenging behaviour; outcomes involving treatment of coexisting conditions
• Study design	• RCTs The GDG agreed by consensus that where there were no RCTs found in the evidence search, or the results from the RCTs were inconclusive, that the following studies would be included in the review of evidence: • observational • quasi-experimental • case series
• 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.
• Restriction by date?	No
• Minimum sample size	• RCT/observational/quasi-experimental studies:- N=10 per arm (ITT) • Case series studies:- N=10 in total 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, tertiary, health and social care and healthcare settings (including prisons and forensic services) • Others in which NHS services are funded or provided, or NHS professionals are working in multi-agency teams
Electronic databases	AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, Medline, PsycINFO, Sociological Abstracts, SSA
Date searched	Systematic reviews: 1995 up to 09/09/2011. RCT, QE, OS, case-series: inception of database up to 09/09/2011.
Searching other resources	Hand-reference searching of retrieved literature

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.
	• Narratively review literature that takes into consideration any amendments due to common mental health disorders.
	• 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?
	  • age
	  • the presence of sensory sensitivities (including pain thresholds)
	  • IQ
	  • language level

Note. Autism=Autism Spectrum Disorders; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; RCT = Randomised Controlled Trial; QE = Quasi-Experiemental; OS = Observational Study; AEI = Australian Education Index; AMED = Allied and Complementary Medicine; ASSIA = Applied Social Services Index and Abstracts; BEI = British Education Index; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts and Reviews of Effectiveness; Embase = Excerpta Medica database; ERIC = Education Resources in Curriculum; HMIC =Health Management Information Consortium; Medline = Biomedical Information Database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

7.1.3 Outcomes

A large number of outcomes were reported by the psychosocial studies. Those that reported sufficient data to be extractable and were not excluded are in Table 35.

Table 35: Outcomes extracted from psychosocial studies

Category	Sub-category	Scale
Core autistic symptoms	Communication	• Number of nouns generalized (designed for Elliott *et al.*, 1991) • Vineland Adaptive Behaviour Scale (VABS)

		(Sparrow *et al*., 1984) Communication subscale
	Social interaction	• Cambridge Mindreading (CAM) Face-Voice Battery (Golan *et al*., 2006) • Empathy Quotient (EQ) (Baron-Cohen & Wheelwright, 2004) • Facial Discrimination Battery (FDB)-Spanish version (García-Villamisar *et al*., 2010) • Social Responsiveness Scale (SRS) (Constantino, 2002) • Social Skills Rating System (SSRS) (Gresham & Elliot, 1990) • Test of Adolescent Social Skills Knowledge (TASSK) (Laugeson & Frankel, 2006) • Video recording of social interaction (designed for Herbrecht *et al*., 2009)
Autistic behaviours		• Childhood Autism Rating Scale (CARS) (Schopler & Reichler, 1971; Schopler *et al*., 1980)
Challenging behaviour	Total score	• Part 2 of the AAMD Adaptive Behavior Scale (Nihira *et al*., 1974)
	Irritability	• Aberrant Behaviour Checklist (ABC) Irritability subscale (Aman *et al*., 1985)
Anger management		• Anger Inventory (Benson & Ivins, 1992) • Anger Inventory for Mentally Retarded Adults (Benson *et al*., 1986) • Dundee Provocation Inventory (DPI) (Lindsay, 2000) • Provocation Inventory (PI) (Novaco, 2003) • Videotaped roleplay test: aggressive gestures (designed for Benson *et al*., 1986)
Activities of daily living	Toileting	• Behaviour Maturity Checklist II-1978 (Soule *et al*., 1978)
	Showering	• Task-specific checklist (designed for Matson *et al*., 1981)
Self-care	Weight management	• Weight loss (in kg; used in Harris & Bloom, 1984)
Anti-victimization skills		• Bullying Questionnaire (Mencap, 1999) • Protective Behaviour Skills Evaluation (PBSE) (Mazzucchelli, 1996) • Self Social Interpersonal Decision Making Scale (Khemka, 1997)
Parenting skills		• Task-specific target child-care behaviour checklist (designed for Feldman *et al*., 1999)
Cognitive skills	Executive function	• Cambridge Neuropsychological Tests: Automated Battery (CANTAB): 'Stockings of Cambridge' (SOC) Planning task (Cambridge Cognition, 2002)
Quality of life		• Quality of Life Survey (QLS) (Sinnot-Oswald *et al*., 1991) • Quality of Life Questionnaire-Spanish version (QOL) (Caballo *et al*., 2005; Scaholck & Keith, 1993)
Employment		• Number of job placements (objective measurement used in Howlin *et al*., 2005)
Co-existing conditions	OCD	• Yale-Brown Obsessive Compulsive Scale (YBOCS) severity scale (Goodman *et al*., 1989a; 1989b)
Parental outcomes	Knowledge and awareness of	• Community Resources Scale (Heller & Factor, 1991)

	permanency planning	
	Social support	• Coping Skills Strategy Indicator (CSI; Amirkhan, 1990) – Exploring social support subscale
	Parental depression	• Beck Hopelessness Scale (BHS; Beck *et al*., 1974)

7.2 BEHAVIOURAL THERAPIES AIMED AT COMMUNICATION

7.2.1 Introduction

Autism is characterised by a triad of behavioural impairments: impaired social interaction, impaired communication, and restricted and repetitive interests and activities (APA, 1994). Among other behavioural targets, therapies based on behavioural therapy principles have been aimed at communication impairments in autism. Behavioural therapies, as defined here, are based on learning theory and principles of operant conditioning (Skinner, 1953) and can include the application of techniques such as reinforcement, chaining, prompting, shaping, imitation and video modelling in order to modify behaviour. Behavioural therapies have been targeted at communication in autism and have commonly used imitation and backward chaining techniques. Imitation has been associated with the development of language in neurotypical children (Bates *et al*., 1988) and imitation has been found to be abnormal in autism (Meltzoff & Gopnik, 1994; Rogers, 1999; Rogers & Pennington, 1991; Smith & Bryson, 1994). This association between imitation and social-communicative behaviours in autism has also been corroborated longitudinally with early deficits in imitating body movements found to be associated with the development of expressive language six months later (Stone *et al*., 1997). Behavioural interventions aimed at communication have ranged from highly structured discrete trial teaching to more naturalistic approaches to language teaching (see Ospina *et al*., 2008). Discrete trial teaching is therapist-controlled and involves a highly structured teaching environment where language is broken down into its constituent parts and taught using intensive teaching sessions. In this way acquisition of language can be facilitated through the use of prompting, fading, and contingent reinforcement (Ingersoll & Schreibman, 2006). Conversely more naturalistic behavioural methods have also been aimed at communication in autism (Elliott *et al*., 1991). For instance, the Natural Language Teaching Paradigm (Koegel & Johnson, 1989; Koegel *et al*., 1987). This approach emphasizes the establishment of a normal training environment and teaching language as an incidental part of interactions. Natural language teaching models also involve the therapist taking a modeling rather than a directive role, and reinforcement is directly linked to the meaning of the participants' communications. A number of studies have examined the application of behavioural therapies to communication impairments in children with autism (see Ospina *et al*., 2008). However, less research is available regarding the efficacy of these interventions for adults with autism and this is important given

that functional impairments of communication may be expected to differ as individuals with autism get older.

7.2.2 Studies considered

No RCTs were found which provided relevant clinical evidence in adults with autism and met the eligibility criteria for this review. However, one quasi-experimental crossover study (N=23) was found (Elliott *et al*., 1991 [ELLIOTT1991]). One observational before-and-after study (N=18) was also found and included (Polirstok *et al*., 2003 [POLIRSTOK2003]). Both of these studies were published in peer-reviewed journals between 1991 and 2003. In addition, three studies were excluded as they did not meet eligibility criteria due to mean ages of below 15 years old or failure to meet the sample size criterion of at least ten participants per arm. Further information about included and excluded studies can be found in Appendix 14.

The quasi-experimental study involved a comparison of analog language teaching with natural language teaching in adults with autism (see Table 36).

The observational study reported change from baseline scores for adults with autism who were receiving a behavioural functional communication intervention (see Table 37).

Table 36: Summary study characteristics for included quasi-experimental controlled trials in adults with autism

	Natural language teaching
No. trials (Total participants)	1 (23)
Study IDs	ELLIOTT1991
N/% female	4/17
Mean age	26
IQ	Not reported but severe to profound cognitive delays (average estimated mental age equivalent = 3.3 years)
Axis I/II disorders	100% autism
Comparator	Alternative treatment (analog language teaching)
Length of treatment	1 month per intervention
Length of follow-up	3 months

Table 37: Summary study characteristics for included observational studies in adults with autism

	Functional communication skills training
No. trials (Total participants)	1 (18)
Study IDs	POLIRSTOK2003*
N/% female	18/100
Mean age	Not reported (16-38 years)
IQ	Not reported but ID (mental age: 12-25 months)

Axis I/II disorders	61% autism; 100% ID
Comparator	No comparator
Length of treatment	One year
Length of follow-up	18 months

*Efficacy data not extractable

7.2.3 Clinical evidence for behavioural therapies aimed at communication

Natural language teaching compared with analog language teaching

There were no RCTs which met the eligibility criteria and could be included for behavioural therapies aimed at communication. The single included cross-over quasi-experimental trial compared natural language teaching with analog language teaching in adults with autism (see Table 38). In ELLIOTT1991, analog language teaching attempted to evoke imitative responses through the use of successive trials. Whereas natural language teaching allowed participants to select items, and therefore determine the order of presentation. The primary outcome was language acquisition as measured by the number of nouns generalised. This study failed to find any evidence for a statistically significant difference between these two behavioural techniques as applied to language teaching for adults with autism (test for overall effect: Z=1.65, p=0.1). The authors reported that both techniques increased initial and long-term noun generalisation. However, no statistical analysis was reported which enabled this conclusion to be quantified.

Table 38: Summary evidence profile for natural language teaching compared with analog language teaching in adults with autism

Outcome	**Communication**
Study ID	ELLIOTT1991
Effect size	SMD = -0.71 (-1.55, 0.13)
Quality of evidence (GRADE)	Very low[1,2,3]
Number of studies/participants	(K=1; N=23)
Forest plot	1.1.1, Appendix 15

[1]Downgraded due to risk of bias as the study was non-randomised and non-blind
[2]Downgraded due to imprecision as the study was designed to compare two alternative treatments and not to determine overall treatment efficacy
[3]Downgraded due to imprecision as the sample size was small

Observational study of functional communication skills training

A single observational study of adults with intellectual disability and autism examined change from baseline communication scores following an Intensive Habilitation Programme (IHP) which targeted four main areas of functioning as follows: preoccupational skills, occupational skills, psychomotor skills, and functional communication skills. The primary outcome of interest was communication as measured by the Vineland Adaptive Behaviour Scale (VABS). It was not possible to extract efficacy data for this study. However, the authors

reported evidence for a statistically significant change from baseline score on receptive ($F=22.33$, $p<0.001$) and expressive ($F=15.78$; $p<0.001$) language after behavioural therapies aimed at functional communication skills. However, this evidence is of very low quality (GRADE) due to the lack of a control group and the inability to extract efficacy data, and also due to imprecision conferred by the small sample size.

7.2.4 Clinical evidence summary for behavioural therapies aimed at communication

The limited evidence identified for behavioural therapies aimed at improving communication in adults with autism did not provide high quality efficacy data, either because the study was aimed at comparing two alternative treatments rather than determining overall treatment efficacy or because efficacy data could not be extracted.

7.2.5 Health economics evidence for behavioural therapies aimed at communication

No studies assessing the cost effectiveness of behavioural therapies aimed at communication 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.

7.2.6 From evidence to recommendations

Based on the limited and very low quality evidence for behavioural therapies aimed at communication in autism the GDG concluded that there was insufficient evidence to make a recommendation about the use of behavioural therapies for the core autistic symptom of communication impairments in adults with autism.

7.3 FACILITATED COMMUNICATION

7.3.1 Introduction

Facilitated communication is a form of Augmentative Alternative Communication (AAC) and describes a controversial therapeutic intervention whereby a facilitator supports the hand or arm of an individual with autism while using a keyboard or other devices with the aim of helping the individual to develop pointing skills and to communicate. The application of this intervention to autism is based on the hypothesis that many of the difficulties faced by people with autism are due to a movement disorder rather than social or communication deficits (Research Autism, 2011a). Positive reports of effectiveness have been based almost exclusively on anecdotal evidence such as case studies and informal accounts (Biklen, 1990; Biklen & Schubert, 1991; Biklen *et al.*, 1992; Biklen *et al.*, 1995; Clarkson, 1994; Crossley & Remington-Gurley, 1992; Heckler, 1994; Janzen-Wilde *et al.*, 1995; Olney, 1995; Sabin & Donnellan, 1993; Sheehan & Matuozzi, 1996; Weiss *et al.*, 1996). Proponents of this approach have made bold claims regarding the benefits of facilitated communication for autism. For instance, that it allows individuals with autism to communicate that they have normal intelligence and social and affective abilities after as few as a single facilitated communication session (Biklen *et al.*, 1991), or even more extravagantly that facilitated communication represents a cure for autism (Biklen & Schubert, 1991). However, where scientific studies have attempted to validate facilitated communication there has been no evidence of unexpected communication abilities when the facilitators lack the information needed to answer questions posed to the individuals being facilitated (Bebko *et al.*, 1996; Beck & Pirovano, 1996; Bomba *et al.*, 1996; Braman & Brady, 1995; Crews *et al.*, 1995; Eberlin *et al.*, 1993; Edelson *et al.*, 1998; Hirshoren & Gregory, 1995; Hudson *et al.*, 1993; Klewe, 1993; Konstantareas & Gravelle, 1998; Montee *et al.*, 1995; Myles & Simpson, 1994; Myles *et al.*, 1996b; Oswald, 1994; Regal *et al.*, 1994; Simon *et al.*, 1996; Simpson & Myles, 1995a; Smith & Belcher, 1993; Smith *et al.*, 1994; Szempruch & Jacobson, 1993; Vázquez, 1994; Wheeler *et al.*, 1993). Proponents of facilitated communication have argued against the scientific validation of this intervention (Crossley, 1992; Biklen & Schubert, 1991) on the grounds that systematic attempts to test the efficacy of facilitated communication violate the trust bond between the facilitator and communicator (Biklen & Schubert, 1991). However, even more concerning than the lack of blinded efficacy data, there is evidence that facilitated communication can lead to significant harm with reports of unsubstantiated claims of sexual abuse against family members being made via facilitated communication (Rimland, 1992; Simpson & Myles, 1995b). Reports by the American Association on Mental Retardation, the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry are all highly critical of facilitated communication and strongly recommend that it is not used (Research Autism, 2011a).

7.3.2 Studies considered

No RCTs were found which provided relevant clinical evidence in adults with autism and met the eligibility criteria for this review. One observational study (N=12) was found and included (Myles *et al*., 1996a [MYLES1996A]). In addition, three observational studies were excluded on the basis of a duplication of data with the included study in one case, and on the basis that data could not be extracted as no statistical analysis was reported for the two other studies.Further information about included and excluded studies can be found in Appendix 14.

The single included observational study in adults with autism (see Table 39) compared pre-facilitated communication intervention and post-intervention behavioural observations with no control group.

Table 39: Summary study characteristics for included observational studies of facilitated communication in adults with autism

	Facilitated communication
No. trials (Total participants)	1 (12)
Study IDs	MYLES1996A
N/% female	3/25
Mean age	19
IQ	Not reported but ID
Axis I/II disorders	100% autism
Comparator	No comparator
Length of treatment	14 weeks
Length of follow-up	17 weeks (including 3-week pre-intervention baseline observation period)

7.3.3 Clinical evidence for facilitated communication

There was only a single before-and-after observational study with no control group which could be included for the review of facilitated communication, and it was not possible to extract efficacy data for this study. This study examined the frequency of seven behaviours and social interaction outcomes (requesting, getting attention, protesting, giving information, expressing feelings, interacting socially, and non-focused response) at baseline, during the facilitated communication intervention, and in the final few weeks of the intervention. The authors reported no evidence for significant improvement in any of the target behaviours over time (all $p>0.05$).

7.3.4 Clinical evidence summary for facilitated communication

There was very little evidence for facilitated communication intervention in adults with autism and the very low grade evidence which could be narratively reviewed presents results suggestive of no significant treatment effects associated with facilitated communication.

7.3.5 Health economics evidence for facilitated communication

No studies assessing the cost effectiveness of facilitated communication 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.

7.3.6 From evidence to recommendation

No evidence could be found for the efficacy of facilitated communication interventions in adults with autism. The GDG also considered the harms which have been previously reported for facilitated communication and the GDG took the view that facilitated communication should not be used for adults with autism.

7.3.7 Recommendation

7.3.7.1 Do not offer facilitated communication to adults with autism.

7.3.8 Research recommendation

7.3.8.1 What is the clinical and cost effectiveness of augmented communication devices for adults with autism?

Why is this important?

Many people with autism experience significant communication problems (for example, the absence of any spoken language, significant deficits in interpersonal skills), which have a profound effect on their ability to lead a full and rewarding life. It is probable that these problems are related to the core symptoms of autism and are likely to persist for most people given the life-long course of autism and the lack of effective interventions for these core symptoms. A number of communication devices have been developed for autism but few, if any, have been subjected to a proper evaluation in adults. Despite this lack of formal evaluation, individual services have made considerable investments in augmented communication devices. Research that provides high-quality evidence on the acceptability and the clinical and cost effectiveness of augmented communication devices could bring about significant improvements in the lives of adults with autism.

The suggested programme of research would need to identify current devices for which there is: (a) some evidence of benefit (for example, case series and small-scale pilot studies); (b) some evidence that it meets a key communication need for people with autism (based on reviews of people's need in this area); and (c) indication that the device is feasible for routine use. The identified device(s) should then be formally evaluated in a large-scale randomised trial.

7.4 BEHAVIOURAL THERAPIES AIMED AT BEHAVIOUR MANAGEMENT

7.4.1 Introduction

Behavioural therapies based on the principles of learning theory and operant conditioning are commonly used to target challenging behaviour and to teach adaptive skills for community living, particularly in residential and educational settings. Much of the early intensive intervention in autism is based on these behavioural principles and there is some evidence for short-term efficacy of such programmes (Matson, 2007; Matson & Smith, 2008). However, as with other types of psychosocial interventions there is less evidence with regards to the efficacy of behavioural therapies for adults with autism. From a behaviour management perspective, challenging behaviours are more common in individuals with autism and intellectual disability than in individuals with intellectual disability alone and have been found to persist into adulthood and to co-vary with the severity of autism (Matson & Rivet, 2008). However, there have been some doubts expressed as to the efficacy of behavioural therapies in bringing about long-term changes in challenging behaviour. For instance, Matson and Rivet (2008) report that 28% of their autistic sample showed challenging behaviour in all four areas of aggression/destruction, stereotypy, self-injurious behaviour and disruptive behavior, despite having learning-based treatment plans in place aimed specifically at these challenging behaviours. In addition to concerns regarding the longevity of treatment effects there is also very little evidence pertaining to the generalisability of treatment effects across challenging behaviours or adaptive skill areas, or across settings. Traditionally, challenging behaviour and adaptive behaviour outcomes have been identified as a greater problem for individuals with autism and coexisting intellectual disability with higher levels of language and intellectual functioning generally being associated with better outcomes (Billstedt *et al*., 2005; Howlin *et al*., 2004; Paul & Cohen 1984). However, recent studies have suggested that there is a gap between intellectual and adaptive functioning, even in 'high-functioning' (IQ>70) autistic individuals and this discrepancy appears to widen with age (Kanne *et al*., 2011; Klin *et al*., 2007; Szatmari *et al*., 2003). Thus, determining the efficacy of behavioural therapies aimed at acquiring or increasing adaptive behaviour skills is of particular importance in adults with autism.

7.4.2 Studies considered

No RCTs, observational, quasi-experimental, or case series were found which provided relevant clinical evidence in adults with autism and met the eligibility criteria for this review. Based on the rules for extrapolation, the decision was taken to extrapolate from studies of adults with intellectual disability for behavioural interventions aimed at behaviour management. One RCT (N=72) met the extrapolation eligibility criteria and was included (Matson *et al*., 1981 [MATSON1981]). There was also one quasi-experimental parallel group controlled study (N=21) included (Harris & Bloom, 1984 [HARRIS1984]), and two observational

before-and-after studies (N=69), (Bat-Haee, 2001 [BATHAEE2001] and Feldman *et al*., 1999 [FELDMAN1999]). All of these studies were published in peer-reviewed journals between 1981 and 2001. In addition, 44 studies were excluded as they did not meet eligibility criteria. The most common reasons for exclusion were that data could not be extracted which gave any measure of effect size, or the mean age of the sample was below 15 years old, or the sample size was less than ten participants per arm. Further information about included and excluded studies can be found in Appendix 14.

The single included RCT compared an intervention called independence training with a no-treatment control group (see Table 40).

The quasi-experimental study compared a behavioural weight control programme with a no-treatment control group who were composed of study dropouts (see Table 41).

Finally, of the two observational studies one reported change from baseline scores for participants receiving adaptive skills training and one reported change from baseline scores for self-instructional pictorial manuals to teach child-care skills (see Table 42).

Table 40: Summary study characteristics for included RCTs of behavioural therapies in adults with intellectual disability

	Independence training
No. trials (Total participants)	1 (72)
Study IDs	MATSON1981
N/% female	26/36
Mean age	32
IQ	Not reported - moderate to severe ID
Axis I/II disorders	100% ID
Comparator	No-treatment control group
Length of treatment	4 months
Length of follow-up	7 months (including 3-month post-test follow-up)

Table 41: Summary study characteristics for included quasi-experimental trials of behavioural therapies in adults with intellectual disability

	Behavioural weight control programme
No. trials (Total participants)	1 (21)
Study IDs	HARRIS1984
N/% female	17/81
Mean age	25
IQ	Range not reported (mean 52.5)
Axis I/II disorders	100% ID
Comparator	No-treatment control group (study dropouts)
Length of treatment	7 weeks
Length of follow-up	26 weeks (including 19 week post-test follow-up)

Table 42: Summary study characteristics for included observational studies of behavioural therapies in adults with intellectual disability

	Adaptive skills training	Self-instructional pictorial child care manuals
No. trials (Total participants)	1 (59)	1 (10)
Study IDs	BATHAEE2001*	FELDMAN1999*
N/% female	45/76	10/100
Mean age	44	28
IQ	Not reported (mental age 2-17 months)	71-76 (mean 73.8)
Axis I/II disorders	100% ID	100% ID
Comparator	No comparator	No comparator
Length of treatment	10 years	Until mothers reached training criterion of 80% or higher for two sessions
Length of follow-up	10 years	3 years

*Efficacy data not extractable.

7.4.3 Clinical evidence for behavioural interventions for behaviour management

Independence training compared with no treatment control group

There were no included RCT, quasi-experimental or observational studies which could be included for behavioural therapies aimed at behaviour management in adults with autism. Based on GDG expert judgement and the rules of extrapolation, data were included for adults with intellectual disability and a single RCT was found which provided relevant clinical evidence and met eligibility for inclusion criteria. MATSON1981 compared independence training with a no treatment control group (see Table 43). The independence training was aimed at teaching showering behaviours and used behavioural therapy techniques such as modelling and prompting while also emphasizing self-evaluation and social reinforcement, with participants providing prompts to each other on showering skills. The primary outcome was successful acquisition/performance of activities of daily living. The target behavior, showering, was broken down into 27 task-analyzed steps and rated using a task-specific checklist. This study found evidence for a statistically significant treatment effect (test for overall effect: $Z=11.71$, $p<0.00001$) with participants who received independence training showing superior showering skills compared to the participants receiving no treatment. However, this evidence was of a very low quality due to downgrading based on risk of bias (conferred by non-blind ratings and lack of an attention-placebo control group), on the basis of indirectness (as extrapolating from adults with intellectual disability), and on the basis of imprecision (as the outcome measure was designed specifically for this study and no formal assessments of reliability and validity was reported).

Observational study of adaptive skills training

One of the two included observational studies for behavioural therapies aimed at behaviour management in adults with intellectual disability examined the change from baseline scores for activities of daily living with no control group over two consecutive five year periods (BATHAEE2001). Efficacy data could not be extracted for this study. However, the authors reported evidence for statistically significant change-from-baseline scores over the first five-year period from 1987-88 to 1992-93 in dressing ($t=2.26$, $p<0.03$; N=59), grooming ($t=2.85$, $p<0.005$; N=59), eating ($t=2.52$, $p<0.01$; N=59) and toileting ($t=2.82$; $p<0.005$; N=59) as assessed using the Behaviour Maturity Checklist II-1978 and the significant changes in toileting remained statistically significant over the second five-year period from 1992-93 to 1997-98 ($t=2.18$; $p<0.03$; N=51). These results are suggestive of beneficial long-term treatment effects of adaptive skills training on activities of daily living. However, this study is of very low quality, crucially because efficacy data cannot be extracted.

Behavioural weight control program compared with no treatment control group

The single included quasi-experimental study examining the effects of behavioural therapies on behaviour management in adults with intellectual disability compared a behavioural weight control programme with a no-treatment control group (see Table 43). The behavioural weight control programme in HARRIS1984 included training about diet, emphasising the importance of exercise, identifying external stimuli associated with food intake, using positive reinforcement, and focusing on long-term and short-term goals. The primary outcome was self-care, which in this case was reflected by weight loss. This study found no evidence for a significant treatment effect (test for overall effect: $Z=0.99$, $p=0.32$) with participants who received the behavioural therapy losing no more weight than participants who received treatment as usual. In addition, there were serious methodological concerns with this study as the no-treatment control group were composed of the participants who had dropped out of the behavioural weight control programme and control and experimental groups were therefore not selected independently of potentially confounding factors. This concern, together with the indirectness of the evidence, contributed to the downgrading of the evidence to very low quality.

Table 43: Summary evidence profile for behavioural therapies versus no treatment control for adults with intellectual disability

Outcome	**Activities of daily living**	**Self care**
Study ID	MATSON1981	HARRIS1984
Effect size	MD = 8.40 (6.99, 9.81)	SMD = 0.44 (-0.43, 1.30)
Quality of evidence (GRADE)	Very low[1,3,4]	Very low[2,3,5]
Number of studies/participants	(K=1; N=72)	(K=1; N=21)
Forest plot	1.1.2, Appendix 15	1.1.2, Appendix 15

[1]Downgraded due to risk of bias as there was no attention-placebo control group so participants did not receive same care apart from the intervention, and there was no blinding conferring a risk of performance and detection bias

[2]Downgraded due to risk of bias as the control group consisted of dropouts from the experimental group so there was high risk for selection bias. The study was also non-randomised and non-blind increasing the risk of performance and detection bias

[3]Downgraded due to indirectness as extrapolating from adults with intellectual disability
[4]Downgraded due to imprecision as the outcome measure was designed specifically for this study and lacks formal assessments of reliability and validity
[5]Downgraded due to imprecision as the sample size is small

Observational study of self-instructional pictorial childcare manuals

Finally, the second of the two included observational studies examining behavioural therapies aimed at behaviour management in adults with intellectual disability involved an examination of the effects of self-instructional pictorial manuals to teach child-care skills, with no control group (FELDMAN1999). Efficacy data could not be extracted for this study. However, the authors report evidence for significant change-from-baseline scores in percentages of correct parenting skill steps ($t=6.12$; $p<0.001$), suggesting that self-instruction based on behavioural principles may be beneficial for improving child care skills in adults with intellectual disability. However, this is very low quality evidence from an indirect and small sample and efficacy data cannot be extracted.

7.4.4 Clinical evidence summary for behavioural interventions for behaviour management

The single included RCT trial provides limited evidence for the efficacy of behavioural therapies in developing skills in the activities of daily living for adults with intellectual disability, and these findings are supported by the results of the observational study of adaptive skills training. However, this evidence is of very low quality and in addition to concerns regarding indirectness, imprecision and risk of bias, there is also uncertainty regarding the generalisability of these findings. For three of the four included studies a task-specific outcome measure designed specifically for the study is used, and whether these beneficial effects will generalise across skill areas or across settings is uncertain.

7.4.5 Health economics evidence for behavioural interventions for behaviour management

No studies assessing the cost effectiveness of behavioural interventions for behaviour management 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.

7.4.6 From evidence to recommendations

There is limited evidence for the efficacy of behavioural therapies in training activities of daily living for adults with intellectual disability but problems in these areas significantly impair the day-to-day functioning of many people with autism. With this issue in mind the GDG drew on their knowledge and expertise and decided that adaptive skills training based on behavioural principles could be beneficial for adults with autism who need help with developing daily living life skills. It was concluded that such programmes should be structured and

predictable, in line with both the knowledge of effectiveness of behavioural interventions beyond autism and the particular importance of structure and consistency for people with autism. There was no evidence for the use of behavioural interventions for challenging behaviour in adults with autism. However, the GDG judged that this was an important issue in autism and that these interventions may be beneficial, thus, based on GDG expert knowledge and judgement it was decided that behavioural interventions for challenging behaviour should be considered for managing challenging behaviour in the context of a comprehensive behaviour management and treatment approach (see also challenging behaviour recommendations in Chapter 8).

7.4.7 Recommendations for behavioural interventions for behaviour management

7.4.7.1 For adults with autism of all ranges of intellectual ability, who need help with activities of daily living, consider a structured and predictable programme based on behavioural principles.

7.4.8 Recommendations for interventions for challenging behaviour

7.4.8.1 Base the choice of interventions to address challenging behaviour on the nature and severity of the problem and a consideration of:

- the person's physical needs
- functional analysis of the behaviour
- the physical and social environment
- the preferences of the person with autism and their family or carer(s)
- past history of treatment.

7.4.8.2 Offer psychosocial interventions based on behavioural principles, and informed by a functional analysis of behaviour as initial treatment for the management of challenging behaviour. Interventions should:

- clearly identify the behaviours with agreed outcomes
- assess and modify environmental factors that may trigger or maintain the behaviour
- have a clearly defined intervention strategy
- have a clear schedule of reinforcement and capacity to offer reinforcement promptly and contingently on demonstration of the desired behaviour
- have a specified timescale to meet treatment goals (modifying intervention strategies that do not lead to change within a specified time).

7.5 COGNITIVE AND BEHAVIOURAL THERAPIES

7.5.1 Introduction

Cognitive behavioural therapy (CBT) was originally developed for the treatment of depression (Beck *et al*., 1979) but has since been adapted for use, and found to be effective for treating a range of mental health problems including anxiety disorders (see Butler *et al*., 2006; Salkovskis, 1999), psychosis (Tarrier *et al*., 1998) and eating disorders (Fairburn *et al*., 1993). Cognitive behavioural therapies are typically discrete, time-limited, structured interventions. They involve collaborative patient and therapist interaction in order to: identify the types and effects of thoughts, beliefs and interpretations on current symptoms; develop skills to identify, monitor and then counteract problematic thoughts, beliefs and interpretations related to the target symptoms/problems; and learn a repertoire of coping skills appropriate to the target thoughts, beliefs and/or problem areas.

Several authors have recommended the use of CBT for adults with autism (Attwood, 1998, 2004, 2006b; Cardaciotto & Herbert, 2004; Gaus, 2000, 2007; Hare & Paine, 1997; Tsai, 2006). However, the evidence base for the efficacy of CBT in adults with autism is essentially limited to case studies of, for instance, the use of CBT for treating coexisting depression in adults with autism (Hare, 1997; Hare & Paine, 1997) or coexisting social anxiety disorder (Cardaciotto & Herbert 2004). There are controlled studies for the use of CBT to treat coexisting conditions in children and adolescents with autism. However, the evidence for efficacy is generally limited (see Howlin, 2010), with only a handful of positive RCTs reported (Chalfant *et al*., 2007; Reaven *et al*., 2009; Sofronoff *et al*., 2005, 2007; Wood *et al*., 2009). In addition, concerns have been raised about the suitability of CBT approaches for individuals with autism given that the therapy is based on techniques such as abstraction that may require greater social/emotional understanding than may be possible for many people with autism (see Howlin, 2010). In light of this it is important when reviewing the evidence for CBT to treat coexisting conditions in adults with autism to consider the adaptations which may need to be made to the standard treatment of coexisting conditions. For instance, a number of autism-specific adaptations to CBT have been suggested, including a greater use of written and visual material, avoidance of the use of metaphor and abstract concepts in favour of concrete examples, and where appropriate involvement of a family member or key worker as a co-therapist in order to improve generalization of skills (Anderson & Morris, 2006).

Traditionally, CBT was considered as unsuitable for individuals with intellectual disability due to the heavily cognitive emphasis. However, cognitive behavioural therapies have been successfully adapted for individuals with intellectual disability (see Hatton, 2002; Willner, 2005; Taylor *et al*., 2008) and an area where there has been a number of controlled trials in adults with intellectual disability is in the use of CBT for anger management. Anger management programmes have been largely based on the work of Novaco (1975, 1976, 1979) and typically involve functional analysis of

anger provoking situations, psychoeducation, appraisal of hypothetical anger provoking situations, and stress inoculation (see Lindsay *et al.,* 2004).

The review of CBT for coexisting conditions or for anger management in adults with autism is of clinical significance given the high prevalence of coexisting conditions in individuals with autism (Hofvander *et al*., 2009; see Howlin, 2000) and the higher incidence of aggression towards others and objects found in individuals with autism and intellectual disability compared to individuals with intellectual disability alone (Cohen *et al*., 2010).

7.5.2 Studies considered

No RCTs were found which provided relevant clinical evidence for cognitive behavioural therapies in adults with autism and met the eligibility criteria for this review. There was, however, one quasi-experimental parallel group controlled trial in adults with autism (N=24) which was found and included (Russell *et al*., 2009 [RUSSELL2009]). Based on GDG expert judgement and the rules for extrapolation the decision was taken to extrapolate from adults with intellectual disability for cognitive behavioural therapies aimed at behaviour management. Two RCTs (N=81) were included (Khemka, 2000 [KHEMKA2000]; Khemka *et al*., 2005 [KHEMKA2005]), five quasi-experimental parallel group controlled trials (N=249) were also found and included (Lindsay *et al*., 2004 [LINDSAY2004]; Mazzucchelli, 2001 [MAZZUCCHELLI2001]; McGrath *et al*., 2010 [MCGRATH2010]; Rose *et al*., 2005 [ROSE2005]; Taylor *et al*., 2005 [TAYLOR2005]). Finally, two observational studies (N=65) in adults with intellectual disability met the extrapolation eligibility criteria and were included (Benson *et al*., 1986 [BENSON1986]; King *et al*., 1999 [KING1999]). All of these studies were published in peer-reviewed journals between 1986 and 2010. In addition, 11 studies were excluded as they did not meet eligibility criteria. The reasons for exclusion included mean age of below 15 years old, sample size of less than ten participants per arm, descriptive paper, or data could not be extracted that could be entered into a meta-analysis or narratively reviewed. Further information about included and excluded studies can be found in Appendix 14.

The quasi-experimental trial in adults with autism involved a comparison of cognitive behavioural therapy with treatment as usual (see Table 44) to treat coexisting OCD.

The two RCTs in adults with intellectual disability involved a comparison of anti-victimization skills training with treatment as usual (see Table 45). Three of the five included quasi-experimental studies also involved a comparison of anger management treatment with either treatment as usual or a waitlist control (see Table 46). There were also two observational studies that reported change from baseline scores for adults with intellectual disability receiving an anger management programme (see Table 47).

Finally, the remaining two included quasi-experimental studies involved a comparison of anti-victimization skills training with waitlist control (see Table 46).

Table 44: Summary study characteristics for included RCTs of cognitive behavioural therapies in adults with autism

	Cognitive behavioural therapy (CBT) for obsessive compulsive disorder
No. trials (Total participants)	1 (24)
Study IDs	RUSSELL2009
N/% female	3/13
Mean age	24 & 32
IQ	Range not reported (means: Mean VIQ 100.3; mean PIQ 95.5)
Axis I/II disorders	100% autism; 100% OCD
Comparator	Treatment as usual control group
Length of treatment	10-50 (mean=27.5) treatment sessions
Length of follow-up	Mean of 15.9 months

Table 45: Summary study characteristics for included RCTs of cognitive behavioural therapies in adults with intellectual disability

	Anti-victimization skills training
No. trials (Total participants)	2 (81)
Study IDs	(1) KHEMKA2000 (2) KHEMKA2005
N/% female	(1) 45/100 (2) 36/100
Mean age	(1) 36 (2) 34
IQ	(1) Range not reported (mean 60.89) (2) Range not reported (mean 55.92)
Axis I/II disorders	(1) 100% ID (2) 100% ID
Comparator	(1) Treatment as usual control group (2) Treatment as usual control group
Length of treatment	(1) 10 training sessions spread over several weeks (2) 6-12 weeks
Length of follow-up	(1) 10 training sessions (2) 12 weeks

Table 46: Summary study characteristics for included quasi-experimental controlled trials of cognitive behavioural therapies in adults with intellectual disability

	Anti-victimization skills training	**Anger management**
No. trials (Total participants)	2 (58)	3 (169)

Study IDs	(1) MAZZUCCHELLI2001 (2) MCGRATH2010	(1) LINDSAY2004 (2) ROSE2005 (3) TAYLOR2005
N/% female	(1) 15/75 (2) 30/50	(1) 14/30 (2) 15/17 (3) 0/0
Mean age	(1) 31 & 37 (2) 33 & 36	(1) 24 & 28 (2) 35 & 39 (3) 29 & 30
IQ	(1) Range not reported (means 56 & 60) (2) Not reported (borderline, mild, or moderate ID)	(1) Range not reported (means 65 & 66) (2) 24-113 (mean 72) (3) Range not reported (means 67 & 71)
Axis I/II disorders	(1) 100% ID (2) 100% ID	(1) 100% ID (2) 100% ID (3) 100% ID
Comparator	(1) Waitlist control group (2) Waitlist control group	(1) Treatment as usual (2) Waitlist control group (3) Treatment as usual
Length of treatment	(1) 4 weeks (2) 10 sessions	(1) 9 months (approx. 40 sessions) (2) 16 2-hour sessions (3) 18 sessions
Length of follow-up	(1) 9 weeks (2) 3 months	(1) 9 months (2) 6 months (3) 4 months

Table 47: Summary study characteristics for included observational studies of cognitive behavioural therapies in adults with intellectual disability

	Anger management
No. trials (Total participants)	2 (65)
Study IDs	(1) BENSON1986* (2) KING1999*
N/% female	(1) 17/31 (2) 4/36
Mean age	(1) 32 (2) 30
IQ	(1) Not reported (mild or moderate ID) (2) Not reported (mild ID)
Axis I/II disorders	(1) 100% ID (2) 100% ID
Comparator	(1) No comparator (2) No comparator
Length of treatment	(1) 12 weekly sessions (2) 15 weekly sessions
Length of follow-up	(1) 19 weeks (2) 27 weeks

*Efficacy data not extractable.

7.5.3 Clinical evidence for cognitive behavioural therapies

Cognitive behavioural therapies compared with treatment as usual for coexisting conditions

A single quasi-experimental study was included for cognitive behavioural therapies in adults with autism (see Table 48). RUSSELL2009 compared cognitive behavioural therapy with treatment as usual in adults with autism and coexisting OCD. The intervention involved exposure and response prevention, and cognitive appraisal of OCD-related beliefs. The primary outcome was treatment effects on the coexisting OCD symptoms, as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS) severity scale. The authors report that OCD symptoms were carefully distinguished from the repetitive phenomena typically seen in autism, however, they did not elaborate on the way in which this was achieved. This study failed to find evidence for significant treatment effects (test for overall effect: $Z=0.79$, $p=0.43$), with participants receiving CBT showing no significant difference in severity of OCD symptoms compared to participants receiving treatment as usual.

Table 48: Summary evidence profile for cognitive behavioural therapy versus treatment as usual for coexisting conditions in adults with autism

Outcome	**Severity of OCD symptoms**
Study ID	RUSSELL2009
Effect size	MD = 2.42 (-3.60, 8.44)
Quality of evidence (GRADE)	Very low[1,2]
Number of studies/participants	(K=1; N=24)
Forest plot	1.1.3, Appendix 15

[1]Downgraded due to risk of bias as there was no attention-placebo control group so participants did not receive same care apart from intervention, and non-randomised and non-blind so risk of selection, performance and detection bias

[2]Downgraded for imprecision as the sample size is small

Anti-victimization skills training compared with waitlist control

Two RCT studies in adults with intellectual disability involved a comparison of anti-victimization skills training programmes with waitlist control groups (see Table 43). These interventions used a cognitive-behavioural approach to attempt to teach participants to anticipate and avoid potential situations of abuse or bullying. The anti-victimization skills training programmes involved instruction in independent decision-making skills through the use of simulated interpersonal situations of abuse. The interventions emphasised self-directed decision-making which combined instruction on cognitive and motivational aspects of decision-making. Two quasi-experimental parallel-group controlled trials also compared anti-victimization skills training programmes with waitlist control. Meta-analysis which combined continuous measures of anti-victimization skills revealed a statistically significant treatment effect (test for overall effect: $Z=4.29$, $p<0.0001$) suggesting that participants receiving the intervention showed superior anti-victimization skills compared with control participants. However, there is significant heterogeneity for

the meta-analysis (I^2=78%, p=0.01) suggesting that it may not be valid to combine the results from these trials into a meta-analysis. Nevertheless, when considered individually the treatment effects remain statistically significant for the RCTs (tests for overall effect: Z=6.18, p<0.00001; and Z=3.13, p=0.002 for mean differences in KHEMKA2000 and KHEMKA2005 respectively) but not for the quasi-experimental study (test for overall effect: Z=0.65, p=0.51 for MAZZUCCHELLI2001). The second of the included quasi-experimental studies comparing anti-victimization training with waitlist control examined dichotomous data for rates of bullying in the sample following the intervention (see Table 49) and again failed to find evidence for a significant treatment effect (test for overall effect: Z=0.91, p=0.36). To summarise, the evidence for the use of CBT programmes for training anti-victimization skills in adults with intellectual disability is largely positive and suggestive of significant treatment effects. However, this evidence is indirect as it was extrapolated from a population of adults with intellectual disability. There are also methodological limitations which necessitate caution in the interpretation of results.

Table 49: Summary evidence profile for cognitive behavioural therapy versus treatment as usual or waiting list control in adults with intellectual disability

Outcome	**Anti-victimization skills (continuous)**	**Anti-victimization skills (dichotomous)**	**Anger management**
Study ID	(1) KHEMKA2000 (2) KHEMKA2005 (3) MAZZUCCHELLI2001	MCGRATH2010	(1) LINDSAY2004 (2) ROSE2005 (3) TAYLOR2005
Effect size	SMD = 1.07 (0.58, 1.56)	RR = 0.64 (0.25, 1.67)	SMD = -0.59 (-0.90, -0.27)
Quality of evidence (GRADE)	Very low[1,2,3,4]	Very low[1,2]	Very low[1,2]
Number of studies/participants	(K=3; N=80)	(K=1; N=38)	(K=3; N=169)
Forest plot	1.1.3, Appendix 15	1.1.3, Appendix 15	1.1.3, Appendix 15

[1]Downgraded for risk of bias as there is no attention-placebo control group so participants did not receive same care apart from intervention, and non-blind so risk of performance and detection bias

[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

[3]Downgraded for imprecision as the reliability and validity of the outcome measures is unclear

[4]Two RCTs (KHEMKA2000 & KHEMKA2005) and one QE (MAZZUCCHELLI2001) combined with high heterogeneity

Anger management compared with treatment as usual or waitlist control

Three of the five included quasi-experimental studies in adults with intellectual disability compared anger management programmes with treatment as usual or waitlist control groups (see Table 49). These interventions were based on the work of Novaco and included behavioural relaxation training, stress inoculation, discussion on appropriate and inappropriate behaviour, problem-solving strategies, and role-play. The primary outcome was anger as measured by provocation or anger inventories (such as the Dundee Provocation Inventory, the Anger Inventory and the Provocation Inventory). These studies were combined in a meta-analysis and provide limited evidence for statistically significant beneficial effects of CBT intervention for anger management in adults with intellectual disability (test for overall effect: $Z=3.60$, $p=0.0003$).

Observational studies of anger management

Finally two observational studies with no control groups examine the effects of anger management training in adults with intellectual disability (BENSON1986; KING1999). Efficacy data cannot be extracted for these studies. However, the authors report data suggestive of positive treatment effects. BENSON1986 reported statistically significant change from baseline scores for aggressive gestures on the videotaped roleplay test ($t=3.71$; $p<0.0005$). While, KING1999 reported statistically significant change from baseline for anger inventory scores ($t=5.19$; $p<0.05$). Thus, these two observational studies provide limited evidence for positive treatment effects of CBT on anger management in adults with intellectual disability, and as these results are consistent with the quasi-experimental studies they lend support to the efficacy of this intervention.

7.5.4 Clinical evidence summary for cognitive behavioural therapies

The single included study in adults with autism compared cognitive behavioral therapy with treatment as usual for the severity of coexisting OCD symptoms. However, this trial reported no evidence for significant treatment effects of CBT on coexisting OCD. The study also failed to detail any autism-specific modifications that were made to the standard CBT treatment and this may reflect the fact that no such adaptation took place and could, in part, account for the lack of efficacy. In contrast the evidence for cognitive behavioural therapies aimed at anti-victimization skills or anger management in adults with intellectual disability provide more promising results with limited evidence for positive treatment effects for CBT on both outcomes. However, it is important to bear in mind that this evidence is of very low quality and is indirect. Thus, it is important to consider any adaptations that may need to be made in order to generalise results to adults with autism

7.5.5 Health economics evidence for cognitive behavioural therapies

No studies assessing the cost effectiveness of cognitive behavioural therapies 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.

7.5.6 From evidence to recommendations

The evidence concerning the cognitive behavioural treatment of coexisting conditions is very limited and provides no specific evidence to support the development of adaptations to CBT to make it potentially more effective for people with autism. Effective psychological interventions, predominantly CBT, exist for depression and anxiety and there is extensive NICE guidance on them. The GDG consider that they would be appropriate for many adults with autism. However, the evidence reviewed in this guideline does not provide any guidance on autism-specific adaptations to existing psychological interventions for coexisting conditions. In the absence of such evidence and given the high prevalence of depression and anxiety disorders in adults with autism the GDG drew on their knowledge and expertise both of psychological interventions and autism to develop some recommendations on how CBT (and other psychological interventions) might be adapted in order to increase their effectiveness in autism. These included a more concrete, structured, approach with a greater use of written and visual information than might typically be the case in CBT. The GDG were of the view that an emphasis on the behavioural rather than the cognitive aspects of CBT could be beneficial as could shorter sessions or regular breaks. Careful consideration should be given to the use of group based approaches and the excessive use of metaphors or hypothetical situations should be avoided. Consideration should also be given to the increased involvement of a family member or key worker as co-therapist to support the generalisation of benefits.

The evidence for cognitive behavioural therapies for anti-victimization skills and anger management in adults with intellectual disability was somewhat more promising and addressed a key area of concern for people with autism and their families and carers. The GDG therefore recommended the use of these interventions for adults with autism, but did not recommend that specific adaptations of the method for autism be considered. However, for interventions for coexisting disorders and for delivery of anti-victimisation skills and anger management training the GDG were of the view that an individual delivering such intervention should be familiar with the impact of autism on a person's psychological functioning. Where concerns arose about the adaptation of delivery of an intervention they should consider seeking advice from a specialist in autism if they do not have particular knowledge and expertise.

7.5.7 Recommendations

7.5.7.1 For adults with autism and coexisting mental health disorders, offer a range of psychosocial interventions informed by existing NICE guidance for the specific condition.

7.5.7.2 Staff delivering interventions for coexisting conditions for adults with autism should have a basic understanding of autism and should seek advice from the specialist autism team regarding adaptating interventions for people with autism.

7.5.7.3 Adaptations to the method of delivery of cognitive and behavioural interventions for adults with autism and coexisting common mental health disorders should include:

- a more concrete and structured approach with a greater use of written and visual information (which may include worksheets, thought bubbles, images and 'tool boxes')
- placing greater emphasis on changing behaviour, rather than cognitions, and using the behaviour as the starting point for intervention
- making rules explicit and explaining their context
- using plain English and avoiding excessive use of metaphor and hypothetical situations
- involving a family member or key worker as co-therapist (if the person with autism agrees) to improve the generalisation of skills
- maintaining the person's attention by offering regular breaks and incorporating their special interests into therapy if possible.

7.5.7.4 For adults with autism who are at risk of victimisation, consider anti-victimisation interventions based on teaching cognitive decision-making and problem-solving skills.

7.5.7.5 Anti-victimisation interventions should focus on:

- identifying and, where necessary, modifying situations associated with abuse
- developing decision-making skills in these situations
- developing personal safety skills.

7.5.7.6 For adults with autism who have problems with anger and aggression, offer an anger management intervention, adjusted to the needs of adults with autism.

7.5.7.7 Anger management interventions should include the following key components:

- functional analysis of anger and anger-provoking situations
- coping-skills training and behaviour rehearsal
- relaxation training

- development of problem-solving skills.

7.5.8 Research recommendation

7.5.8.1 What is the clinical and cost effectiveness of facilitated self-help for the treatment of mild anxiety and depressive disorders in adults with autism?

Why is this important?

Anxiety and depressive disorders commonly coexist in people with autism and are associated with poorer health outcomes and quality of life. This may occur because of the direct impact of the anxiety or depression but also because of a negative interaction with the core symptoms of autism. There is limited access and poor uptake of facilitated self-help by people with autism largely due to limited availability, but also because current systems for the delivery of such interventions are not adapted for use by people with autism. In adults without autism, facilitated self-help is an effective intervention for mild to moderate depression and anxiety. The development of novel methods for the delivery of facilitated self-help could make effective interventions available to a wider group of people.

The suggested programme of research would need to: (a) develop current methods for the delivery of self-help measures to take into account the impact of autism and possibly include developments in the nature of the materials, the methods for their delivery and the nature, duration and extent of their facilitation; (b) test the feasibility of the novel methods in a series of pilot studies; and (c) formally evaluate the outcomes (including symptoms, satisfaction and quality of life) in a large-scale randomised trial.

7.6 LEISURE PROGRAMMES

7.6.1 Introduction

For individuals with autism, leisure pursuits may well involve isolated activities such as playing video games and watching television (Jennes-Coussens *et al*., 2006; Wagner *et al*., 2005). However, inclusion in social, leisure and community activities is increasingly being seen as a contributor to quality of life (Baker & Palmer, 2006; Iwasaki, 2007), and there is research suggesting a positive relationship between leisure participation, quality of life and stress reduction as described by the World Health Organization Quality of Life Assessment Working Group (The Group, WHOQOL, 1998). Previous research has found an increased prevalence of stress and associated anxiety in individuals with autism (Bellini, 2004; Gillot *et al*., 2001; Green *et al*., 2000; Kim *et al*., 2000), and many of the problem behaviours which can be associated with autism, including aggression, self-injury, and property destruction, have been seen as related in some way to stress (Prior & Ozonoff, 1998; Groden *et al*., 1994). Thus, given the role of leisure as a means of enhancing quality of life and as a coping mechanism for dealing with acute and chronic life stressors (Hutchinson *et al*., 2003; 2008), introduction of therapeutic interventions based on developing structured leisure activities has been hypothesised to be beneficial for individuals with autism. However, many individuals with autism have been denied access to the full range of recreation opportunities because of others' misconceptions about them (Coyne, 2004), and there is a need to systematically develop and evaluate programmes designed to provide opportunities for individuals with autism to experience leisure (García-Villamisar & Dattilo, 2011).

7.6.2 Studies considered

There were two RCTs found which provided relevant clinical evidence in adults with autism (N=111) and met the eligibility criteria for this review group (García-Villamisar & Dattilo, 2010 [GARCIAVILLAMISAR2010]; García-Villamisar & Dattilo, 2011 [GARCIAVILLAMISAR2011]). Both of these studies were published in peer-reviewed journals between 2010 and 2011. Further information about included studies can be found in Appendix 14.

The two RCTs in adults with autism (see Table 50) both involved a comparison of a leisure programme intervention with a waiting list control.

Table 50: Summary study characteristics for included RCTs of leisure programme interventions in adults with autism

	Leisure programme
No. trials (Total participants)	2 (111)
Study IDs	(1) GARCIAVILLAMISAR2010

	(2) GARCIAVILLAMISAR2011
N/% female	(1) 30/42 (2) 16/40
Mean age	(1) 31 & 30 (2) 32
IQ	(1) Not reported (2) Not reported
Axis I/II disorders	(1) 100% autism (3% Asperger syndrome) (2) 100% autism
Comparator	(1) Waitlist (2) Waitlist
Length of treatment	(1) One year (2) One year
Length of follow-up	(1) One year (2) One year

7.6.3 Clinical evidence for leisure programme interventions

Leisure programme versus waitlist control

GARCIAVILLAMISAR2010 compared a leisure programme intervention with a waitlist control group (see Table 51). The leisure programme intervention consisted of a group recreation context from 17:00-19:00 (2 hours) each day (5 days/week) for participants to interact with media (CD player, radio, magazines), engage in exercise (swim, play catch, play Frisbee, hike, bowling), play games and do crafts (computer games, puzzles, collections, printing, darts), attend events (parties, fairs, cinema, concerts, museums) and participate in other recreation activities (socialising, youth groups). The criteria for activity selection included activities that were understandable (flexible, structured, well-defined beginning and end, clear visual presentation of instructions, minimal verbal direction), reactive (provide reinforcement through sensory feedback), comfortable (commensurate with participant's skills and challenging), and active (frequent changes between activities). GARCIAVILLAMISAR2010 found evidence for a significant beneficial effect of the leisure programme on quality of life (test for overall effect: $Z=5.23$, $p<0.00001$), with participants receiving the leisure intervention showing superior quality of life scores compared to participants in the waitlist control group.

GARCIAVILLAMISAR2011 examined the effects of comparable leisure programme on emotion recognition as assessed by The Facial Discrimination Battery. Again, a significant treatment effect was observed (test for overall effect: $Z=2.35$, $p=0.02$), with participants in the leisure programme intervention group showing significantly higher scores on a test of emotion recognition than the waitlist control group.

Thus, these two RCTs provide evidence of significant treatment effects of a leisure programme intervention on quality of life and emotion recognition in a group of adults with autism. It should, however, be noted that the lack of an attention-placebo control group increases the risk of performance bias.

Table 51: Summary evidence profile for leisure programme versus waitlist control in adults with autism

Outcome	**Quality of life**	**Emotion recognition**
Study ID	GARCIAVILLAMISAR2010	GARCIAVILLAMISAR2011
Effect size	MD = 8.33 (5.21, 11.45)	MD = 12.77 (2.12, 23.42)
Quality of evidence (GRADE)	Moderate[1]	Low[1,2]
Number of studies/participants	(K=1; N=71)	(K=1; N=40)
Forest plot	1.1.4, Appendix 15	1.1.4, Appendix 15

[1]Downgraded for risk of performance bias due to the lack of an attention-placebo control group

[2]Downgraded for imprecision as the sample size is small

7.6.4 Clinical evidence summary for leisure programme interventions

The results from these two trials suggest that leisure programmes can improve quality of life and emotion recognition. The authors concluded that participation in recreational activities positively influenced the stress and quality of life of adults with autism and had positive effects on social-emotional cognition. Given the findings that individuals with autism have higher levels of loneliness and social dissatisfaction compared to their typically developing peers (Huang & Wheeler, 2006), these results suggest that a leisure programme which is designed to encourage and support participation of adults with autism in group recreation activities may have tangible benefits.

7.6.5 Health economics evidence for leisure programme interventions

No studies assessing the cost effectiveness of leisure programme interventions 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.

7.6.6 From evidence to recommendations

The two trials from adults with autism present limited evidence for the beneficial effects of leisure programmes which provide regular group recreation in order to provide structure and support for leisure activities and encourage a focus on the interests and abilities in adults with autism. The leisure programmes were found to have a positive effect on quality of life and also to impact on a core symptom of autism as reflected in improvements in social-emotional cognition. As adults with autism often experience social

exclusion and the inclusion in social, community and leisure activities has been found to reduce stress which is a significant coexisting problem in autism, the GDG were of the view that interventions to develop structured leisure activities should be recommended for adults with autism of all intellectual abilities.

7.6.7 Recommendations

7.6.7.1 Consider a structured leisure activity programme for adults with autism of all ranges of intellectual ability.

7.6.7.2 A structured leisure activity programme should typically include:

- a group who meet regularly for a valued leisure activity
- a focus on the interests and abilities of the participants
- the provision of structure and support.

7.7 SOCIAL LEARNING INTERVENTIONS

7.7.1 Introduction

Impairments in social interaction are one of the core symptoms of autism. The prevalence of friendships and participation in social groups is low for adults with autism. For instance, studies have found that, regardless of intellectual functioning, the estimate for adults with autism who have no peer relationships or no particular friend with whom they share activities was around 50% (Mawhood *et al*., 2000; Orsmond *et al*., 2004). In addition, individuals with autism who do have friends often report atypical definitions of what a friend is and experience friendships that are based on common interests and characterised by minimal social interaction (Orsmond *et al*., 2004). However, the low incidence of social relationships and differences in friendships does not necessarily reflect a lack of desire for such relationships but more likely a lack of the necessary skills for developing such relationships. For instance, adolescents with autism report wanting friends (Marks *et al*., 2000) and higher levels of loneliness have been found for individuals with autism compared with typically developing peers (Bauminger & Kasari, 2000; Bauminger *et al*., 2003). Impairments in social interaction impact upon many aspects of life for an individual with autism. For instance, social skills have been associated with employment success (Chadsey-Rusch, 1992) and individuals with autism who have normal intelligence often find obtaining and keeping a job difficult as a consequence of their social impairments (Barnard *et al*., 2000; Morgan, 1996). Individuals with autism and intelligence in the normal range often know the social rules and can learn the skills but do not know to apply those skills (Hillier *et al*., 2007). Interventions based on social learning principles have used techniques including instruction, discussion, modelling (including video modelling), feedback, role play and reinforcement, to teach adolescents and adults with autism the 'rules' of social interaction in the context of social skills groups that have the additional advantage of allowing social skills to be learned and practised at the same time within the group context (Herbrecht *et al*., 2009; Hillier *et al*., 2007; Howlin & Yates, 1999; Laugeson *et al*., 2009; Tse *et al*., 2007; Webb *et al*., 2004). Other interventions have been aimed at improving social interaction skills in adults with autism by targeting fundamental autistic impairments such as 'theory of mind' deficits (Hadwin *et al*., 1995; Ozonoff & Miller, 1995) and computer software programme interventions have been developed to teach emotion recognition (Golan & Baron-Cohen, 2006). The social skills group interventions date back to the 1980s and were aimed at improving communication and interaction skills and at facilitating positive social experience with peers for children with autism (Mesibov, 1984; Ozonoff & Miller, 1995). Participants often value the friendships they gain more than the skills learned during the course of social skills group interventions (Hillier *et al*., 2007). Social skills groups vary in terms of the teaching techniques, frequency and duration of group sessions, group composition, and so on,

however, certain common principles have emerged such as the teaching of social skills in concrete terms, a predictable and structured learning environment, and the opportunity to engage with peers within a positive environment (Barry *et al*., 2003; Herbrecht *et al*., 2009; Krasny *et al*., 2003; Williams *et al*., 2006). There is evidence for the efficacy of social skills group interventions in children with autism (see Williams *et al*., 2006). However, the generalisability of effects outside of the social skills groups and to new social situations and interactions is unclear, with only limited evidence for generalisation outside the group context (Tse *et al*., 2007).

7.7.2 Studies considered

There was one RCT found which provided relevant clinical evidence for social learning interventions in adults with autism (N=41) and met the eligibility criteria for this review (Golan & Baron-Cohen, 2006 [GOLAN2006]). There were also two observational studies of social learning interventions in adults with autism (N=23) (Hillier *et al*., 2007 [HILLIER2007]; Howlin & Yates, 1999 [HOWLIN1999]). Based on GDG expert judgement the decision was taken to extrapolate from adolescents (mean age ≥ 15 years) with autism for social learning interventions aimed at social interaction. There was one RCT for adolescents with autism (N=33) (Laugeson *et al*., 2009 [LAUGESON2009]). There were also three observational studies (N=73) found and included for adolescents with autism (Herbrecht *et al*., 2009 [HERBRECHT2009]; Tse *et al*., 2007 [TSE2007]; Webb *et al*., 2004 [WEBB2004]). Finally the GDG agreed, as previously mentioned, to extrapolate from adults with intellectual disability for interventions aimed at behaviour management. On this basis, one RCT (N=48) which examined the effects of a social learning intervention on challenging behaviour in adults with intellectual disability was included (Lee, 1977 [LEE1977]). All of these studies were published in peer-reviewed journals between 1977 and 2009. In addition, 30 studies were excluded as they did not meet eligibility criteria. The most common reasons for exclusion were a mean age of below 15 years old or a sample size of less than ten participants per arm. Further information about included and excluded studies can be found in Appendix 14.

The RCT in adults with autism involved a comparison of an emotion recognition computer software programme intervention with treatment as usual (see Table 52).

The RCT in adolescents with autism involved a comparison of a social skills group with a waitlist control group (see Table 53).

The RCT in adults with learning disabilities involved a comparison of a social skills group with treatment as usual (see Table 54).

Finally, all of the observational studies reported change from baseline scores for participants receiving social skills group interventions (see Table 55 for adults with autism; and see Table 56 for adolescents with autism).

Table 52: Summary study characteristics for included RCTs of social learning interventions in adults with autism

	Emotion recognition computer software programme
No. trials (Total participants)	1 (41)
Study IDs	GOLAN2006
N/% female	10/24
Mean age	31
IQ	80-140 (mean VIQ 108 & 110; mean PIQ 112 & 115)
Axis I/II disorders	100% autism (Asperger syndrome & high-functioning autism)
Comparator	Treatment-as-usual
Length of treatment	10 weeks (minimum of 10 hours)
Length of follow-up	15 weeks

Table 53: Summary study characteristics for included RCTs of social learning interventions in adolescents with autism

	Social skills group
No. trials (Total participants)	1 (33)
Study IDs	LAUGESON2009
N/% female	5/15
Mean age	15
IQ	Range not reported (mean VIQ 88 & 96)
Axis I/II disorders	100% autism (70% high-functioning autism, 27% Asperger's Disorder; 3% PDD-NOS)
Comparator	Waitlist control group
Length of treatment	12 weeks
Length of follow-up	24 weeks

Table 54: Summary study characteristics for included RCTs of social learning interventions in adults with intellectual disability

	Social skills group
No. trials (Total participants)	1 (48)
Study IDs	LEE1977
N/% female	26/54
Mean age	Median: 37
IQ	12-87 (mean 47)
Axis I/II disorders	100% ID
Comparator	Treatment-as-usual
Length of treatment	10 weeks
Length of follow-up	10 weeks

Table 55: Summary study characteristics for included observational studies of social learning interventions in adults with autism

	Social skills group
No. trials (Total participants)	2 (23)
Study IDs	(1) HILLIER2007* (2) HOWLIN1999*
N/% female	(1) 2/15 (2) 0/0
Mean age	(1) 19 (2) 28
IQ	(1) 81-141 (mean 108.08) (2) Non-verbal IQ 86-138 (mean 109)
Axis I/II disorders	(1) 100% autism (8% autism, 31% PDD-NOS, 62% Asperger's Syndrome) (2) 100% autism
Comparator	(1) No comparator (2) No comparator
Length of treatment	(1) 8 weeks (2) One year
Length of follow-up	(1) 8 weeks (2) One year

*Efficacy data not extractable.

Table 56: Summary study characteristics for included observational studies of social learning interventions in adolescents with autism

	Social skills group
No. trials (Total participants)	3 (73)
Study IDs	(1) HERBRECHT2009* (2) TSE2007* (3) WEBB2004*
N/% female	(1) 2/12 (2) 18/39 (3) 0/0
Mean age	(1) 15 (2) 15 (3) 15

IQ	(1) Range not reported (mean 93.4) (2) Not reported (3) 81-132 (mean 100.5)
Axis I/II disorders	(1) 100% autism; 18% OCD, 12% impulsivity or aggression, 6% hyperactivity (2) 100% autism (3) 100% autism
Comparator	(1) No comparator (2) No comparator (3) No comparator
Length of treatment	(1) 5 months (2) 12 weeks (3) 6.5 weeks
Length of follow-up	(1) 11 months (2) 12 weeks (3) 10 weeks

*Efficacy data not extractable.

7.7.3 Clinical evidence for social learning interventions

Emotion recognition training versus treatment-as-usual

There was one included RCT which compared a computer-based emotion recognition software programme with treatment as usual in adults with autism (see Table 57). GOLAN2006 trained emotion recognition in adults with autism using 'Mind Reading', a computer-based interactive guide to emotions and mental states. The primary outcome was emotion recognition as assessed by the recognition of complex emotions in faces and voices measured using The Cambridge Mindreading (CAM) Face-Voice Battery. This study found no evidence for a significant treatment effect on the CAM face task (test for overall effect: Z=1.06, p=0.29) with no significant differences in recognizing emotion in the face found in participants receiving emotion recognition training compared to participants receiving treatment as usual.

Table 57: Summary evidence profile for social learning versus treatment as usual in adults with autism

Outcome	**Emotion recognition**
Study ID	GOLAN2006
Effect size	MD = 2.70 (-2.27, 7.67)
Quality of evidence (GRADE)	Low[1,2]
Number of studies/participants	(K=1; N=40)
Forest plot	1.1.5, Appendix 15

[1]Downgraded for risk of bias as there was no attention-placebo control group so participants did not receive same care apart from intervention, and non-blind so risk of performance and detection bias

[2]Downgraded for imprecision as the sample size is small

Social skills group interventions

There were no included RCTs which compared social skills group interventions with treatment as usual or waitlist control groups in adults with autism. However, there were two observational studies which examined the effects of social skills group interventions in adults with autism. HILLIER2007examined the effects of a social skills group ('Aspirations'), which aimed to foster understanding of a range of social and vocational issues, to enhance insight and awareness, and to provide social opportunities for group members. Similarly in HOWLIN1999 the intervention took the form of a social skills group where techniques such as role-play, team activities, structured games, and feedback based on behavioural observations, were used to focus on major issues raised by group members and core features of conversational ability. Efficacy data could not be extracted for these studies. However, the authors of both studies report results suggestive of beneficial treatment effects. HILLIER2007reported a statistically significant change from baseline score on the Empathy Quotient ($z=2.520$; $p=0.012$), suggesting that a social learning intervention may have significant positive effects on a measure of core autistic symptoms pertaining to social interaction. While, HOWLIN1999 reported evidence for a statistically significant treatment effect of the social skills group on the percentage of conversation maintaining/initiating observed during a video recording of simulated social activities, in this case, a 'party' scenario ($z=-2.43$; $p=0.015$). To sum up these two studies reported limited evidence for a positive treatment effect for social skills groups on social interaction skills in adults with autism.

Based on GDG expert judgment and the rules of extrapolation the decision was taken to include studies from adolescents with autism for social learning interventions in adolescents with autism. A single RCT study compared a social skills group intervention with a waitlist control group in adolescents with autism (see Table 58). The social skills intervention in LAUGESON2009 was called the PEERS intervention and involved parents and teenagers attending separate concurrent sessions that instructed them on key elements about making and keeping friends. This study found evidence for a statistically significant treatment effect (test for overall effect: $Z=6.24$, $p<0.00001$) with the social skills group intervention participants showing superior scores on the Test of Adolescent Social Skills Knowledge compared with the waitlist control group.

There were also three observational studies examining the effects of social skills groups on social interaction skills in adolescents with autism (HERBRECHT2009; TSE2007; WEBB2004). Efficacy data could not be extracted for these studies. However, the results reported by the authors provide mixed evidence for beneficial treatment effects of social skills groups. HERBRECHT2009 examined the effects of the Frankfurt social skills training (KONTAKT) programme, that used techniques including teaching of rules, social interaction games, role play, and group discussion, to focus on learning

to initiate social overtures, conversation skills, understanding social rules and relationships, identification and interpretation of verbal and non-verbal social signals, problem-solving, coping strategies and improvement of self-confidence. HERBRECHT2009 failed to find evidence for significant treatment effects on the only blinded measure of social interaction, a blind-expert video rating (F=1.5; p=0.24). WEBB2004 also failed to find evidence for a significant treatment effect of a social skills group (t=1.287; p=0.230) with no significant change from baseline score on the Social Skills Rating System as a consequence of participating in the social skills group. Conversely, TSE2007 reported evidence suggestive of beneficial effects of social skills groups. This social skills group combined psychoeducational and experiential methods to teach social skills, with an emphasis on learning through role play. TSE2007 reported evidence for statistically significant change-from-baseline scores for social interaction as measured by the parent-completed Social Responsiveness Scale (SRS) (effect size 0.39; p=0.003) and challenging behavior as measured by the Aberrant Behaviour Checklist (ABC) Irritability subscale (effect size = 0.72; p=0.002).

Finally, based on GDG expert judgement a single RCT study was included which compared a social skills group with treatment as usual for behavior management in adults with intellectual disability (see Table 59). LEE1977 examined the effects of social adjustment training on challenging behaviour as assessed by Part 2 of the AAMD Adaptive Behavior Scale. However, this study failed to find evidence for a significant treatment effect on challenging behavior (test for overall effect: Z=0.41, p=0.68).

Table 58: Summary evidence profile for social learning versus waitlist control in adolescents with autism

Outcome	**Social interaction**
Study ID	LAUGESON2009
Effect size	MD = 6.30 (4.32, 8.28)
Quality of evidence (GRADE)	Very low[1,2,3]
Number of studies/participants	(K=1; N=33)
Forest plot	1.1.5, Appendix 15

[1]Downgraded for risk of bias as there was no attention-placebo control group so participants did not receive same care apart from intervention, and non-blind so risk of performance and detection bias

[2]Downgraded for indirectness as extrapolating from adolescents with autism

[3]Downgraded for imprecision as the sample size is small

Table 59: Summary evidence profile for social learning versus treatment as usual in adults with learning disabilities

Outcome	**Maladaptive behaviour**
Study ID	LEE1977
Effect size	MD = -2.03 (-11.79, 7.73)
Quality of evidence (GRADE)	Very low[1,2,3]

Number of studies/participants	(K=1; N=44)
Forest plot	1.1.5, Appendix 15

[1]Downgraded for risk of bias as there was no attention-placebo control group so participants did not receive same care apart from intervention, and non-blind so risk of performance and detection bias

[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

[3]Downgraded for imprecision as the sample size is small

7.7.4 Clinical evidence summary for social learning interventions

The evidence for social learning interventions is inconsistent. There is no evidence for beneficial effects of emotion recognition training in adults with autism. Conversely, the evidence for social skills groups is more mixed. The evidence from observational studies in adults with autism, and from the RCT in adolescents with autism, is positive. However, the evidence from the observational studies in adolescents with autism is more mixed with one study reporting limited evidence for significant treatment effects of a social skills group intervention on social interaction, and the other two studies failing to find evidence for significant beneficial effects.

7.7.5 Health economics evidence for social learning interventions

No studies assessing the cost effectiveness of social learning interventions 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.

7.7.6 From evidence to recommendations

The efficacy data for social learning interventions for social interaction is limited and variable. However, these interventions address an important area that could improve significant problems of isolation for people with autism. In adults with autism there is one RCT for emotion recognition training that finds no evidence for a treatment effect. However, the observational studies in adults with autism suggest positive effects associated with social skills groups. For adolescents with autism the single RCT trial of a social skills group intervention provides evidence for significant treatment effects while the observational studies provide a more mixed outcome. However, the limited evidence from adults with autism suggests that individuals with autism may benefit from such interventions. The limited evidence does not allow for a thorough analysis or understanding of these inconsistencies. However, based on the positive evidence from adults and the GDG expert knowledge, the GDG judged that social skills group interventions may help to address significant issues for adults with autism, including social isolation, which may in turn impact on other outcomes such as employment.

7.7.7 Recommendations

7.7.7.1 For adults with autism of all ranges of intellectual ability, who have identified problems in social interaction, consider a social learning programme focused on improving social interaction.

7.7.7.2 Group-based social learning programmes to improve social interaction should typically include:

- modelling
- peer feedback
- discussion and decision-making.

7.7.7.3 For adults with autism who find group-based activities difficult, consider an individually-delivered social learning programme, which should typically include:

- modelling
- individual feedback
- discussion and decision-making.

7.8 SUPPORTED EMPLOYMENT

7.8.1 Introduction

Adults with autism experience high unemployment. For instance, a recent survey found that only 15% of all adults with autism are in full-time employment (National Autistic Society, 2008). Moreover, follow-up studies have found that employment outcomes are not good even among high-functioning individuals with autism, for instance, Howlin and colleagues (2004) found that the proportion of individuals with autism in work rarely exceeded 30%, and the majority of jobs were unskilled and poorly paid. Adults with autism are also more likely to switch jobs frequently, have difficulty adjusting to new job settings, and earn lower wages than typically developing peers (Howlin, 2000; Hurlbutt & Chalmers, 2004; Jennes-Coussens *et al*., 2006; Müller *et al*., 2003), or compared with individuals with less severe language disorders or learning disabilities (Cameto *et al*., 2004). As well as conferring financial and economic benefits, regular employment can also bring psychological and social benefits to individuals with autism, including improved self-esteem and greater social integration. Individuals with autism may possess the technical skills required for a job. However, they may not be able to convey this in interviews due to problems with engaging in reciprocal conversation, and difficulties in thinking and responding quickly to interview questions (Berney, 2004; Romoser, 2000). Moreover, even if individuals are successful at getting through the potentially major stumbling block of the interview process, there are frequently problems with maintaining employment due to atypical social communication with employer and/or fellow employees, and sensory issues (Hurlbutt & Chalmers, 2004). The inability to make appropriate use of their training and skills, or to find suitable work despite sometimes many years of trying, can result in frustration, loss of self-esteem and, for some individuals, entry into a cycle of anxiety and depression or other psychiatric disturbance (Howlin, 1997).

Research in individuals with intellectual disability has suggested that the outcome of supported employment programmes appear to be superior to sheltered workshop or other day service options, in terms of financial gains for employees, wider social integration, increased worker satisfaction, higher self-esteem, and savings on service costs (Beyer & Kilsby, 1996; McCaughrin *et al*., 1993; Noble *et al*., 1991; Rhodes *et al*., 1987; Stevens & Martin, 1999). Specialised supported employment schemes enable individuals with autism to secure and maintain a paid job in a regular work environment. These programmes involve: placing an emphasis on using individual strengths and interests, identifying appropriate work experience and jobs and ensuring the appropriate 'fit' between employment and employee; preparing individuals for employment using structured teaching techniques; using a job coach to provide individualized training and support for the supported employee in the workplace; and collaborating with families, caregivers, and employers in

order to provide necessary long-term support. The key elements associated with successful schemes include careful job placement, prior job training, advocacy, follow-up monitoring and long-term support to ensure job retention (Keel *et al*., 1997; Mawhood & Howlin, 1999; Trach & Rusch, 1989; Wehman & Kregel, 1985). The aim of supported employment programmes is to enable individuals with autism to be a contributing member of the workforce through the provision of a stable and predictable work environment, and supported employment can increase feelings of self-worth for the individual with autism whilst also helping to increase public awareness and understanding of autism. One of the few specialised employment services for individuals with autism in the UK is 'Prospects', which was established by the National Autistic Society in 1994 and offers work-preparation programmes, job-finding support, interview support and in-work support tailored to the needs of job seekers with autism (National Audit Office, 2009).

7.8.2 Studies considered

No RCTs were found which provided relevant clinical evidence for supported employment interventions in adults with autism and met the eligibility criteria for this review. However, three quasi-experimental parallel group controlled trials (N=145) were found (García-Villamisar *et al*., 2000 [GARCIAVILLAMISAR2000]; García-Villamisar *et al*., 2002 [GARCIAVILLAMISAR2002]; García-Villamisar & Hughes, 2007 [GARCIAVILLAMISAR2007]; and Mawhood & Howlin, 1999 [MAWHOOD1999]). One of these studies was reported across two papers with different outcomes in each, data was extracted from both, but in terms of sample size participants (N=51) were only counted once (GARCIAVILLAMISAR2000/2002). One observational before-and-after study (N=89) was also included (Howlin *et al*., 2005 [HOWLIN2005]). In addition to data from a new group of 89 participants, this study reported follow-up data for one of the quasi-experimental trials. This data was only extracted once to avoid duplication. All four of these studies were published in peer-reviewed journals between 1999 and 2007. In addition, three studies were excluded as data could not be extracted for efficacy analysis. Further information about included and excluded studies can be found in Appendix 14.

Of the three included quasi-experimental parallel group controlled trials (four papers) in an autism population (see Table 60), one involved a comparison of a supported employment programme with a sheltered workshop programme; one compared a supported employment programme with a waitlist control group; and one compared a supported employment programme with a treatment as usual control group.

The observational study (see Table 61) reported change from baseline scores for participants in a supported employment programme.

Table 60: Summary study characteristics for included quasi-experimental studies in adults with autism

	Supported employment
No. trials (Total participants)	3 (145)
Study IDs	(1) GARCIAVILLAMISAR2000/2002* (2) GARCIAVILLAMISAR2007 (3) MAWHOOD1999
N/% female	(1) 12/24 (2) 12/27 (3) 3/6
Mean age	(1) 21 (2) 24 & 26 (3) 28 & 31
IQ	(1) Range not reported (means 56 & 57) (2) Range not reported (means 81 & 82) (3) 66-128 (means 98 & 99)
Axis I/II disorders	(1) 100% autism; 43% epilepsy (2) 100% autism (3) 100% autism
Comparator	(1) Sheltered workshop (2) Waitlist control (3) Treatment as usual control
Length of treatment	(1) Mean 30 months (2) Mean 30 months (3) Mean 17 months
Length of follow-up	(1) 3 years (2) Mean 30 months (3) 24 months

*Studies combined for study characteristics as these two papers report different outcomes from the same study

Table 61: Summary study characteristics for included observational studies in adults with autism

	Supported employment
No. trials (Total participants)	1 (89)
Study IDs	HOWLIN2005*
N/% female	17/19
Mean age	31
IQ	60-139 (mean 110.7)
Axis I/II disorders	100% autism
Comparator	No comparator
Length of treatment	One year
Length of follow-up	One year

*Efficacy data not extractable.

7.8.3 Clinical evidence for supported employment programmes

Supported employment versus sheltered workshop

GARCIAVILLAMISAR2000/2002 found that supported employment programmes had statistically significant beneficial effects on autistic behaviours as measured by the Childhood Autism Rating Scale (test for overall effect: Z=2.96, p=0.003) and quality of life as measured by the Quality of Life Survey (test for overall effect: Z=4.06, p<0.0001) compared to sheltered workshop programmes (see Table 62). However, there were a number of methodological concerns with this trial which suggest caution in the interpretation of results and are reflected in the lower grade of the evidence. For instance, the lack of randomisation in group allocation increases the risk of bias. However in addition, the sample size figures reported varied throughout the paper with no explanation as to the changing values and no indication of which were the correct figures. The sample sizes used for analysis were selected from the demographic table based on the assumption that this was reflective of the intention to treat sample.

Table 62: Summary evidence profile for supported employment programme versus sheltered workshop group

Outcome	**Autistic behaviours**	**Quality of life**
Study ID	GARCIAVILLAMISAR2000	GARCIAVILLAMISAR2002
Effect size	MD = -6.07 (-10.09, -2.05)	MD = 5.20 (2.69, 7.71)
Quality of evidence (GRADE)	Very low[1,2]	Very low[1,2]
Number of studies/ participants	(K=1; N=51)	(K=1; N=51)
Forest plot	1.1.6, Appendix 15	1.1.6, Appendix 15

[1]Downgraded for risk of bias as group allocation was not randomised
[2]Downgraded for imprecision as sample size figures varied throughout the paper with no explanation as to the changing values. The sample sizes used for analysis were selected from the demographic table but not clear that this assumption valid or correct

Supported employment versus waitlist control

GARCIAVILLAMISAR2007 found statistically significant effects of a supported employment programme on executive function as measured by the 'Stockings of Cambridge' (SOC) Planning task from the Cambridge Neuropsychological Tests: Automated Battery (CANTAB) which is a computerized version of the Tower of London Planning Task (see Table 63). This study found that the average planning time required for this task was significantly shorter for the supported employment group compared with the waitlist control group (test for overall effect: Z=3.26, p=0.001). However, this study was also methodologically flawed in that the sample sizes for each group were not reported. Analysis was conducted on the assumption of equal sample sizes across the two groups. Though, this assumption may be invalid. As a result the quality of this evidence is downgraded based on imprecision, in addition to the downgrading based on lack of randomised allocation to groups.

Table 63: Summary evidence profile for supported employment programme versus waitlist control group

Outcome	**Executive function**
Study ID	GARCIAVILLAMISAR2007
Effect size	MD = -2.75 (-4.41, -1.09)
Quality of evidence (GRADE)	Very low[1,2,3]
Number of studies/ participants	(K=1; N=44)
Forest plot	1.1.6, Appendix 15

[1]Downgraded for risk of bias as group allocation was not randomised
[2]Downgraded for imprecision as the sample size was not reported for each group and this analysis was based on the assumption of equal numbers in each group but this may be invalid.
[3]Downgraded for imprecision as the sample size is small

Supported employment versus treatment as usual control

MAWHOOD1999 also found evidence for a significant benefit of a supported employment programme compared with treatment as usual control (see Table 64) in terms of the number of participants finding paid employment (test for overall effect: $Z=2.26$, $p=0.02$). The risk ratio indicates that the participants on the supported employment programme were over two and a half times more likely to find paid employment than the control group. Moreover, narrative results reported in HOWLIN2005 provide support for longevity of treatment effects, as at seven to eight year follow-up 68% of those who originally found paid employment remained in permanent jobs.

Table 64: Summary evidence profile for supported employment programme versus treatment as usual control group

Outcome	**Job placements**
Study ID	MAWHOOD1999
Effect size	RR = 2.53 (1.13, 5.67)
Quality of evidence (GRADE)	Very low[1]
Number of studies/ participants	(K=1; N=50)
Forest plot	1.1.6, Appendix 15

[1]Downgraded for risk of bias as group allocation was not randomised

Observational studies of supported employment

HOWLIN2005 compared before-and-after outcomes for 89 current supported employment programme clients with autism. This study also reports long-term follow-up data for MAWHOOD1999 as reported above. It was not possible to extract efficacy data for this study. However, the authors reported significant change-from-baseline scores for job placements before and after the supported employment programme with 28 more clients in work after joining Prospects ($X^2=17.62$, $p<0.001$).

7.8.4 Clinical evidence summary for supported employment programme

The data from supported employment programmes is consistently positive. A number of methodological limitations with the studies as detailed above suggest some caution in the interpretation of results and this is reflected in the very low quality of the data. However, the initial results are promising, and crucially follow-up results are suggestive of long-term beneficial effects with significant job retention 7-8 years after initiation of the supported employment programme.

7.8.5 Health economics evidence – systematic literature review

The systematic search of the economic literature undertaken for the guideline identified one eligible study on employment support services for adults with autism, conducted in the UK (Mawhood & Howlin, 1999). Details on the methods used for the systematic review of the economic literature are described in Chapter 3; reference to the included study and the evidence table of the study are provided in Appendix 14. A completed methodology checklist of the study is provided in Appendix 17. Economic evidence profiles of studies considered during guideline development (i.e. studies that fully or partly met the applicability and quality criteria) are presented in Appendix 19, accompanying the respective GRADE clinical evidence profiles.

Mawhood and Howlin (1999) conducted an economic analysis alongside an RCT comparing employment support service with usual control (MAWHOOD1999). The study population was adults with high functioning autism (IQ > 70). The primary measure of outcome was the proportion of people employed in each arm at the end of the study. The time horizon of the analysis was 2 years. Costs included intervention costs only. The study provided the resource use of employment support programme in terms of total numbers of hours worked by the intervention providers in the first and second year.

According to the study findings, 63% of the employment support scheme group and 25% of the control group were employed at the end of the two years of the study. In both groups, the average time to find employment was eight months; and the individuals who found employment worked 35 hours per week. The monthly cost of the employment support scheme was calculated at £672 per client in the first year and £388 in the second year in 1994/95 prices (equivalent to a monthly cost of £1,143 and £635 in the first and second year, respectively, in 2009/10 prices). The cost per hour worked in the first year is £14.64 and £5.72 in the second year in 1994/95 prices. The costs of job finding were substantial and the support needs of clients were high at the beginning of the job which contributed in high cost in the first year of the two-year employment support programme. The control group in the

study received the standard usual service. However, no resource use or cost data were reported for the control group.

The study by Mawhood and Howlin (1999) is directly applicable to the guideline. However, it has potentially serious limitations as the study did not report (or measure) the resource use or the cost of standard service used by the control group. In addition, the study did not estimate other potential cost implications of employment, such as a change in the type of accommodation of people with autism. The time horizon of two years is also short to fully take into account benefits of the programme accrued after the second year and it did not provide the incremental analysis. Nevertheless, the study provides an indication of the costs associated with provision of an employment support scheme in the UK.

7.8.6 Health economics evidence - Economic modelling

Introduction – objective of economic modelling

Provision of supported employment in adults with autism is an area with potentially major resource implications. An economic model was therefore developed to assess the cost effectiveness of supported employment schemes for adults with autism. Supported employment schemes can be and are delivered by a range of different providers including health, social care and third sector organisations. The economic analysis considered the individual placement and support approach (IPS), according to guidance published by the Department of Health (Department of Health, 2006b), and used resource use estimates within the NHS and personal social services (PSS) perspective, as reported in Curtis (2010). The economic analysis draws heavily on MAWHOOD1999, which compared supported employment with standard care in the UK and reported the number of participants who found paid employment in each group. In addition, the model considered follow-up data (employment rates) for the supported employment group of MAWHOOD1999, which are reported in HOWLIN2005.

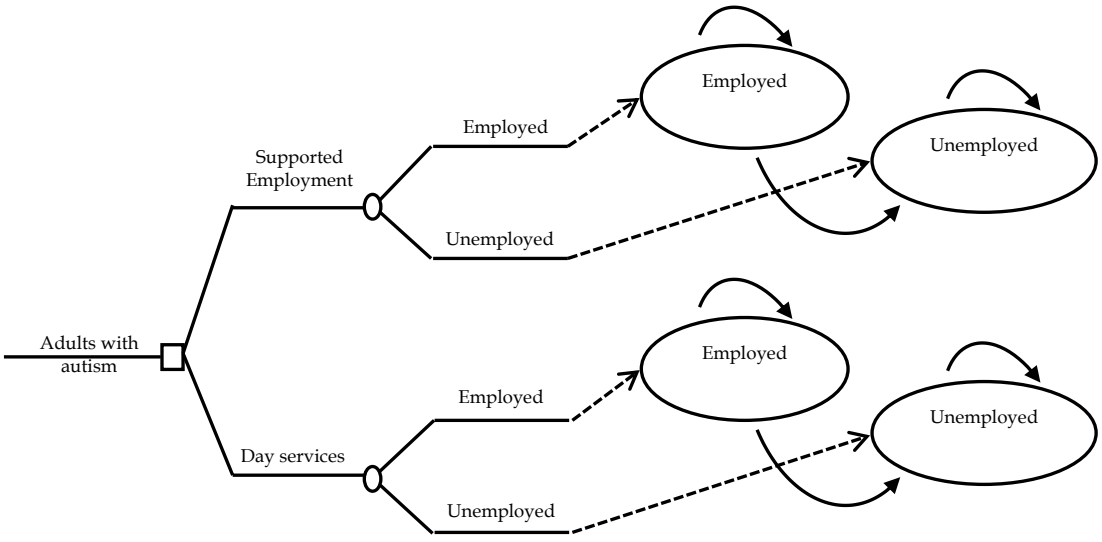
Interventions assessed

According to MAWHOOD1999, supported employment was provided by support workers who were responsible for the assessment of clients (regarding their level of functioning and their past educational and job history), for job finding and work preparation, as well as for ensuring that clients could cope with all the social and occupational requirements of employment. They also spent time educating and informing potential and existing employers, and advising work colleagues and supervisors on how to deal with or avoid problems. Standard care is not described in MAWHOOD1999, but it was estimated to consist of day services, which is also reported as an alternative to supported employment in Curtis (2010).

Model structure

A simple decision-tree followed by a two-state Markov model was constructed using Microsoft Excel XP in order to assess the costs and outcomes associated with provision of supported employment versus standard care to adults with autism actively seeking work. According to the decision-tree, which was based on data reported in MAWHOOD1999, interventions were provided over a period of 17 months. Over this period, a number of participants in both groups found paid employment; the amount of time spent in employment was 8 months (MAWHOOD1999 reports that participants were registered with the supported employment scheme over a period of 17 months on average; the mean length of time spent in paid work during the study evaluation period was 8.1 months for those participants who found employment in the intervention group and 8.4 months for those participants who found employment in the control group). Subsequently, a Markov model was developed to estimate the number of adults remaining in employment every year, from endpoint of the decision-tree (i.e. from the end of provision of the intervention) and up to 8 years, using the 8-year follow-up data reported in HOWLIN2005. The Markov model consisted of the states of 'employed' and 'unemployed' and was run in yearly cycles. People in 'employed' state could remain in this state or move to 'unemployed' state. In contrast, people in the 'unemployed' state could only remain in that state (absorbing state). It must be noted that people in the 'employed' state were assumed to spend only a proportion of each year (and not the full year) in employment. A schematic diagram of the economic model is presented in Figure 8.

Figure 8. Schematic diagram of the economic model structure constructed for the assessment of the cost effectiveness of supported employment versus treatment as usual (day services)



Costs and outcomes considered in the analysis

The economic analysis adopted the perspective of the NHS and PSS, as recommended by NICE (2009e). Costs consisted of intervention costs only in the main analysis. In two secondary analyses, costs consisted of a. intervention and accommodation costs; and b. intervention and other NHS and PSS costs (including mental health care, primary and secondary care, as well as local authority costs). The measure of outcome was the Quality Adjusted Life Year (QALY).

Clinical input parameters of the economic model

Data on employment rates following standard care and the relative effect of supported employment versus standard care at the end of intervention period were taken from MAWHOOD1999. The annual transition probability of moving from the 'employed' to the 'unemployed' health state over 8 years from the end of intervention period was estimated using data reported in HOWLIN2005. The study reported that 68% of the participants in the employment support scheme described in MAWHOOD1999 who had found employment during the study period remained in permanent employment at 8-year follow-up. From this data it was possible to estimate the annual transition probability from employed to unemployed status, assuming a constant rate of moving to unemployment over the 8-year follow-up period. We conservatively applied this rate to both intervention and standard care groups, although it was considered that people attending a supported employment scheme are more likely to retain their jobs after the end of the intervention compared with those under standard care. If this is the case, then the economic analysis has underestimated the long-term relative effect (in terms of remaining in paid employment) of supported employment versus standard care.

The mean time in employment of every person who remained in the 'employed' state of the Markov model each year following completion of intervention was derived from a systematic review of RCTs on IPS in people with severe mental illness (Bond et al., 2008) according to which, among IPS participants who obtained competitive work, the average duration of employment was 47% within every year of employment.

Clinical input parameters of the economic analysis are provided in Table 65.

Utility data and estimation of QALYs

In order to express outcomes in the form of QALYs, the health states of the economic model needed 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.

The systematic search of the literature identified no studies reporting utility scores for adults with autism. In order to estimate QALYs for adults with autism being in the two health states of 'employed' and 'unemployed' we utilised data reported in the economic analysis that was undertaken to support the NICE public guidance on managing long-term sickness absence and incapacity for work (NICE, 2009f). The economic analysis (Pilgrim *et al.*, 2008) used utility scores for the health states of 'being at work' and 'being on long term sick leave' estimated based on findings of a study aiming to predict the HRQOL of people who have been or are currently on long term sick leave (Peasgood *et al.*, 2006); the latter utilised data from the British Household Panel Survey (BHPS). The BHPS is a longitudinal annual survey designed to capture information on a nationally representative sample of around 10,000 – 15,000 of the non-immigrant population of Great Britain that began in 1991. Utility scores were estimated from SF-36 data using the SF-6D algorithm (Brazier *et al.*, 2002). In the economic analysis (Pilgrim *et al.*, 2008), the utility scores associated with being at work or being in long term sick leave were assumed to be the same for all individuals in each state, independent of their health status; in other words, it was assumed the quality of life of the individual is more greatly affected by being at work or on sick leave than by the illness itself. In addition, the utility scores for people at work and those on sick leave were assumed to capture wage and benefit payments, respectively. Utility scores were reported separately for 4 age categories (age <35 years; age 35-45 years; age 45-55 years; and age >55 years).

The economic analysis undertaken for this guideline used the utility scores reported in Pilgrim and colleagues (2008) for adults aged below 35 years, in consistence with the average age of participants in MAWHOOD1999 (31 years). The difference in utility between the states of 'being at work' and 'being on sick leave' was smaller in this age group (0.17) compared with the age group of 35-45 years (0.21), thus providing a more conservative estimate and potentially underestimating the benefit and the cost effectiveness of supported employment. It must be noted that the utility of the 'unemployed' state is likely to be lower than the utility of 'being on sick leave', and therefore the analysis is likely to have further underestimated the benefit of supported employment. In addition, the utility scores used in the analysis refer to the general population and are not specific to adults with autism. It is possible that adults with autism get greater utility from finding employment compared with the general population, as employment may bring them further psychological and social benefits, including improved self-esteem and greater social integration (Sesami Research and Practice Partnership, 2007).

Utility data used in the economic analysis are reported in Table 65.

Cost data

Intervention costs for supported employment and day services were based on Curtis (2010). The report provides unit costs for IPS for 4 different grades of

staff, two with professional qualifications (e.g. psychology, occupational therapy) and two with no particular qualifications, ranging from Band 3 to Band 6, and for different caseloads, ranging from 10 to 25. Estimation of unit costs for IPS took into account the following cost components: wages, salary on-costs, superannuation, direct and indirect overheads, capital, team leaders who would supervise no more than 10 staff and would be available to provide practical support, and marketing budget. For this analysis, it was assumed that supported employment was provided by specialists in Band 6 at a caseload of 20 clients. The average annual cost per person under these conditions was £2,746 per client.

Curtis (2010) also provides unit costs for the equivalent of IPS in day care. In the economic analysis day care was conservatively assumed to be provided by unqualified staff in Band 3, also at a caseload of 20 clients. Curtis (2010) reports that the number of day care sessions ranges from 34 to 131 annually. The lower number of sessions (34) was selected for the economic analysis, resulting on an annual cost of £1,632.

It should be noted that the economic model utilised a 17-month cost for both interventions.

Secondary analysis including accommodation costs

Change in employment status may have important implications on the type of accommodation in adults with autism. Knapp and colleagues (2009) estimated that 79% of non-intellectually disabled adults with autism live in private accommodation, 5% live in supported accommodation, and 16% live in residential care. If gaining employment shifts a percentage of people living in supported accommodation and residential care to private accommodation, this may lead to substantial savings to PSS. Therefore, a sub-analysis estimated the impact on the cost effectiveness of supported employment following an increase in private accommodation by 1% (i.e. reaching 80%) and a reduction in both supported accommodation and residential care by 0.5% (i.e. falling at 4.5% and 15.5%, respectively) in those adults with autism who found employment and remained employed beyond 8 months (i.e. those entering the Markov model in the 'employed' state). However, the model assumed that once people moved out of employment (transitioned from 'employed' state to 'unemployed' state), they returned to their previous type of accommodation. The cost of private accommodation to the NHS and PSS is zero. The costs of supported accommodation and residential care comprise costs of staff employed in such settings or supporting the residents and were taken from Curtis (2010).

Secondary analysis including NHS and PSS costs

The impact of supported employment on health and social care service usage by adults with autism is not known. Schneider and colleagues (2009) estimated the changes in costs to mental health, primary and secondary care,

local authority and voluntary day care services incurred by people with mental health problems (mainly schizophrenia, bipolar disorder, anxiety or depression) associated with gaining employment following registration with supported employment schemes. The study reported baseline and 12-month follow-up data for people remaining unemployed throughout the study (n=77), people who found employment during the 12 months between baseline and follow-up (n=32), and people who were already in employment at baseline and remained in employment at follow-up (n=32). Cost data on people who found employment between baseline and follow-up were utilised in the economic analysis; cost data at baseline were used for the state of 'unemployed' and cost data at follow-up were used for the state of 'employed' in both the decision-tree and the Markov part of the model. Service costs included mental health services (contacts with psychiatrist, psychologist, community psychiatric nurse, attendance at a daycentre, counselling or therapeutic group work, and inpatient mental health care), primary care (contacts with GP, district nurse, community physiotherapist, dentist or optician), local authority services (day centres run by social services, home care and social work inputs), other secondary NHS care (hospital outpatient appointments and inpatient care for needs other than mental health) and a negligible amount of voluntary day care run by not-for-profit agencies that are independent of the public sector (about 0.3-0.5% of the total cost). This secondary analysis did not consider potential changes in accommodation type and respective changes in costs, because it already included local authority service costs and there was the risk of double-counting services.

All costs were expressed in 2010 prices, uplifted, where necessary, using the Hospital & Community Health Services (HCHS) Pay and Prices Index (Curtis, 20010). Discounting of costs and outcomes was undertaken at an annual rate of 3.5%, as recommended by NICE (NICE, 2009e).

Table 65 presents the values of all input parameters utilised in the economic model.

Table 65 Input parameters utilised in the economic model of supported employment versus standard care for adults with autism

Input parameter	Deterministic value	Probabilistic distribution	Source of data - comments
Clinical data			
Probability of employment – standard care	0.25	**Beta distribution** $\alpha = 5, \beta = 15$	MAWHOOD1999
Risk ratio of employment – supported employment versus standard care	2.53	**Log-normal distribution** 95% CIs: 1.13 to 5.67	MAWHOOD1999; note that the probability of employment under supported employment was not allowed to exceed 0.90 in probabilistic analysis
Probability of employment at 8 years follow-up	0.68	**Beta distribution** $\alpha = 13, \beta = 6$	HOWLIN2005; data for supported employment utilised in both supported employment and standard care
Annual transition probability from 'employed' to 'unemployed'	0.0463	**Distribution dependent on above distribution**	
Proportion of time employed within 'employed' state	0.47	**Beta distribution** $\alpha = 158.39$, $\beta = 178.61$	Bond et al., 2008; distribution determined according to method of moments
Utility scores			
Employed	0.83	**Beta distribution** $\alpha = 83$, $\beta = 17$	Pilgrim *et al.*, 2008; utility scores for general population being in work or on sick leave; distribution parameters based on assumption
Unemployed	0.66	$\alpha = 66$, $\beta = 34$	
Cost data (2010 prices)			
Annual intervention cost		**Gamma distribution**	Curtis, 2010; standard error of intervention cost assumed to be 30% of its mean estimate
Supported Employment	£2,746	$\alpha = 11.11, \beta = 247.14$	
Standard care (day services)	£1,632	$\alpha = 11.11, \beta = 146.88$	
SECONDARY ANALYSIS			
Annual accommodation cost			
Private accommodation	£0	N/A	
Supported accommodation	£64,486	$\alpha = 11.11, \beta = 5,804$	Curtis, 2010; standard error of accommodation cost assumed to be 30% of its mean estimate
Residential Care	£67,449	$\alpha = 11.11, \beta = 6,070$	

% of unemployed in different types of accommodation		**No distribution assigned**	Knapp *et al.*, 2009
Private accommodation	0.79		
Supported accommodation	0.05		
Residential Care	0.16		
Change in accommodation when finding employment		**Beta distribution**	Assumption
Private accommodation	+0.010	$\alpha = 0.10$, $\beta = 9.90$	
Supported accommodation	-0.005	following above distribution	
Residential Care	-0.005	following above distribution	
SECONDARY ANALYSIS		**Gamma distribution**	Schneider *et al.*, 2005
Weekly health and social service cost – unemployed	£46	$\alpha = 0.77$ $\beta = 59.80$	
Weekly health and social service cost – employed	£35	$\alpha = 0.19$ $\beta = 182.27$	
Discount rate	0.035	N/A	NICE, 2009e

Data analysis and presentation of the results

In order to take into account the uncertainty characterising the model input parameters, a probabilistic analysis was undertaken, in which input parameters were assigned probability distributions, rather than being expressed as point estimates (Briggs *et al.*, 2006). Subsequently, 1,000 iterations were performed, each drawing random values out of the distributions fitted onto the model input parameters. Mean costs and QALYs for each intervention were then calculated by averaging across 1,000 iterations. The Incremental Cost Effectiveness Ratio (ICER) was then estimated for the main analysis and the two secondary analyses, expressing the additional cost per extra QALY gained associated with provision of supported employment instead of standard care.

The probability of employment for standard care and the probability of employment at 8-years were given a beta distribution. Beta distributions were also assigned to utility values, the proportion of time employed within 'employed' state, and the percentage increase in private accommodation when finding employment. The risk ratio of employment of supported employment versus standard care was assigned a log-normal distribution. Costs were assigned a gamma distribution. The estimation of distribution ranges was based on available data in the published sources of evidence and assumptions, where relevant data were not available. Table 65 provides details on the types of distributions assigned to each input parameter and the methods employed to define their range.

Results of probabilistic analysis in main and secondary analyses are also presented in the form of Cost Effectiveness Acceptability Curves (CEACs), which demonstrate, in each of the analyses undertaken (main and two secondary analyses) the probability of supported employment being cost-effective relative to standard care at different levels of willingness-to-pay per QALY, that is, at different cost effectiveness thresholds the decision-maker may set (Fenwick *et al.*, 2001).

One-way sensitivity analyses (run with the point estimates rather than the distributions of the input parameters) explored the impact of the uncertainty characterising the model input parameters on the main analysis: the intervention cost for supported employment and standard care was changed by 50% to investigate whether the conclusions of the analysis would change. In addition, a threshold analysis explored the minimum relative effect of the supported employment that is required in order for the intervention to be cost-effective using the NICE cost-effectiveness threshold.

Results

Main analysis

The results of main analysis are presented in Table 66. Supported employment is associated with a higher cost but also produces a higher number of QALYs

compared with standard care. The ICER of supported employment versus standard care is £7,657 per QALY gained, which is below the NICE cost effectiveness threshold of £20,000-£30,000/QALY (NICE, 2009e), indicating that supported employment may be a cost-effective option when compared with standard care.

Table 66 Results of main analysis – mean total costs and QALYs of each intervention assessed per adult with autism seeking employment

Intervention	Supported employment	Standard care	Difference
Total cost	£3,916	£2,335	£1,581
Total QALYs	5.31	5.11	0.20
ICER	£7,657/QALY		

The cost effectiveness plane showing the incremental costs and QALYs of supported employment versus standard care resulting from 1,000 iterations of the model are shown in Figure 9. Figure 10 provides the CEAC showing the probability of supported employment being cost-effective relative to standard care for different levels of willingness-to-pay per extra QALY gained. According to the CEAC, the probability of supported employment being cost-effective at the NICE lower cost effectiveness threshold of £20,000/QALY is 78.3%.

Figure 9. Cost effectiveness plane showing incremental costs and QALYs of supported employment versus standard care per person with autism. Results of main analysis, based on 1,000 iterations.

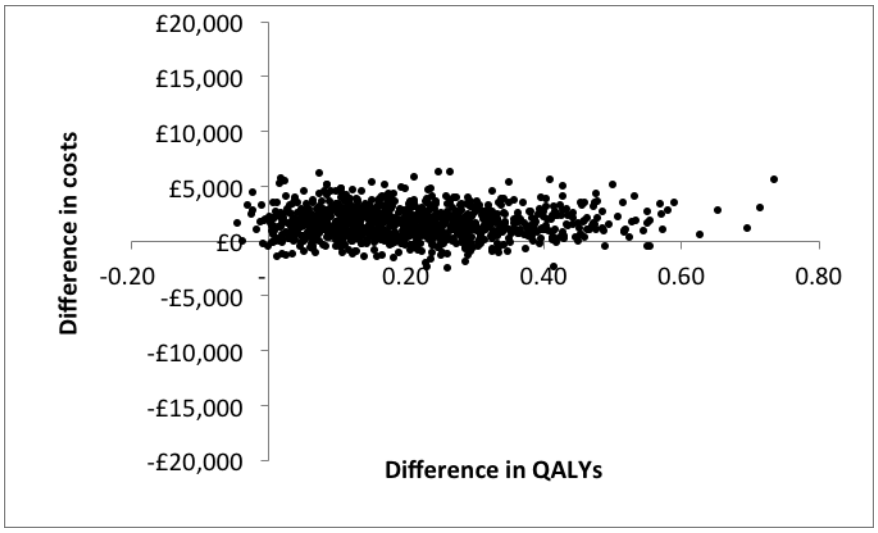
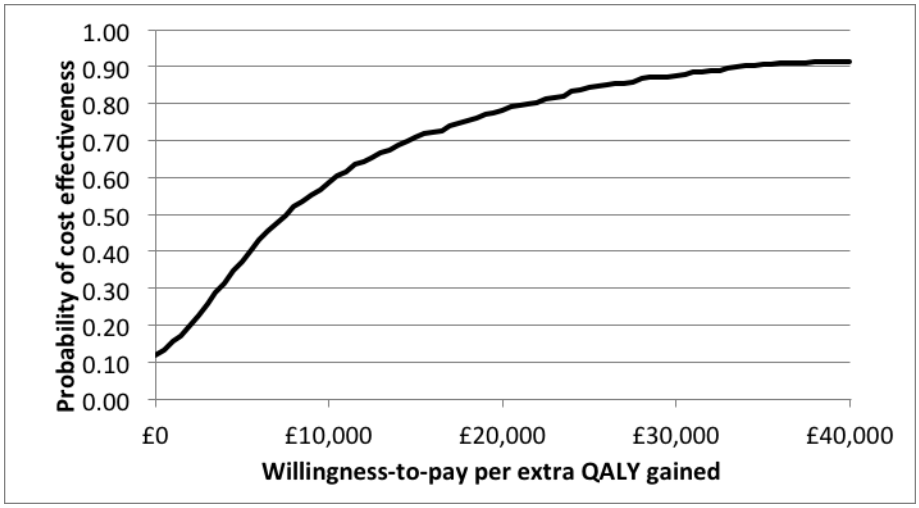


Figure 10: Cost Effectiveness Acceptability Curve of supported employment versus standard care. Results of main analysis. X axis shows the level of willingness-to-pay per extra QALY gained and Y axis shows the probability of supported employment being cost-effective at different levels of willingness-to-pay.



Secondary analysis including accommodation costs

The results of the secondary analysis including accommodation costs are presented in **Table 67**. Supported employment is still associated with a higher cost compared with standard care but the difference in costs is reduced and the ICER has fallen at £1,739 per QALY gained.

Table 67 Results of secondary analysis including accommodation cost – mean total costs and QALYs of each intervention assessed per adult with autism seeking employment

Intervention	Supported employment	Standard care	Difference
Total cost	£98,314	£97,971	£343
Total QALYs	5.33	5.13	0.20
ICER	£1,739/QALY		

The cost effectiveness plane is shown in **Figure 11**. **Figure 12** provides the CEAC for this analysis. The probability of supported employment being cost-effective at the NICE lower cost effectiveness threshold is 82.4%.

Figure 11. Cost effectiveness plane showing incremental costs and QALYs of supported employment versus standard care per person with autism. Results of secondary analysis including accommodation costs, based on 1,000 iterations.

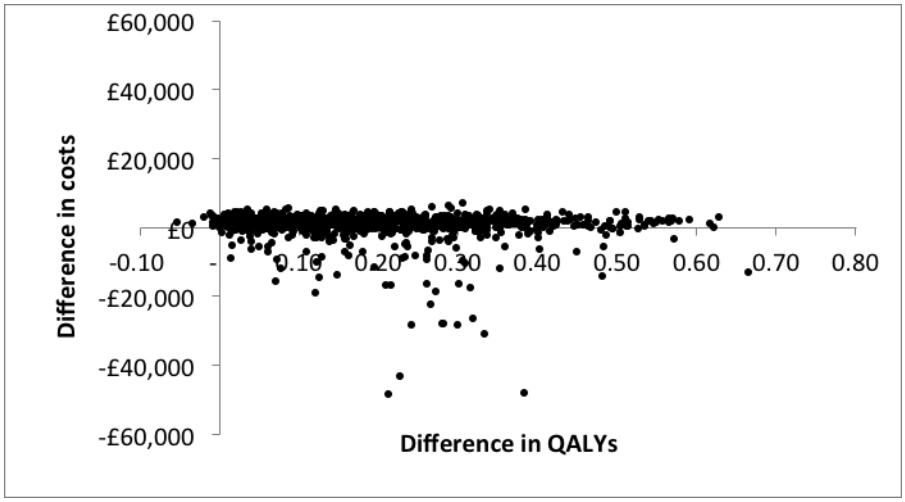
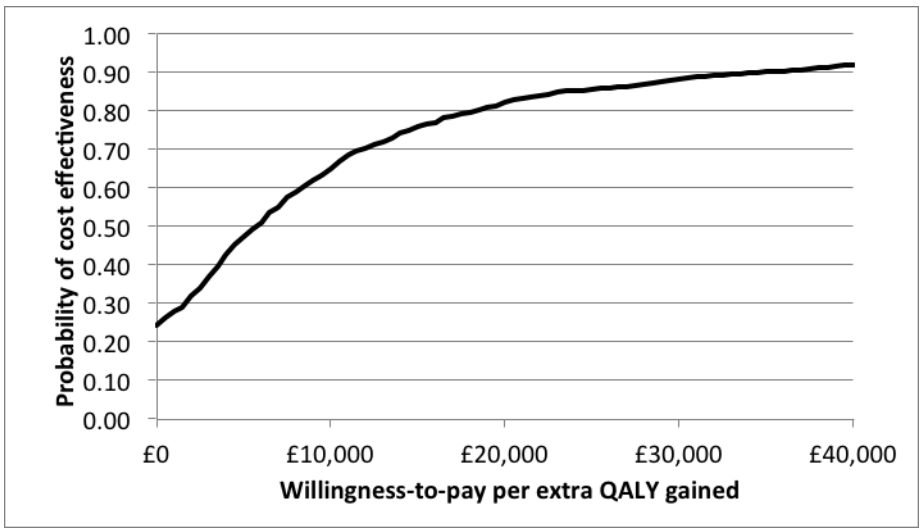


Figure 12: Cost Effectiveness Acceptability Curve of supported employment versus standard care. Results of secondary analysis including accommodation costs.



Secondary analysis including NHS and PSS costs

The results of the secondary analysis including NHS and PSS costs are presented in **Table 68**. Supported employment results in a higher number of QALYs at the same cost with standard care and therefore is the dominant option.

Table 68 Results of secondary analysis including NHS and PSS costs – mean total costs and QALYs of each intervention assessed per adult with autism seeking employment

Intervention	Supported employment	Standard care	Difference
Total cost	£18,911	£18,914	-£3
Total QALYs	5.30	5.10	0.20

ICER	Supported employment dominant

The cost effectiveness plane is shown in **Figure 13**. It can be seen that the difference in costs has a wide range across iterations, which is attributable to the uncertainty characterising the cost estimates of NHS and PSS costs due to the small number of observations in the study that provided these estimates. **Figure 14** presents the CEAC and shows that the probability of supported employment being cost-effective at £20,000/QALY is 72.2%, which is lower than the estimates of the main and the other secondary analysis, probably due to the uncertainty characterising the cost estimates considered in this secondary analysis.

Figure 13. Cost effectiveness plane showing incremental costs and QALYs of supported employment versus standard care per person with autism. Results of secondary analysis including NHS and PSS costs, based on 1,000 iterations.

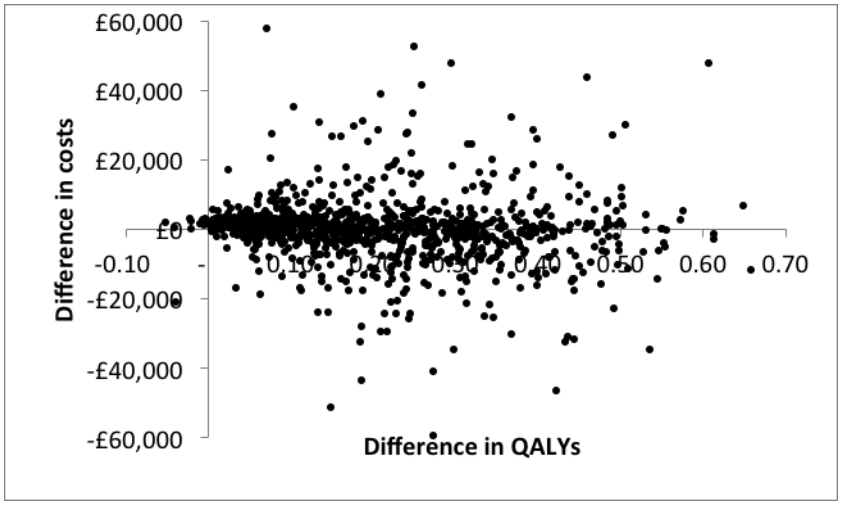
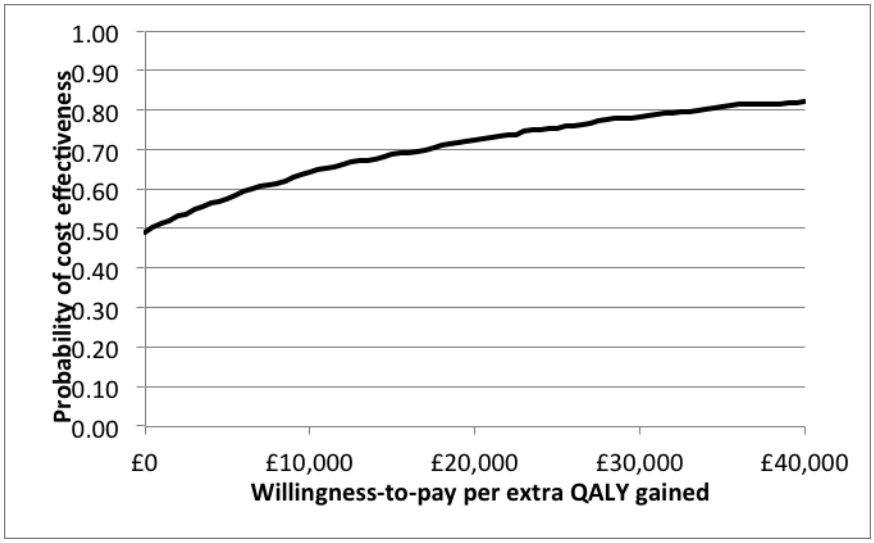


Figure 14: Cost Effectiveness Acceptability Curve of supported employment versus standard care. Results of secondary analysis including NHS and PSS costs.



One-way sensitivity analysis on the findings of main analysis revealed that if the intervention cost of supported employment changed by 50%, the ICER ranged from £16,348/QALY to supported employment being dominant. If the standard care cost changed by 50%, then the ICER ranged from £1,959 to £12,687 per QALY gained. Threshold analysis revealed that the minimum risk ratio of supported employment versus standard care required in order for the intervention to be considered cost-effective according to NICE criteria was 1.38 (using the upper £30,000/QALY threshold) or 1.56 (using the lower £20,000/QALY threshold).

Discussion of findings - limitations of the analysis

The results of the economic analysis indicate that supported employment is likely to be a cost-effective intervention compared with standard care. Supported employment resulted in a higher number of QALYs compared with standard care comprising day services. In the main analysis that considered intervention costs only, the ICER of supported employment versus standard care was £7,657/QALY. In a secondary analysis that assumed a small increase (1%) in adults with autism living in private accommodation after finding employment, the ICER of supported employment versus standard care fell at £1,739/QALY. Finally, in a secondary analysis that considered a reduction in NHS and PSS costs following initiation of employment, supported employment dominated standard care, as it was more effective and overall less costly. The probability of supported employment being cost-effective at the NICE lower cost effectiveness threshold of £20,000/QALY ranged from 72.2% to 82.4% in these three analyses.

The economic analysis was based exclusively, in terms of clinical data, on one study comparing supported employment with standard care (MAWHOOD1999, followed up by HOWLIN2005). The original study had a small sample size (N=50). However, the risk ratio of employment of supported employment versus standard care was significant and the follow-up data indicated the longevity of treatment effects. Another problem was that MAWHOOD1999 did not describe standard care. Based on current practice, GDG estimated that standard care consisted of day services.

At the development of the economic model the GDG needed to make a judgment as to whether the economic analysis could be deemed relevant to adults with high functioning autism or to adults with both high and low functioning autism. MAWHOOD 1999 had as an entry criterion to the study an IQ of 70 or above on either the performance or the verbal scale of the WAIS (Wechsler Intelligence Scale), indicating that the population were almost all 'high functioning'; it should however be noted that the range of IQ scores reported in the study indicated that a small percentage had an IQ below 70. The GDG reviewed also a study by Schaller and Yang (2005) of a database of over 800 people with autism in which 23.5% had a diagnosis of mild or moderate intellectual disability (that is, an IQ below 70), which reported a significant association between an IPS model and successful retention in employment. The GDG therefore took the view that the economic model was

relevant to and should include in its study population adults with high *and* low functioning autism.

Three analyses were undertaken: the main analysis included intervention costs only, as no other cost data that could be linked to the employment status of adults with autism were identified in the literature. A secondary analysis assumed that a small proportion of adults with autism living in supported accommodation or residential care would move to private accommodation after finding employment. This secondary analysis was undertaken to explore the potential impact of employment status on costs associated with accommodation, given that supported accommodation and residential care incur substantial costs to PSS; consequently employed individuals moving to private accommodation were expected to reduce significantly the total cost born to PSS. The findings of the secondary analysis confirmed this hypothesis, as a minimal shift to private accommodation (1%) reduced the difference in costs between the supported employment and standard care from £1581 to £343 per person. If financial independence gained from finding employment leads to a more substantial shift to private accommodation, this would lead to greater savings for social services.

Another secondary analysis considered extra NHS and PSS costs associated with employment status. Cost data were taken from Schneider and colleagues (2005), who measured costs incurred by people with mental health problems including schizophrenia, bipolar disorder, anxiety or depression attending employment support schemes. The study reported that study participants entering work showed a substantial decrease in mental health services costs which outweighed a slight increase in other secondary care, making an overall reduction in health and social care costs statistically significant. The authors' estimate was that the reduction in mental health service use was possibly an effect of getting a job, although they did not rule out the possibility that a third variable, such as cognitive impairment, might be driving both employment outcomes and service use reduction. Following this finding, the authors concluded that mental health providers may save money if their service users get jobs. However, it may be that adults with autism have a different pattern of health and social care service usage compared with adults with other mental health problems, and this is why cost data reported by Schneider and colleagues (2005) were considered in a secondary analysis and not in the main analysis. The results of this secondary analysis were characterised by somewhat higher uncertainty compared with the other two analyses undertaken, apparently because the utilised cost data were very skewed and had great variance, as they were based on a small study sample (n=32).

Where data were not available or further estimates needed to be made, the economic analysis adopted conservative estimates that were likely to underestimate the cost effectiveness of supported employment: the intervention cost of supported employment was estimated to be high as it was assumed that the intervention was provided by specialists in Band 6; in contrast it was assumed that day services were

provided by unqualified staff in Band 3 and that the minimum number of sessions per year, from the range reported in the literature, was attended by the standard care group. The transition probability to unemployment was assumed to be the same for supported employment and standard care, although it was estimated that participants in a supported employment scheme are more likely to retain their jobs after the end of the intervention compared with those under standard care.

Utility scores, which are required for the estimation of QALYs, were not available for adults with autism. Utility scores obtained from the general population for the states 'being at work' and 'being on sick leave' were used instead in the analysis, based on data reported in Pilgrim and colleagues (2008). It is acknowledged that utility scores taken from Pilgrim and colleagues (2008) are not directly relevant to adults with autism in employed or unemployed status. Moreover, the utility of the 'unemployed' state is potentially lower than the utility of 'being on sick leave'. Nevertheless, the utility scores used in the economic analysis are likely to capture, if somewhat conservatively, the HRQOL of adults with autism with regard to their employment status. It is possible that adults with autism get greater utility from finding employment compared with the general population, as employment may bring them further psychological and social benefits, including improved self-esteem and greater social integration (Sesami Research and Practice Partnership, 2007).

The analysis adopted the NHS and PSS perspective. Other costs such as lost productivity or wages earned and the tax gains to the exchequer were not taken into account as they were beyond the perspective of the analysis. However, some of these cost categories were partially and indirectly taken into account; Pilgrim and colleagues (2008) considered that the utility scores for people at work and those on sick leave, which were used in this economic analysis, did capture wage and benefit payments, respectively, although these might be valued differently from wages and benefit payments received by adults with autism with/without employment.

In addition to effects considered in the analysis, supported employment has further qualitative effects on adults with autism that find employment that are difficult to quantify, such as job satisfaction of better placed job, social networks due to employment and improvement in self-esteem. In addition, it has a positive effect on the HRQoL of carers and the family of the adult with autism, which was not possible to capture in the economic analysis.

Overall, although based on limited evidence, the findings of the economic analysis indicate that supported employment is likely to be a cost-effective intervention for adults with autism, as it can increase the rate of employment in this population group, improving a person's well-being, and it can also potentially reduce the economic burden to health and social services and the wider society.

7.8.7 From evidence to recommendations

The effect sizes for supported employment programmes are large and the data is consistently positive for the effects of these programmes on increasing the number of job placements. Moreover, positive effects for supported employment programmes appear to stretch beyond the direct impacts on employment, with additional improvements observed for autistic behaviours, quality of life, and executive function. The economic model that was developed for this guideline suggested that supported employment is likely to be a cost-effective intervention for adults with autism. On this basis the GDG judged that supported employment programmes should be recommended for adults with autism and where they are delivered should be individualized but include common core elements of prior and on-the-job training, advocacy, and long-term support to ensure job retention.

7.8.8 Recommendations

7.8.8.1 For adults with autism of all ranges of intellectual ability, who are having difficulty obtaining or maintaining employment, consider an individual supported employment programme.

7.8.8.2 An individual supported employment programme should typically include:

- help with writing CVs and job applications and preparing for interviews
- training for the identified work role and work-related behaviours
- carefully matching the person with autism with the job
- advice to employers about making reasonable adjustments to the workplace
- continuing support for the person after they start work
- support for the employer before and after the person starts work.

7.9 SUPPORT FOR FAMILIES AND CARERS

7.9.1 Introduction

Caring for an adolescent or adult with autism can have great impact upon the psychological wellbeing of the carer (Seltzer *et al*., 2001). An increased prevalence of stress has been found among parents of children with autism compared with parents of typically developing children (Dyson, 1993; Wolf *et al*., 1989) or parents of children with other developmental disorders such as Down syndrome (Boyd, 2002; Sanders & Morgan, 1997). Parents of children with autism also report more symptoms of anxiety and marital dissatisfaction than parents of children with other types of disabilities (Dunn *et al.,* 2001; Holroyd & McArthur, 1976; Konstantareas & Homatidis, 1989). However, although there has been an abundance of research examining the impact of caring for a young child with autism, very few studies have examined the impact of caring for an adolescent or adult with autism (see Lounds *et al*., 2007). Hare and colleagues (2004) interviewed the families of adults with autism who either lived at home or maintained close contact with their families and found that most of their sample received very little family or informal support, although levels of formal support, such as respite and day care, were quite high. In addition, this study highlighted the need for greater support of parents of older people with autism, for instance, many parents reported attending parent support groups when their child was younger but did not do so currently. Interventions aimed at the support of families and carers reviewed here include direct support for families and carers such as support services (including support groups) and information for families and carers of people with autism at the point of diagnosis and throughout the care pathway, as well as interventions which facilitate the role of the family in supporting the delivery of interventions.

7.9.2 Studies considered

No RCTs were found which provided relevant clinical evidence for support for families and carers of adults with autism and met the eligibility criteria for this review. However, one quasi-experimental parallel group controlled study (N=20) was found which included parents of adolescents with autism with a mean age of 14 and 15 years (for control group and experimental groups respectively) and based on GDG expert judgement and the extrapolation rules this study was included (Ergüner-Tekinalp & Akkök, 2004 [ERGUNERTEKINALP2004]). This study was published in a peer-reviewed journal in 2004. In addition, eight studies were excluded predominantly because the mean age of the children with autism was under 15 years old. Based on GDG judgement and the extrapolation rules an additional search was performed for support for families and carers of adults with intellectual disability. One RCT was found which provided relevant clinical evidence for support for families and carers of adults with intellectual disability and was included (Botsford & Rule, 2004 [BOTSFORD2004]). This study was published in a peer-reviewed journal in 2004. In addition, 33 studies were excluded

predominantly because the mean age of the children with intellectual disability was under 15 years old. Further information about included and excluded studies can be found in Appendix 14.

The single included quasi-experimental study which came out of the search for support for families and carers of adults with autism involved a comparison of a coping skills training programme with a treatment as usual group (see Table 69).

The single included RCT study of support for families and carers of adults with intellectual disability involved a comparison of a psychoeducational group permanency planning intervention with a treatment as usual group (see Table 70).

Table 69: Summary study characteristics for included quasi-experimental studies in mothers of adolescents with autism

	Coping Skills Training Programme for Mothers of Adolescents with Autism
No. trials (Total participants)	1 (20)
Study IDs	ERGUNERTEKINALP2004*
N/% female	20/100
Mean age	Mother: 39 & 42 years Offspring: 14 & 15 years
IQ	Not reported
Axis I/II disorders	Mothers of offspring with autism
Comparator	Treatment as usual
Length of treatment	4 weeks
Length of follow-up	4 weeks

*Efficacy data not extractable

Table 70: Summary study characteristics for included RCT studies in mothers of adults with intellectual disability

	Psychoeducational Permanency Planning
No. trials (Total participants)	1 (27)
Study IDs	BOTSFORD2004
N/% female	27/100
Mean age	Mother: 64 years Offspring: 34 years
IQ	Not reported
Axis I/II disorders	Mothers of offspring with intellectual disability
Comparator	Treatment as usual
Length of treatment	6 weeks
Length of follow-up	6 weeks

7.9.3 Clinical evidence for support for families and carers

Coping skills training programme versus treatment as usual

There were no RCTs for interventions to support families and carers of adults with autism. The single included quasi-experimental study in mothers of adolescents with autism compared a coping skills training programme with treatment as usual. The coping skills training programme in ERGUNERTEKINALP2004 consisted of eight group sessions where techniques such as instruction, discussion, sharing and application of techniques were applied in order to provide support for understanding stress and coping, teaching general coping strategies, problem solving, relaxation training, positive thinking, and social support. Efficacy data could not be extracted for this study as mean and standard deviation values were not reported. However, the authors reported statistically significant endpoint differences between experimental and control groups in social support as measured by the Coping Strategy Indicator (Mann Whitney U=16.00, p=0.01) and hopelessness as measured by the Beck Hopelessness Scale (Mann Whitney U=7.50, p=0.001). The authors concluded that participating in this group intervention helps mothers of adolescents with autism to feel socially supported and more positive about themselves and their lives. However, this study is of a very low quality (GRADE) due to the non-randomised group allocation, the fact that efficacy data cannot be extracted, the short duration of the follow-up and the small sample size.

Psychoeducational permanency planning programme versus treatment as usual

Based on the extrapolation rules an additional search was conducted for interventions to support families and carers of adults with intellectual disability. This search resulted in one included RCT study. BOTSFORD2004 compared a psychoeducational permanency planning group intervention with treatment as usual (see Table 71). This group intervention provided opportunities for parents to express concerns about the future of their offspring, aimed to increase participants' awareness and knowledge about options and resources, to identify obstacles to planning, to strengthen relationships with professionals, and to teach problem solving on specific planning issues and concerns. Group sessions included both parent discussion and interaction, and speakers on residential, financial and legal resources followed by group discussion. The primary outcome of this study was mothers' awareness and knowledge of planning as measured by clustered variables which emerged from coded interviews with mothers using standardized (including Heller & Factor's [1991] Community Resources Scale) and original scales. BOTSFORD2004 found evidence for statistically significant treatment effects from their multivariate analysis of covariance on the outcome clusters of knowledge and awareness about planning (test for overall effect: Z=2.43, p=0.02), competence and confidence to plan (test for overall effect: Z=3.19, p=0.001) and residential and legal

planning (test for overall effect: Z=2.48, p=0.01). Whereas no significant treatment effects were observed for the outcome variables of appraisals of the planning process or intermediate planning behaviours (tests for overall effect: Z=1.55, p=0.12; and Z=1.25, p=0.21 respectively). However, this study was also of very low quality due to downgrading on the basis of risk of bias (because of non-blind allocation, administration and assessment; unclear randomization methods; relatively short duration of follow-up; and concerns regarding the reliability and validity of outcome measures), for indirectness (extrapolating from adults with intellectual disability), and for imprecision (due to small sample size and the fact that group N was not clear).

Table 71: Summary evidence profile for psychoeducational group permanency planning intervention compared with treatment as usual for mothers of adults with intellectual disability

Outcome	**Knowledge and awareness about planning**	**Competence and confidence to plan**	**Appraisals of the planning process**	**Intermediate planning behaviours**	**Residential and legal planning**
Study ID	BOTSFORD2004	BOTSFORD2004	BOTSFORD2004	BOTSFORD2004	BOTSFORD2004
Effect size	SMD = -0.99 (-1.79, -0.19)	SMD = -1.36 (-2.20, -0.53)	SMD = -0.61 (-1.39, 0.16)	SMD = -0.49 (-1.25, 0.28)	SMD = -1.02 (-1.82, -0.21)
Quality of evidence (GRADE)	Very low [1,2,3]	Very low [1,2,3]	Very low [1,2,3]	Very low [1,2,3]	Very low [1,2,3]
Number of studies/ participants	(K=1; N=27)	(K=1; N=27)	(K=1; N=27)	(K=1; N=27)	(K=1; N=27)
Forest plot	1.1.7, Appendix 15	1.1.7, Appendix 15	1.1.7, Appendix 15	1.1.7, Appendix 15	1.1.7, Appendix 15

[1]Downgraded for risk of bias due to: non-blind allocation, administration and assessment; unclear randomisation methods; unclear whether the control group received the same care apart from the intervention; the relatively short duration of follow-up; and concerns regarding the reliability and validity of outcome measures

[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

[3]Downgraded for imprecision as the sample size is small and the group N is not clear (assumed N=13 in experimental and N=14 in control but not clear that this assumption is correct)

7.9.4 Clinical evidence summary for support for families and carers

There is limited evidence that for both mothers of adolescents with autism and mothers of adults with intellectual disability group interventions which incorporate discussion, teaching, and social support can be beneficial in terms of increasing mothers' positive feelings about themselves and their lives and in terms of increasing awareness and knowledge about permanency planning. In reviewing this evidence the GDG also considered the outcome of the review of family and carer experience in Chapter 4 on the Experience of Care. However, there is only a single study for each population and all the evidence is of a very low quality (GRADE).

7.9.5 Health economics evidence for support for families and carers

No studies assessing the cost effectiveness of support for families and carers 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.

7.9.6 From evidence to recommendations

There was limited evidence for the efficacy of group-based interventions in the support of families and carers of adolescents or adults with autism or intellectual disability. Evidence from a single quasi-experimental study of a group-based coping skills training programme suggests beneficial treatment effects on maternal wellbeing for mothers of adolescents with autism. While, the single RCT reviewed for parents of adults with intellectual disability provides limited evidence for beneficial effects of a psychoeducational group-based programme in raising awareness and increasing knowledge about permanency planning issues. On this basis the GDG concluded that for families and carers of adults with autism health and social care professionals should consider offering information on, and supported in accessing support groups and should be offered an assessment of their own needs including the need for support, advice on accessing this support, and needs for future care planning. In developing these recommendations the GDG also drew on the reviews conducted in Chapter 4 on the Experience of Care. The GDG took the view that it was important that all the interventions should provide the psychoeducational components and any associated information in an accessible format, for instance, in both written and verbal form. Finally, the GDG, drawing on their expert knowledge and experience of services, recognised the additional support needs of adults with autism who become parents or for parents of adults with autism who do not have autism themselves but may be delivering interventions to their autistic offspring and who will need to be supported, advised and trained in doing so.

7.9.7 Recommendations

7.9.7.1 Offer families and carers of adults with autism an assessment of their own needs including:

- personal, social and emotional support

- support in their caring role, including respite care and emergency plans
- advice on and support in obtaining practical support
- planning of future care for the person with autism.

7.9.7.2 Offer families and carers information on, and support accessing, a range of support groups including those specifically designed to assist the families of people with autism.

7.9.7.3 Offer parents who are involved in interventions for their autistic son or daughter specific training and support from professionals experienced in the care of adults with autism.

7.9.7.4 Offer parents who have autism specific advice and support in their parenting role by professionals experienced in the care of adults and children with autism.

8 BIOMEDICAL INTERVENTIONS

8.1 INTRODUCTION

Psychosocial interventions remain the predominant treatment approach for adults with autism. However, increasing interest is being directed towards pharmacological treatments as single agents and in combination with psychosocial interventions (Broadstock *et al*., 2007). These treatments may be aimed at the core autistic symptoms of social interaction, communication, and repetitive interests/activities but more usually drugs are used to target coexisting behavioural problems including aggression, irritability, hyperactivity, and self-injury. Autism is a risk factor for challenging behaviour (Murphy *et al*., 2005) and children with autism tend not to 'grow out' of behavioural problems (Matson & Shoemaker, 2009). In fact, challenging behaviour becomes an issue of even greater significance in adults with autism, particularly those with intellectual disabilities, due to issues of physical size and the longer history of these problems (Matson *et al*., 2011). In addition to the potential to manage behaviour and reduce harm, it has been suggested that pharmacological interventions may also improve response rates to psychological interventions which are aimed at core autism symptoms (Findling, 2005; Malone *et al*., 2005; McDougle *et al*., 2003), and may assist individuals with autism to live outside of institutional settings (Posey & McDougle, 2001).

Pharmacological interventions which have been used for individuals with autism include antipsychotics, anticonvulsants, drugs affecting cognition (largely cognitive enhancers), hormones (for example, oxytocin), and alternative approaches including diet, vitamins, and supplements. Drugs aimed at coexisting conditions in autism have also been investigated, such as stimulants for coexisting hyperactivity disorder/ADHD, antidepressants for depression, and hormones (for example, melatonin) for insomnia.

Esbensen and colleagues (2009) examined medication use in 286 adolescents and adults with autism over a four and a half year period and found evidence for increasing medication prevalence over time, both in terms of the number of psychotropic and non-psychotropic medications, and the proportion of individuals taking these medications. For participants aged over 20 years, at the start of the study 77% were taking medication, and of those 37% were taking an antidepressant, 26% were taking an antipsychotic and 29% an anticonvulsant. These figures increased over the study period with 88% taking medication, 44% taking an antidepressant, 38% taking an antipsychotic and 31% taking an anticonvulsant four and a half years later. However, despite the widespread use of medication in individuals with autism, very little is known about the efficacy and safety of these drugs in an autistic population, as there have been few placebo-controlled trials, particularly in adults.

The majority of the research studies investigating pharmacological interventions in autism have focused on children and young people. However, developmental differences in pharmacological response and symptomology may mean that findings from studies with children are not directly transferable to an adult population and vice versa (Broadstock *et al*., 2007). For example, coexisting psychiatric disorders, including depression and behavioural problems, have been found to increase in adolescence and adulthood (Korkmaz, 2000; Larsen & Mouridsen, 1997; Rumsey *et al*., 1985).

The atypical antipsychotics, risperidone and aripiprazole, are the only medications that have US Food and Drug Administration (FDA) approval for the treatment of behavioural problems associated with autism, specifically irritability. However, these drugs are indicated for use in children, not adults. No pharmaceutical intervention has autism as a licensing indication in the UK. This means that recommendations for specific pharmacological interventions would be for off-licence indications.

8.1.1 Clinical review protocol (biomedical 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 72 (further information about the search strategy can be found in Appendix 9).

Table 72: Clinical review protocol for the review of biomedical interventions

Component	Description
Review question	For adults with autism, what is the effectiveness of biomedical interventions (for example, dietary interventions, pharmacotherapy, and physical-environmental adaptations)? (CQ – C4)
Sub-question	For adults with autism, is the effectiveness of interventions moderated by: • the nature and severity of the condition? • the presence of coexisting conditions? • age? • the presence of sensory sensitivities (including pain thresholds)? • IQ? • language level? (CQ – C5) For adults with autism, what amendments, if any, need to be made to the current recommendations for psychosocial and pharmacological treatment (including the nature of drug interactions and side effects) for coexisting common mental health disorders? (CQ-C6)
Objectives	To evaluate the clinical effectiveness of biomedical interventions for autism.
Criteria for considering studies for the review	
• Population	Adults and young people aged 18 years and older with suspected autism across the range of diagnostic groups (including atypical autism, Asperger's syndrome and pervasive developmental disorder). Consideration should be given to the specific needs of: • people with coexisting conditions • women • older people • people from black and minority ethnic groups • transgender people Excluded groups include: children (< 18 years of age) However, the GDG made a consensus-based decision that we would need to extrapolate from literature involving children (<18 years) for interventions where there was not sufficient evidence from an adult population and where the mechanisms of biomedical interventions were judged by the GDG to be equivalent in children and adults. For interventions concerned with the management of behaviour, and where data from adult autism populations was not sufficient, the GDG decided that extrapolating from an intellectual disability population was valid.
• Intervention(s)	• **Pharmacotherapy** (for example, antipsychotics, antidepressants, anticonvulsants) • **Vitamins and dietary supplements** (for example, omega-3 fatty acid supplements, vitamin B12, vitamin A)

	• **Hormones** (for example, oxytocin, secretin, melatonin)
• Comparison	Placebo-controlled, other active interventions
• Critical outcomes	Outcomes involving core features of autism (social interaction, communication, repetitive interests/activities); overall autistic behaviour; symptom severity/improvement; management of challenging behaviour; outcomes involving treatment of coexisting conditions; side effects.
• Study design	• RCTs The GDG agreed by consensus that where there were no RCTs found in the evidence search, or the results from the RCTs were inconclusive, that the following studies would be included in the review of evidence: • observational • quasi-experimental • case series
• 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.
• Restriction by date?	No
• Minimum sample size	• RCT/observational/quasi-experimental studies:- N=10 per arm (ITT) • Case series studies:- N=10 in total 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, tertiary, health and social care and healthcare settings (including prisons and forensic services) • Others in which NHS services are funded or provided, or NHS professionals are working in multi-agency teams
Electronic databases	AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, Embase, ERIC, HMIC, Medline, PsycINFO, Sociological Abstracts, SSA
Date searched	Systematic reviews: 1995 up to 09/09/2011. RCT, QE, OS, case-series: inception of database up to 09/09/2011.
Searching other resources	Hand-reference searching of retrieved literature
	•
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. • Narrative review of the literature that takes into consideration any amendments due to common mental health disorders.

	• 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
	  • age
	  • the presence of sensory sensitivities (including pain thresholds)
	  • IQ
	  • language level

Note. Autism=ASD; DB = Database; DSM = Diagnostic and Statistical Manual; ICD = International Classification of Diseases; RCT = Randomised Controlled Trial; QE = Quasi-Experiemental; OS = Observational Study; SR = Systematic Review; AEI = Australian Education Index; AMED = Allied and Complementary Medicine; ASSIA = Applied Social Services Index and Abstracts; BEI = British Education Index; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; DARE = Database of Abstracts and Reviews of Effectiveness; Embase = Excerpta Medica database; ERIC = Education Resources in Curriculum; HMIC =Health Management Information Consortium; Medline = Biomedical Information Database; PsycINFO = Psychological Information Database; SSA = Social Services Abstracts	

8.1.2 Outcomes

A large number of outcomes were reported by the biomedical studies. Those that reported sufficient data to be extractable and were not excluded (see Appendix 14) are in Table 73.

Table 73: Outcomes extracted from biomedical studies

Category	Sub-category	Scale
Core autistic symptoms	Communication	• Clinical Global Impression –Improvement Language (CGI-I Language) (c) (Chez *et al*., 2007) • DSM-IV clinical evaluation (c) (Mousain-Bosc *et al*., 2006) • Language Development Survey (LDS) (Rescorla, 1989) (cg) • Preschool Language Scale-3 (PLS-3) (c) (Zimmerman *et al*., 1992)
	Social interaction	• DSM-IV clinical evaluation (c) (Mousain-Bosc *et al*., 2006) • Joint Attention Measure from the Early Social Communication Scales (Mundy *et al*., 2003) (JAMES) (c) • Reading of the Mind in the Eyes Test (Baron-Cohen *et al*., 2001b)
	Repetitive behaviour	• Children's Yale-Brown Obsessive Compulsive Scales-PDD (CYBOCS-PDD) (c) (Scahill *et al*., 2006) • DSM-IV clinical evaluation (c) (Mousain-Bosc *et al*., 2006) • Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (c) (Goodman *et al*., 1989a, 1989b)
Autistic behaviours		• Autism Behaviour Checklist (AUBC) (cg) (Krug *et al*., 1993) • Childhood Autism Rating Scale (CARS) (c) (Schopler

		et al., 1980) • Children's Psychiatric Rating Scale Autism Factor (c) (Fish, 1985) • DIPAB (Diagnose of Psykotisk Adferd hos Børn [Diagnosis of Psychotic Behaviour in Children; Haracopos & Kelstrup, 1975]) (c) • Ritvo-Freeman Real-life Rating Scale (c) (Freeman *et al*., 1986)
Symptom severity/ improvement		• Behavioral Summarized Evaluation (BSE) (c) (Barthelemy *et al*., 1990) • Clinical Global Impressions (CGI) scale (c) Subscales: Severity (CGI-S); Global Improvement (CGI-I) (Guy, 1976a) • CGI-I Behaviour (c) (Chez *et al*., 2007)
Challenging behaviour	Total score	• Aberrant Behaviour Checklist – Community Version (ABC-C) (cg) (Aman *et al*., 1995a) • General Assessment Parents Scale (GAPS) (cg) (Buitelaar *et al*., 1992) • Global Behaviour Rating Scale (GBRS) (cg) (Levy *et al*., 2003)
	Aggression	• Conners Parent Scale (CPS) – Conduct subscale (cg) (Goyette *et al*., 1978) • General Assessment Parent Scale (GAP) (Buitelaar *et al*., 1992) • Modified Overt Aggression Scale (MOAS) (c) (Sorgi *et al*., 1991) • Overt Aggresion Scale (OAS) (cg) (Yudofsky *et al*., 1986) • Self-Injurious Behaviour Questionnaire (SIB-Q) (c) (Gualtieri, 2002)
	Irritability	• Aberrant Behaviour Checklist (ABC). Subscale: Irritability (cg) (Aman *et al*., 1985) • CGI-Irritability (c) (Hollander *et al*., 2010) • Nurse's Observation Scale for In-patient Evaluation (NOISE-30). Subscale: Irritability (c) (Honigfeld *et al*., 1966)
	Hyperactivity	• Aberrant Behaviour Checklist (ABC). Subscale: Hyperactivity (cg) (Aman *et al*., 1985)
Quality of life		• Composite Autonomic Symptom Scale (COMPASS) (cg). Subscales: Home life; Activity; Skills checklist (cg) (Suarez *et al*., 1999)
Side effects	Global	• Checklist derived from Physicians' Desk Reference (1997) (c) • Clinical Global Assessment (CGA) derived from CGI (c) (Singh & Owino, 1992) • Clinical Global Impressions (CGI) scale (c) (Guy, 1976a) • Dosage Treatment Emergent Symptom Scale (DOTES) (c) (Guy, 1976b)
Coexisting conditions	Insomnia	• Actigraph • Sleep Disturbance Scale for Children (SDSC) (cg) (Bruni *et al*., 1996)
	Gastrointestinal symptoms	• Additional Rating Scale (ARS) gastrointestinal symptoms subscale (cg) (Munasinghe *et al*., 2010)

(c) clinician-rated
(cg) caregiver-report

8.2 ANTIPSYCHOTICS FOR BEHAVIOUR MANAGAMENT

8.2.1 Introduction

Antipsychotic drugs have been used to treat challenging behaviours in autism, and are generally used alone, in combination with or as an adjunct to psychological interventions, in order to facilitate the introduction of behavioural interventions aimed at the treatment of core autistic symptoms. Antipsychotics primary mode of action is to block receptors in the brain's dopamine pathways. Antipsychotic drugs have been usually classified as typical and atypical antipsychotics, although that distinction is increasingly called into question (Kendall, 2011). Typical antipsychotics include haloperidol, chlorpromazine, fluphenazine, and sulperide. Atypical antipsychotics include aripiprazole, olanzapine, and risperidone. Some atypical antipsychotics differ from the typical antipsychotics in that they exhibit antagonism of serotonin (5-hydroxytryptamine [5-HT]) type 2A receptors in addition to blocking dopamine (see Posey *et al.,* 2008).

For this guideline, the GDG followed rules developed for extrapolation, that the primary data concerning antipsychotics for behaviour management in adults with autism could be supplemented, if necessary, by evidence from an intellectual disability population (see 3.5.8 in the methods chapter for further explanation on the rationale and rules for extrapolation). Intellectual disability, like autism, is a risk factor for challenging behaviour (Murphy *et al*., 2005). In addition, in the management of individuals with intellectual disability, antipsychotics are often used to treat challenging behaviour (Matson & Neal, 2009).

Review of the use of antipsychotics in autism (and intellectual disability populations where primary data is lacking), is important as antipsychotics are widely prescribed for the treatment of challenging behaviour in autism. However, there appears to be limited evidence with regards to their efficacy and safety. Moreover, little is known about the potential for atypical response to medications in autism. Antipsychotics have been associated with a number of adverse effects, for instance, weight gain, diabetes, increased prolactin levels, involuntary repetitive body movements (tardive dyskinesia), extra-pyramidal side effects, and lowering of seizure threshold (see Matson & Hess, 2011).

There is controversy surrounding the use of antipsychotics for managing challenging behaviour in autism and intellectual disability. For instance, Spreat and Conroy (1998) note that over 90% of antipsychotic drug prescriptions for individuals with intellectual disability in residential settings were for "behavioural control".

Current practice

Antipsychotic drugs have been found to be widely used in individuals with autism. For instance, a longitudinal study of 286 adolescents and adults in the USA found that antipsychotics were the second most commonly taken drug among an over-20-year old age group (38%), after antidepressants (44%) (Esbensen *et al*., 2009). In a UK audit of drug use for challenging behaviour in a learning disabilities sample (in which the commonest coexisting diagnosis was autism) 96% were prescribed antipsychotic medication (Marshall, 2004). In another community sample of people with learning difficulties, Dhumad and Markar, (2007) report that autism was the reason for prescribing antipsychotic medication in 20% of cases.

8.2.2 Studies considered[43]

Three RCTs (N = 107) providing relevant clinical evidence in adults with autism met the eligibility criteria for this review. All three of these were published in peer-reviewed journals between 1998 and 2006. Due to the lack of primary data, and based on GDG consensus decision, a separate search was conducted for antipsychotics for behaviour management in intellectual disability. Nine RCTs (N=564) provided relevant clinical evidence, met eligibility criteria and were included. All nine of these studies were published in peer-reviewed journals between 1966 and 2008. However, data could not be extracted for the calculation of effect sizes for four of these RCTs and so analysis will be restricted to a narrative synthesis for these studies. Five RCTs (N=308) in an intellectual disability population did allow for extraction of efficacy data. Two observational studies in intellectual disability populations (N=40) were considered in a narrative synthesis. These studies were published in peer-reviewed journals between 2006 and 2007. In addition, 19 studies were excluded from the analysis. The most common reasons for exclusion were that the papers did not have efficacy data that could be entered into a meta-analysis or be included in a narrative synthesis, or participants had a co-morbid psychotic disorder. Further information about both included and excluded studies can be found in Appendix 14.

Of the three included trials in an autism population (see Table 74), two involved a comparison of risperidone and placebo (Hellings *et al*., 2006 [HELLINGS2006]; McDougle *et al*., 1998a [MCDOUGLE1998A]), and one involved a comparison of haloperidol and placebo (Remington *et al*., 2001 [REMINGTON2001]).

Of the nine included RCT trials in an intellectual disability population (see Table 76), three involved a comparison of risperidone and placebo (Gagiano *et al*., 2005 [GAGIANO2005]; Tyrer *et al*., 2008 [TYRER2008]; Vanden Borre *et al*., 1993 [VANDENBORRE1993]), and one of these studies was a three-armed trial and also compared haloperidol with placebo or risperidone (TYRER2008). Three studies involved a comparison of zuclopenthixol and placebo (Haessler *et al*., 2007

[43] 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).

[HAESSLER2007]; Izmeth *et al*., 1988 [IZMETH1988]; Singh & Owino, 1992 [SINGH1992]), one study compared prothipendyl with placebo (McKenzie & Roswell-Harris, 1966 [MCKENZIE1966]), one study compared pipamperone with placebo (van Hemert, 1975 [VANHEMERT1975]), and one study compared two antipsychotics: cis(z)-clopenthixol with haloperidol (Karsten *et al*., 1981 [KARSTEN1981]).

Of the two included observational trials in an intellectual disability population (see Table 75), one involved open-label olanzapine (Handen & Hardan, 2006 [HANDEN2006]), and one open-label risperidone (Read & Rendall, 2007 [READ2007]).

Table 74: Summary study characteristics of included placebo-controlled trials of antipsychotics for behaviour management in adults with autism

	Risperidone	**Haloperidol**
No. trials (Total participants)	2 RCTs (71)	1 RCT (36)
Study IDs	(1) HELLINGS2006 (2) MCDOUGLE1998A	REMINGTON2001
N/% female	(1) 17/43 (2) 9/29	6/17
Mean age	(1) 22 (2) 28	16
IQ	(1) Not reported (27.5% mild ID, 22.5% moderate ID, 27.5% severe ID, & 22.5% profound ID) (2) Mean 54.6	Not reported
Axis I/II disorders	(1) 90% autism (70% Autistic Disorder; 20% PDD-NOS); 100% ID (2) 100% autism (55% autism; 45% PDD-NOS)	100% autism
Dose	(1) 1mg/day for children and adolescents; 2mg/day for adults (2) mean dose 2.9mg/day	Final dose 1-1.5mg/day
Comparator	(1) Placebo (2) Placebo	Placebo
Length of treatment	(1) 3-5 weeks per intervention (2) 12 weeks	6 weeks per intervention
Length of follow-up	(1) 22 weeks (open-label continuation) (2) 24 weeks (open-label continuation)	21 weeks

Table 75: Summary study characteristics of included open-label observational trials of antipsychotics for behaviour management in adults with intellectual disability

	Olanzapine	Risperidone
No. trials (Total participants)	1 Observational (16)	1 Observational (24)
Study IDs	HANDEN2006*	READ2007*
N/% female	6/38	5/21
Mean age	15	27
IQ	36-79 (mean 55)	Not reported (75% with severe or profound ID)
Axis I/II disorders	100% disruptive behaviour disorders (DBD; ADHD; ODD; CD); 100% ID	33% autism, 54% epilepsy, 46% organic behaviour disorder; 100% ID
Dose	2.5-20mg/day (mean dose 13.7mg/day)	Final dose 0.5-6mg/day (mean Final dose 2.92mg/day)
Comparator	No comparator	No comparator
Length of treatment	8 weeks	4-103 days (mean duration of treatment: 76.4 days)
Length of follow-up	8 weeks	Mean follow-up 76.4 days

*Efficacy data not extractable.

Table 76: Summary study characteristics of included placebo-controlled and alternative treatment-controlled trials of antipsychotics for behaviour management in adults with intellectual disability

	Risperidone	Risperidone or Haloperidol	Zuclopenthixol	Prothipendyl	Pipamperone	Cis(z)-clopenthixol
No. trials (Total participants)	2 RCTs (114)	1 RCT (86)	3 RCTs (204)	1 RCT (40)	1 RCT (20)	1 RCT (100)
Study IDs	(1) GAGIANO2005 (2) VANDENBORRE1993*	TYRER2008*	(1) HAESSLER2007 (2) IZMETH1988 (3) SINGH1992	MCKENZIE1966	VANHEMERT1975*	KARSTEN1981
N/% female	(1) 30/39 (2) Not reported	33/38	(1) Not reported (2) 45/40 (3) 24/46	20/50	20/100	44/44
Mean age	(1) Not reported (18-59) (2) 31	38-43	(1) Not reported (18-50) (2) 30-32 (3) 34-38	21-26	33 (median)	25-27
IQ	(1) 35-83 (mean not reported) (2) Not reported (severe or profound ID)	Not reported (1% borderline ID; 35% mild ID; 48% moderate ID; 16% severe/profound ID)	(1) 30-70 (mean not reported) (2) 20-80 (means 48 & 51) (3) Not reported (2% mild ID; 33% moderate ID; 65% severe ID)	19-58 (means 25 & 34)	Not reported (45% moderate ID; 50% severe ID; and 5% profound ID)	Not reported
Axis I/II disorders	(1) 100% disruptive behaviour disorder (ASPD; CD; DBD; IED; ODD); 100% ID (2) 100% ID	16% autism; 100% ID	(1) 100% ID (2) 21% psychiatric disorder, 26% epilepsy; 100% ID (3) 40% physical disorders, 29% epilepsy, 17% psychiatric disorders; 100% ID	100% ID	100% ID	100% ID
Dose	(1) 1-4mg/day (mean	risperidone:	(1) 2-20mg/day (mean	80mg (1 tablet) -	40-80mg/day	cis(z)-

	dose 1.45mg/day) (2) 4-12mg/day (mean final dose 8.3mg/day)	1mg-2mg/day haloperidol: 2.5mg-5mg/day	11.4mg/day) (2) 119mg/week (intramuscular injection) (3) 10-150mg/day (modal dose 20mg/day)	320mg (4 tablets) 6-hourly		clopenthixol: available as 5 & 25mg tablets haloperidol: available as 1 & 4mg tablets
Comparator	(1) Placebo (2) Placebo	Risperidone, haloperidol, or placebo	(1) Placebo (2) Placebo (3) Placebo	Placebo	Placebo	Haloperidol
Length of treatment	(1) 4 weeks (2) 3 weeks per intervention	12 weeks	(1) Up to 12 weeks (discontinuation period) (2) 12 weeks (3) 12 weeks	16 weeks	3 weeks per intervention	12 weeks
Length of follow-up	(1) 52 weeks (open-label continuation) (2) 8 weeks	26 weeks (optional continuation)	(1) 18 weeks (6 week open-label phase followed by discontinuation) (2) 12 weeks (3) 18 weeks (open-label continuation)	16 weeks	4 months (open-label continuation)	12 weeks

[*]Efficacy data not extractable.

8.2.3 Clinical evidence for antipsychotics

Risperidone versus placebo for behaviour management

Two of the three included RCT studies for adults with autism involved a comparison of risperidone with placebo (see Table 77). Meta-analysis which combined results from HELLINGS2006 and MCDOUGLE1998A revealed statistically significant beneficial treatment effects of risperidone on challenging behaviour (test for overall effect: Z=3.06, p=0.002).

In addition, MCDOUGLE1998A examined the effects of risperidone on autistic behaviours (as measured by the Ritvo-Freeman Real-life Rating Scale), the core autism symptom of repetitive behaviours (as measured by the Yale-Brown Obsessive Compulsive Scale [Y-BOCS]) and symptom severity/improvement (as measured by the Clinical Global Impression [CGI) scale, global improvement subscale] and found significant treatment effects for all outcomes (test for overall effect: Z= 1.95, p=0.05; Z=2.47, p=0.01; and Z=3.48, p=0.0005 respectively).

MCDOUGLE1998A reported observational data for adverse events and found some evidence for mild, transient sedation but concluded that risperidone was well-tolerated with no evidence of extrapyramidal side effects, cardiac events or seizures. HELLINGS2006 also presented only observational data with regards to adverse events. However, in HELLINGS2006 results were suggestive of side-effects of increased appetite and weight gain. For instance, weight gain greater than 3 kg occurred in 70% of the participants, and mean weight gain over the 46 weeks was 7.9 kg for children, 8.3kg for adolescents and 6.0 kg for adults.

In summary, the evidence from adults with autism suggests that risperidone may have a modest effect in the treatment and management of challenging behaviour. However, it is important to bear in mind the methodological limitations of the studies, notably the small sample sizes, as reflected by their moderate GRADE rating for quality. It is also important to note that although results are suggestive of adverse events associated with risperidone, the studies only examined short-term side effects and only reported observational data for side-effect profiles. Therefore more long-term studies are needed. However, existing NICE guidance on the use of antipsychotics in schizophrenia (NICE, 2009c) provides evidence on adverse events associated with antipsychotics and this evidence may be extrapolated to adults with autism.

Based on GDG expert judgement data from adults with intellectual disability were included in order to extrapolate to adults with autism. Three of the nine included RCTs from an intellectual disability population compared risperidone with placebo; one of these studies also included a haloperidol comparison group. Efficacy data could only be extracted for two of these studies (see Table 78).

Both studies which allowed extraction of efficacy data (GAGIANO2005 and TYRER2008) examined the effects of risperidone on symptom

severity/improvement. Meta-analysis revealed a trend for a statistically significant positive treatment effect of risperidone on symptom severity/improvement (test for overall effect: Z=1.71, p=0.09). However, the evidence was inconsistent with GAGIANO2005 reporting a statistically significant difference between participants receiving risperidone and participants receiving placebo (test for overall effect: Z=1.95, p=0.05) and TYRER2008 reporting no significant difference between the two groups (test for overall effect: Z=0.38, p=0.70). However, it should be noted that the quality of the data from GAGIANO2005 was downgraded on the basis of indirectness as in addition to participants having intellectual disability and not autism, the participants in this study also had coexisting psychiatric conditions including conduct disorder, disruptive behaviour disorder, intermittent explosive disorder, oppositional defiant disorder, and antisocial personality disorder. It is also important to note that the addition of the TYRER2008 data to the meta-analysis may not be legitimate given that the data is skewed, and although medians and interquartile ranges were reported, the mean and standard deviation scores were requested in order to be entered into the current meta-analysis.

TYRER2008 also examined the effects of risperidone on challenging behaviour, aggression, and quality of life and found no evidence for any significant differences between participants receiving risperidone and participants receiving placebo for any of these outcomes (test for overall effects: Z=0.69, p=0.49; Z=0.21, p=0.84; and Z=1.04, p=0.30 respectively). TYRER2008 concluded that antipsychotic drugs should no longer be regarded as an acceptable routine treatment for aggressive challenging behaviour in people with intellectual disability. However, GAGIANO2005 concluded that risperidone is effective in managing disruptive behaviour disorders in adults with intellectual disability.

Side effect outcomes were not reported in TYRER2008 and GAGIANO2005 concluded that risperidone was well tolerated. It is important to note, however, that although side effects were reported equally by risperidone and placebo groups in GAGIANO2005 during the double-blind phase, observational data for the open-label continuation phase suggests a high incidence of somnolence and statistically significant weight gain with an overall mean change in weight of 3.8 kg ($p \leq 0.001$) over the 48 weeks.

Efficacy data could not be extracted for the remaining included RCT in adults with intellectual disability. VANDENBORRE1993 does not report mean and standard deviation scores. However, the authors report statistically significant (p=0.01) differences in challenging behaviour (as measured by the Aberrant Behaviour Checklist total score) with a larger change from baseline score in the risperidone group compared with the control group. The paper also reports a significant difference between risperidone and placebo groups for endpoint scores in symptom severity/improvement ($p<0.01$). Thus, these results are suggestive of efficacy. However, the authors also report that adverse reactions were more numerous under risperidone treatment with ten times more reporting of sedation and six times more reporting of drowsiness as a treatment-emergent side effect.

In summary, the evidence from RCTs in adults with intellectual disability for the efficacy and tolerability of risperidone for treating and managing challenging behaviour is inconsistent. The results from GAGIANO2005 when entered into meta-analysis and the narratively described results of VANDENBORRE1993 corroborate the results found in an autism population and suggest that risperidone may have a positive treatment effect on symptom severity/improvement and challenging behaviour, but a negative treatment effect in terms of adverse events, in this case increasing incidence of sedation in addition to the weight gain reported in the autism studies. However, TYRER2008 found no significant differences between participants receiving risperidone and participants receiving placebo for any of the outcomes examined including challenging behaviour, aggression, symptom severity/improvement, or quality of life. This inconsistency is reflected in the downgrading of the quality of the evidence to very low.

Open-label risperidone for behaviour management

One open-label observational study examined the effects of risperidone in adults with intellectual disability without a control group (READ2007). Efficacy data could not be extracted. However, the authors report significant change from baseline scores with risperidone for challenging behaviour (as measured by the Aberrant Behaviour Checklist total score), symptom severity ($p<0.001$), and quality of life (for three subscales of home life, activity, and skills checklist: range $p<0.001$-$p=0.014$). The authors conclude that risperidone was efficacious and well tolerated for managing violent and self-injurious behaviour and improving quality of life in adults with intellectual disability. However, there was a trend for statistically significant weight gain ($p=0.061$) with a mean of 1.74 kg increase in body weight over the 12 week trial. Thus, this study provides some support for the findings of GAGIANO2005 and VANDENBORRE1993 reported above.

Table 77: Summary evidence profile for risperidone versus placebo in adults with autism

Outcome	Challenging behaviour (irritability & aggression)	Autistic core symptom: repetitive behaviour	Autistic behaviours	Symptom severity/ improvement
Study ID	HELLINGS2006 MCDOUGLE1998A	MCDOUGLE1998A	MCDOUGLE1998A	MCDOUGLE1998A
Effect size	SMD = -0.79 (-1.29, -0.28)	SMD = -0.94 (-1.68, -0.19)	SMD = -0.72 (-1.45, 0.01)	SMD = -1.40 (-2.18, -0.61)
Quality of evidence (GRADE)	Moderate[1]	Moderate[1]	Moderate[1]	Moderate[1]
Number of studies/participants for analysis	(K=2; N=66)	(K=1; N=31)	(K=1; N=31)	(K=1; N=31)
Forest plot	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15

[1]Downgraded for imprecision as sample size is small

Table 78: Summary evidence profile for risperidone versus placebo in adults with intellectual disability

Outcome	Challenging behaviour	Aggression	Symptom severity/improvement	Quality of life
Study ID	TYRER2008	TYRER2008	GAGIANO2005 TYRER2008	TYRER2008
Effect size	MD = -4.77 (-18.38, 8.84)	MD = 0.58 (-4.90, 6.06)	SMD = -0.30 (-0.64, 0.04)	MD = 2.88 (-2.56, 8.32)
Quality of evidence (GRADE)	Low[1,2]	Low[1,2]	Very low[1,2,3,4]	Low[1,2]
Number of studies/participants	(K=1; N=58)	(K=1; N=58)	(K=2; N=132)	(K=1; N=58)
Forest plot	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15

[1]Data is skewed in TYRER2008 and medians and interquartile ranges were reported. However, means and standard deviation values were requested in order to be entered into meta-analysis and extract efficacy data. However, because data is skewed this analysis is flawed

[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

[3]Downgraded for indirectness as in GAGIANO2005 adults with intellectual disability also had coexisting psychiatric conditions including conduct disorder, disruptive behaviour disorder, intermittent explosive disorder, oppositional defiant disorder, and antisocial personality disorder

[4]Downgraded for inconsistency as GAGIANO2005 found significant differences whereas TYRER2008 did not

Haloperidol versus placebo for behaviour management

One of the three included RCT studies for adults with autism involved a comparison of haloperidol with placebo (see Table 79). REMINGTON2001 was a three-armed trial comparing haloperidol with clomipramine and placebo. Data were not extracted for clomipramine here as this will be reported in the antidepressant section (see 0). REMINGTON2001 found no significant treatment effect for haloperidol compared with placebo for autistic behaviours (test for overall effect: Z=1.18, p=0.24) or for global side effects (test for overall effect: Z=1.66, p=0.10). However, although statistically significant differences were not observed on the side-effect scales, there was a notable attrition rate for the study with 21% dropout during the haloperidol phase as a result of identified side-effects (N=5 fatigue; N=1 dystonia; and N=1 depression), compared with 3% dropout in the placebo phase due to side effects (in this case, nosebleeds).

Table 79: Summary evidence profile for haloperidol versus placebo in adults with autism

Outcome	Autistic behaviours	Side effects (global)
Study ID	REMINGTON2001	REMINGTON2001
Effect size	MD = -2.70 (-7.19, 1.79)	MD = 1.50 (-0.28, 3.28)
Quality of evidence (GRADE)	Very low[1,2,3]	Very low[1,2,3]
Number of studies/participants	(K=1; N=33)	(K=1; N=33)
Forest plot	1.2.1, Appendix 15	1.2.1, Appendix 15

[1]Downgraded for risk of bias as high risk of attrition bias due to higher dropout as a consequence of side effects in the haloperidol group
[2]Downgraded for indirectness as this was an adolescent sample with autism
[3]Downgraded for imprecision as sample size is small

One of the included RCT studies in an adult population with intellectual disability also examined treatment effects of haloperidol in a three-armed comparison of haloperidol, risperidone and placebo (TYRER2008; see above). The results of the comparison of haloperidol with placebo are presented in Table 80. TYRER2008 found no evidence for significant treatment effects of haloperidol on challenging behaviour or quality of life (test for overall effect: Z=0.56, p=0.57; Z=0.67, p=0.51 respectively). However, there was a trend for a statistically significant difference between participants receiving haloperidol and participants receiving placebo for aggression (test for overall effect: Z=1.83, p=0.07), and a statistically significant group difference for symptom severity/improvement (test for overall effect: Z=2.50, p=0.01) with participants receiving haloperidol showing superior scores. In addition, consistent results were found when haloperidol was compared with risperidone with a trend for positive treatment effects in favour of haloperidol for aggression

(test for overall effect: Z=1.90, p=0.06) and a statistically significant difference between the two antipsychotics for symptom severity/improvement (test for overall effects: Z=2.08, p=0.04), with superior scores for participants receiving haloperidol compared with participants receiving risperidone. In summary, TYRER2008 found some evidence for positive treatment effects of haloperidol (compared with placebo or risperidone) on aggression and symptom severity/improvement. However, it should be noted that there is uncertainty about this analysis as the data was skewed and medians and interquartile ranges were reported in the original trial report and may better represent the likely effects of the trial. The quality of this evidence was also downgraded on the basis of indirectness.

Table 80: Summary evidence profile for haloperidol versus placebo in adults with intellectual disability

Outcome	Challenging behaviour	Aggression	Symptom severity/ improvement	Quality of life
Study ID	TYRER2008	TYRER2008	TYRER2008	TYRER2008
Effect size	MD = -4.30 (-19.30, 10.70)	MD = -4.12 (-8.53, 0.29)	MD = -0.88 (-1.57, -0.19)	MD = -1.87 (-7.38, 3.64)
Quality of evidence (GRADE)	Low[1,2]	Low[1,2]	Low[1,2]	Low[1,2]
Number of studies/participants	(K=1; N=57)	(K=1; N=57)	(K=1; N=57)	(K=1; N=57)
Forest plot	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15

[1]Data is skewed in TYRER2008 and medians and interquartile ranges were reported. However, means and standard deviation values were requested in order to be entered into meta-analysis and extract efficacy data. However, because data is skewed this analysis is flawed

[2]Downgraded for indirectness as extrapolating from adults with intellectual disability

Zuclopenthixol versus placebo for behaviour management

There were no RCT, quasi-experimental, or observational studies comparing zuclopenthixol with placebo in adults with autism. Based on GDG expert judgement, data were included from an adult population with intellectual disability. Of the nine included RCTs examining antipsychotics for behaviour management in adults with intellectual disability, three compared zuclopenthixol with placebo (see Table 81). HAESSLER2007 compared participants who discontinued zuclopenthixol and switched to placebo after a six-week open-label trial with participants who continued with zuclopenthixol for a further 12 weeks in a double-blind phase. Dichotomous outcome data was reported with participants showing a deterioration of at least three points on the Modified Overt Aggression Scale at two subsequent visits designated as non-responders and participants without deterioration considered to be responders. A significant difference was observed between zuclopenthixol and placebo (test for overall effect: Z=1.96, p=0.05), with the risk ratio

indicating that participants who received zuclopenthixol were more than seven times more likely to respond to treatment for aggressive challenging behaviour than participants receiving placebo. The authors conclude that discontinuation of zuclopenthixol in adults with intellectual disability leads to an increase in aggressive behaviour.

SINGH1992 also examined the effects of discontinuing zuclopenthixol treatment (following a six week open-label phase) in adults with intellectual disability. Dichotomous data was extracted for 'severity of behavioural disorder' as measured by the Clinical Global Assessment that was derived from the CGI scale. Participants causing fewer problems in management were rated as responders and the number of participants remaining unchanged or causing more problems summed to create a non-responder total. The risk ratio indicated that adults with intellectual disability who continued with zuclopenthixol were nearly four times more likely to respond to treatment in reducing the severity of the behavioural disorder than participants who discontinued and switched to placebo. However, this treatment effect was not statistically significant (test for overall effect: Z=1.31, p=0.19).

Finally, IZMETH1988 examined the effects of discontinuation of zuclopenthixol decanoate injection following a four week open-label trial. Data could not be extracted for endpoint comparison. However, data extracted and analysed for change from baseline scores for symptom severity (of the behavioural disorder) found evidence for a significant treatment effect (test for overall effect: Z=3.04, p=0.002), with significantly greater reduction in severity of illness observed for the zuclopenthixol decanoate group compared to the placebo group at week 12 (endpoint). Statistically significant differences in change from baseline scores for irritability (as measured by the Nurse's Observation Scale for In-patient Evaluation) were also observed (test for overall effect: Z=2.60, p=0.009) with patients who continued treatment with zuclopenthixol decanoate showing greater clinical improvement than participants who discontinued and switched to placebo.

Table 81: Summary evidence profile for zuclopenthixol versus placebo in adults with intellectual disability

Outcome	Challenging behaviour: aggression (endpoint data)	Challenging behaviour: irritability (change from baseline)	Symptom severity/ improvement (endpoint comparison)	Symptom severity/ improvement (change from baseline)
Study ID	HAESSLER2007	IZMETH1988	SINGH1992	IZMETH1988
Effect size	RR = 7.37 (1.00, 54.39)	MD = -2.20 (-3.86, -0.54)	RR = 3.96 (0.50, 31.09)	MD = 0.70 (0.25, 1.15)
Quality of evidence (GRADE)	Low[1, 2]	Very low[1,3,4]	Very low[1,2,3,4]	Very low[1,3,4]
Number of studies/ participants	(K=1; N=39)	(K=1; N=85)	(K=1; N=43)	(K=1; N=85)
Forest plot	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15	1.2.1, Appendix 15

[1]Downgraded for indirectness as extrapolating from adults with intellectual disability
[2]Downgraded for imprecision as sample size is small
[3]Downgraded for risk of bias as high risk of attrition bias because of greater dropout rate in placebo group
[4]Downgraded for indirectness as the study is very old

Prothipendyl versus placebo for behaviour management

There were no RCT, quasi-experimental or observational studies comparing prothipendyl with placebo in adults with autism. As described above, extrapolation data was considered from an adult population with intellectual disability. Of the nine included RCTs examining antipsychotics for behaviour management in adults with intellectual disability, one compared prothipendyl with placebo (see Table 82). Dichotomous outcome data were extracted from MCKENZIE1966 for clinical assessment of symptom severity/improvement with participants showing slight improvement, good improvement, very good improvement, or excellent improvement summed to produce a responders category and participants showing no change or deterioration summed to produce a non-responders category. A significant treatment effect was observed (test for overall effect: Z=1.97, p=0.05), with the risk ratio indicating that participants receiving prothipendyl were over one and a half times more likely to respond to treatment for behavioural disorders than participants receiving placebo. However, it is important to bear in mind the modest size of this effect, and the very low quality of this evidence due to indirectness, pre-trial group differences in IQ, the age of the study, and the small sample size. It should also be noted that prothipendyl has no license for use for any indication in the UK.

Table 82: Summary evidence profile for prothipendyl versus placebo in adults with intellectual disability

Outcome	Symptom severity/improvement
Study ID	MCKENZIE1966
Effect size	RR = 1.69 (1.00, 2.85)
Quality of evidence (GRADE)	Very low[1,2,3,4]
Number of studies/participants	(K=1; N=39)
Forest plot	1.2.1, Appendix 15

[1]Downgraded for risk of bias as high risk of selection bias due to pre-trial group differences in IQ
[2]Downgraded for indirectness as extrapolating from adults with intellectual disability
[3]Downgraded for indirectness as the study is very old
[4]Downgraded for imprecision as the sample size is small

Pipamperone versus placebo for behaviour management

There were no RCT, quasi-experimental, or observational studies comparing pipamperone with placebo in adults with autism. As described above, extrapolation data was considered from an adult population with intellectual disability. Of the nine included RCTs examining antipsychotics for behaviour management in adults with intellectual disability, one compared pipamperone with placebo (VANHEMERT1975). The data reported in VANHEMERT1975 could not be entered into a meta-analysis as neither continuous (mean and standard deviation values) nor dichotomous data were presented. As a result it was not possible to extract efficacy data. However, the authors report that for six of the ten challenging behaviour checklist items (fits of anger, actual aggressiveness, fussiness, impulsiveness, sleep disorders, and manageability), participants who received pipamperone showed a better response than participants treated with placebo ($p<0.05$; range from $p=0.004$ to $p=0.041$). However, without efficacy data it is difficult to quantify these findings. Moreover, the indirectness, small sample size, and age of the study seriously limit the conclusions which can be drawn from this data. It should also be noted that pipamperone has no license for use for any indication in the UK.

Cis(z)-clopenthixol versus haloperidol for behaviour management

The final included RCT which examined antipsychotics in an extrapolation population of adults with intellectual disability compared two active antipsychotic drugs, cis(z)-clopenthixol compared with haloperidol (see Table 83). Dichotomous data were extracted (as reported) with participants showing improved symptoms rated as responders and participants showing unchanged or deteriorated symptoms rated as non-responders. KARSTEN1981 found a statistically significant difference for symptom severity/improvement (test for overall effect: $Z=3.25$, $p=0.001$), with the risk ratio indicating that participants receiving treatment with cis(z)-clopenthixol were over three times more likely to respond to treatment than participants receiving haloperidol. Dichotomous data were also calculated from the data reported in KARSTEN1981 for the clinical global impression of side effects with no side effect rated as 'event' and all side-effect categories (side effects interfering slightly with functioning, side effects interfering moderately with functioning, and

side effects interfering markedly with functioning) summed to produce 'no event' total score. Marginal, but non-statistically significant differences were observed for side effects (test for overall effect: Z=1.36, p=0.17) with the risk ratio indicating that participants receiving cis(z)-clopenthixol were 15% more likely to exhibit side effects than participants receiving haloperidol. In summary this comparison of two antipsychotic drug treatments suggests that cis(z)-clopenthixol may be superior to haloperidol in improving the severity of illness. It is important to note, that for this data as for much of the antipsychotic literature the evidence is only of a low quality due to downgrading for indirectness and the age of the study.

Table 83: Summary evidence profile for cis(z)-clopenthixol versus haloperidol in adults with intellectual disability

Outcome	Symptom severity/ improvement	Side effects
Study ID	KARSTEN1981	KARSTEN1981
Effect size	RR = 3.43 (1.63, 7.21)	RR = 0.85 (0.66, 1.08)
Quality of evidence (GRADE)	Low[1, 2]	Low[1, 2]
Number of studies/participants	(K=1; N=98)	(K=1; N=98)
Forest plot	1.2.1, Appendix 15	1.2.1, Appendix 15

[1]Downgraded for indirectness as extrapolating from adults with intellectual disability
[2]Downgraded for indirectness as the study is very old

Open-label olanzapine for behaviour management

Finally, one open-label observational study examined the effects of olanzapine in adolescents with intellectual disability without a control group (HANDEN2006). Efficacy data could not be extracted. However, the authors report statistically significant changes from baseline for irritability and hyperactivity, and for symptom severity/improvement ($p \leq 0.002$). The authors conclude that olanzapine may be useful in treating disruptive behaviour in adolescents with intellectual disability. However, the authors also suggest that side effects, especially weight gain, are a significant issue, with an average weight gain of 12.7 lb over the 8 week trial and 67% of participants gaining ≥10 lb. Thus, the results from this study are suggestive of positive treatment effects on challenging behaviour, but also with the negative side effect of increased weight gain.

8.2.4 Clinical evidence summary for antipsychotics

The majority of the evidence on the use of antipsychotics for behaviour management in adults with autism compared risperidone with placebo, and there is limited evidence for a modest treatment effect of risperidone on irritability and aggression. In addition, there is some evidence that autistic behaviours, the core autistic symptom of repetitive behaviour, and global symptom severity may respond favourably to treatment with risperidone. However, the data from placebo-controlled and observational studies of risperidone in adults with intellectual disability is inconsistent. In addition, most of the studies, in autism and intellectual disability populations, report data suggestive of adverse events associated with

risperidone, in particular, sedation and weight gain. (Note this is consistent with the evidence of adverse effects of the use of these drugs in schizophrenia.) 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 use in adults with autism.

The evidence on haloperidol was very limited and inconsistent with no evidence for significant treatment effects in adults with autism. The results for clopenthixol provide limited evidence (low quality [GRADE]) for a beneficial effect on the management of challenging behaviour in adults with intellectual disability. The evidence for olanzapine for behaviour management is extremely limited (very low quality [GRADE]) with just one open-label study.

8.2.5 Health economics evidence for antipsychotics

No studies assessing the cost effectiveness of antipsychotics 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.

8.2.6 From evidence to recommendations

The GDG considered the evidence for antipsychotic medication to be of low quality with two drugs risperidone and zuclopenthixol having the most evidence and with more limited evidence for the use of haloperidol. The limited evidence suggested that the effects on these drugs were more likely to be seen on the management of challenging behaviour and not on the core symptoms of autism. The mechanisms by which these drugs exerted any beneficial effect was unclear from the data reviewed and it was unclear whether effects were mediated by an effect on any psychotic symptoms, reduced levels of anxiety or more general sedation.

Therefore, GDG judgement was that antipsychotics should not be used for the treatment of core autistic symptoms but may be considered for the treatment and management of challenging behaviour including irritability, aggression, and self-harm in adults with autism. The GDG recognised that antipsychotics were often used for the management of challenging behaviour without review of the underlying causes of that challenging behaviour and the GDG agreed that a functional analysis of the challenging behaviour should be a core component of treatment. This analysis, along with a consideration of any coexisting mental and physical disorders and the wider social and physical environment, should help determine whether any antipsychotic should be used. The GDG did not think it 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, a service user's past experience of the use of the drug and their personal preferences.

The GDG felt that an integrated approach to treating challenging behaviour in adults with autism was important and consequently judged that antipsychotics should normally be used in conjunction with psychological or other interventions (which

are targeted at the challenging behaviour) except in cases where this is not possible, for example where a person refuses a psychological intervention or it has not been effective or has proved harmful. 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 there should be regular review of the benefits of the drug, any side effects, adherence, and physical health, with particular emphasis on weight gain monitoring where antipsychotics are used for the treatment of challenging behaviour in adults with autism. The recommendations for the monitoring of side effects are true for all biomedical interventions and therefore form general principles. The GDG drew on the NICE guideline on the treatment and management of schizophrenia (NICE, 2009c) when formulating advice on the monitoring and management of side effects and other adverse effects as they did not consider that there would be significant differences in the effects in the population covered by this guideline, save for a potentially greater sensitivity to side effects in general in people with autism.

Given the complexity of treating and managing challenging behaviour, and the fact that antipsychotics represent one of a number of potential psychotropic treatment options for challenging behaviour, the GDG judged that recommendations for antipsychotics needed to be considered in the context of recommendations for biomedical interventions generally (see section 8.2.7), and the treatment of challenging behaviour more broadly (see 8.2.8.1).

8.2.7 Recommendations for general principles for biomedical interventions

8.2.7.1 For any biomedical intervention used in adults with autism, a suitably qualified and experienced professional should regularly review:

- the benefits of the intervention, preferably using a formal rating of the target behaviour(s)
- any side effects
- specific monitoring requirements of pharmacological interventions as highlighted by the summary of product characteristics
- adherence to the intervention
- physical health (and in addition offer advice about the beneficial effects of diet and exercise).

8.2.7.2 When discussing options for pharmacological interventions with adults with autism, be aware of the potential for greater sensitivity to side effects and idiosyncratic responses in people with autism, and consider starting with a lower dose.

8.2.8 Recommendations for antipsychotics

8.2.8.1 Do not use antipsychotic medication for the treatment of core symptoms of autism.

8.2.8.2 Consider antipsychotic medication as part of a comprehensive treatment plan for the treatment and management of problem behaviour including irritability, aggression and self-harm in adults with autism (see section 8.2.9).

8.2.9 Recommendations for challenging behaviour

Interventions for challenging behaviour

8.2.9.1 Psychotropic (anxiolytic, antidepressant or antipsychotic) medication should normally be used in conjunction with psychosocial interventions. Only consider psychotropic medication on its own when:

- psychosocial or other interventions (such as environmental adaptations) alone have not been of benefit
- psychosocial or other interventions could not be delivered because of the severity of the challenging behaviour
- a diagnostic assessment or the functional analysis identified a problem central to the development of the challenging behaviour that may benefit from a pharmacological intervention.

8.3 ANTICONVULSANTS FOR BEHAVIOUR MANAGEMENT

8.3.1 Introduction

Anticonvulsants are routinely used for the treatment of epilepsy. In addition, anticonvulsants are licensed for the treatment of bipolar disorder. Anticonvulsants have also been used off-label to treat challenging behaviour in individuals with autism who do not have coexisting epilepsy. It has been suggested that anticonvulsant medication may assist in the treatment and management of challenging behaviour in autism due to the drugs' potential anti-aggressive and anti-impulsive effects (Hollander *et al.,* 2003a). However, the literature on the use of anticonvulsants for treating agitated or aggressive behaviour in individuals without bipolar disorder has mostly come from single case reports or small retrospective case series (see Ruedrich *et al*., 1999). There reports have concerned a number of different anticonvulsants including carbamazepine, lamotrigine, levetiracetam, sodium valproate and topiramate. Anticonvulsant drugs have diverse mechanisms of action including blockage of voltage-gated ion channels (Na and Ca), reduction of glutamatergic excitation, and enhancement of GABA-ergic inhibition (see Munshi *et al.,* 2010). It has been suggested that the latter of these mechanisms may be relevant to the treatment of challenging behaviour in autism given theories of decreased inhibitory control in autism (Casanova *et al*., 2003). Anticonvulsants have been associated with adverse events, including, weight gain, sedation, gastrointestinal upset, alopecia, tremor, and a higher incidence of certain birth defects when used in pregnancy (Lubetsky & Handen, 2008). It should be noted that there is a higher incidence of epilepsy in people with autism, perhaps up to 20-25% (Canitano, 2007) and individuals with autism may well require treatment with anticonvulsants for coexisting epilepsy.

Current practice

In a longitudinal study of adolescents and adults with autism in the US, Ebersen and colleagues (2009) found that 31% of adults 20-years and older with autism were taking an anticonvulsant medication at the end of the longitudinal study. However, due to the high rate of coexisting epilepsy in this study it is not possible to ascertain the prevalence rate of anticonvulsants targeted at behaviour management from that of medication aimed at symptoms of epilepsy. Tsakanikos and colleagues (2007) examined patterns of change in referral trends for adults with intellectual disability and autism to specialist mental health services in south London from 1983 to 2000 (N=137) and found that 6% of these participants were taking anticonvulsant medication. However, this study does not describe the target of anticonvulsant medication in this population, namely whether these drugs were prescribed for behaviour management or coexisting epilepsy. If it is the latter case, then this might represent an under-prescription of anticonvulsants given the prevalence estimates of coexisting epilepsy of 20-25% (Canitano, 2007).

8.3.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence for anticonvulsants in adults with autism. Due to the lack of primary data, and based on GDG expert judgement, a separate search was conducted for anticonvulsants for behaviour management in intellectual disability. Five studies were found but all were excluded, predominantly on the basis of coexisting epilepsy. Based on GDG expert judgement the decision was made to extrapolate from children with autism for the use of anticonvulsants in behaviour management. Three RCTs (N=92) provided relevant clinical evidence, met extrapolation eligibility criteria, and were therefore included. All three of these studies were published in peer-reviewed journals between 2001 and 2010. However, data could not be extracted for the calculation of effect sizes for one of these RCTs and so analysis will be restricted to a narrative review for that study. One observational study in children with autism (N=15) will also be considered in a narrative review. This study was published in a peer-reviewed journal in 2004. In total, seven studies were excluded from the analysis, predominantly because the sample had coexisting epilepsy. Further information about both included and excluded studies can be found in Appendix 14.

Of the three included RCTs in children with autism (see Table 84), two involved a comparison of valproate with placebo (Hellings *et al*., 2005 [HELLINGS2005]; Hollander *et al*., 2010 [HOLLANDER2010]), and one involved a comparison of lamotrigine with placebo (Belsito *et al*., 2001 [BELSITO2001]).

The one included observational trial in children with autism (see Table 85) involved open-label topiramate (Hardan *et al*., 2004 [HARDAN2004]).

Table 84: Summary study characteristics of included placebo-controlled trials of anticonvulsants for behaviour management in children with autism

	Valproate	Lamotrigine
No. trials (Total participants)	2 (57)	1 (35)
Study IDs	(1) HELLINGS2005 (2) HOLLANDER2010	BELSITO2001*
N/% female	(1) 10/33 (2) 4/15	2/6
Mean age	(1) 11 (2) 9	6
IQ	(1) 20-137 (mean 54) (2) 30-126 (mean 63.3)	Not reported
Axis I/II disorders	(1) 100% autism (N=27 Autistic Disorder; N=1 PDD-NOS; N=2 Asperger's disorder) (2) 100% autism (N=23 autistic disorder; N=4 Asperger's syndrome)	100% autism
Dose	(1) 20mg/kg/day (2) Not reported	Mean dose 5mg/kg per day
Comparator	(1) Placebo	Placebo

	(2) Placebo	
Length of treatment	(1) 8 weeks (2) 12 weeks	12 weeks
Length of follow-up	(1) 8 weeks (2) 12 weeks	18 weeks

*Efficacy data not extractable.

Table 85: Summary study characteristics of included observational open-label trials of anticonvulsants for behaviour management in children with autism

	Topiramate
No. trials (Total participants)	1 (15)
Study IDs	HARDAN2004*
N/% female	3/20
Mean age	15
IQ	Not reported
Axis I/II disorders	100% autism (N=11 autistic disorder; N=2 Asperger's disorder; N=2 PDD-NOS)
Dose	Mean dose 235mg ± 88mg/day
Comparator	No comparator
Length of treatment	8-56 weeks (mean 25 weeks)
Length of follow-up	8-56 weeks (mean 25 weeks)

*Efficacy data not extractable

8.3.3 Clinical evidence for anticonvulsants

Valproate versus placebo for behaviour management

There were no RCT, quasi-experimental, or observational studies comparing valproate with placebo in adults with autism or in adults with intellectual disability. Based on GDG consideration of the rules for extrapolation, data were included from a population of children with autism. Of the three included RCTs examining anticonvulsants for behaviour management in children with autism, two compared valproate with placebo (see Table 86).

HELLINGS2005 failed to find a significant difference between participants receiving valproate and participants receiving placebo for aggression, symptom severity/improvement, or side effects (tests for overall effect: Z=0.09, p=0.93; Z=1.20, p=0.23; and Z=1.15, p=0.25 respectively). HELLINGS2005 also examined the treatment effects of valproate on irritability, as did HOLLANDER2010. However, meta-analysis again failed to find a statistically significant treatment effect for valproate (test for overall effect: Z=0.19, p=0.85). However, the authors of HELLINGS2005 conclude that the null result cannot be viewed as conclusive, partly owing to the large placebo response, the small sample size and the heterogeneity of the sample (with large differences in aggression frequency and severity for different weeks during the eight week period and large standard deviations reported for each of the measures).

HOLLANDER2010 did however find a significant positive treatment effect of valproate on irritability as measured by dichotomous outcome data from the Clinical Global Impressions (CGI) scale focusing on irritability in children with autism (test for overall effect: Z=1.98, p=0.05). The risk ratio indicates that the participants receiving treatment with valproate were nearly two times more likely to respond than the participants receiving placebo. However, even within HOLLANDER2010 the results were not consistent, with no statistically significant treatment effects observed on the continuous outcome measure of irritability as assessed with the Aberrant Behaviour Checklist (test for overall effect: Z=1.09, p=0.28).

To sum up, the data on valproate for behaviour management in children with autism is inconsistent both between-studies and within-study with HELLINGS2006 reporting no effect of valproate on challenging behaviour and HOLLANDER2010 reporting mixed treatment effects on irritability. Moreover, the quality of this evidence is very low to low, with the GRADE rating reflecting downgrading due to inconsistency but also due to imprecision (small sample sizes) and indirectness (extrapolating from children with autism).

Table 86: Summary evidence profile for valproate versus placebo in children with autism

Outcome	Challenging behaviour – Irritability (continuous data)	Challenging behaviour – Irritability (dichotomous data)	Challenging behaviour - Aggression	Symptom severity/ improvement	Side effects
Study ID	HELLINGS2005 HOLLANDER 2010	HOLLANDER 2010	HELLINGS2005	HELLINGS2005	HELLINGS2005
Effect size	SMD = -0.05 (-0.58, 0.48)	RR = 6.87 (1.02, 46.28)	MD = 0.14 (-2.93, 3.21)	MD = -0.37 (-0.97, 0.23)	RR = 1.19 (0.88, 1.61)
Quality of evidence (GRADE)	Very low[1,2,3]	Low[2,3]	Low[2,3]	Low[2,3]	Low[2,3]
Number of studies/participants	(K=2; N=57)	(K=1; N=27)	(K=1; N=30)	(K=1; N=30)	(K=1; N=30)
Forest plot	1.2.2, Appendix 15	1.2.2, Appendix 15	1.2.2, Appendix 15	1.2.2, Appendix 15	1.2.2, Appendix 15

[1]Downgraded for inconsistency as HELLINGS2005 found no significant treatment response and HOLANDER2010 found a positive response for valproate on ABC irritability scores
[2]Downgraded for indirectness as extrapolating from children with autism
[3]Downgraded for imprecision as the sample size is small

Lamotrigine versus placebo for behaviour management

There were no RCT, quasi-experimental, or observational studies comparing lamotrigine with placebo in adults with autism or in adults with intellectual disability. Based on GDG expert judgement, data were included from a population of children with autism. Of the three included RCTs examining anticonvulsants for behaviour management in children with autism, one compared lamotrigine with placebo (BELSITO2001). However, efficacy data could not be extracted for BELSITO2001 as no measure of variability was reported. The authors found no evidence for statistically significant treatment effects with negligible differences observed in change from baseline scores between participants receiving lamotrigine and participants receiving placebo on irritability (p=0.3751) or autistic behaviours (p=0.7941). In summary, narrative review of this single RCT comparing lamotrigine with placebo provides no evidence for beneficial treatment effects of this anticonvulsant for behaviour management in children with autism.

Open-label topiramate for behaviour management

Finally, one open-label observational study examined the effects of topiramate in children and adolescents with autism without a control group (HARDAN2004). Efficacy data could not be extracted. Narrative review of the results suggests a significant change from baseline score on the Conners Parent Scale (CPS) conduct subscale as a measure of challenging behaviour (t=3.04, p=0.009). Significant change from baseline differences were also observed on the inattention (t=3.11, p=0.008) and hyperactivity (t=4.30, p=0.001) subscales of the CPS. However, 20% of the sample (N=3) discontinued the study because of side effects, with two participants experiencing cognitive difficulties (such as disorientation and speech problems including word-finding difficulties) and one participant because of a skin rash. The authors conclude that topiramate may be beneficial for treating secondary symptoms of autism. However, double-blind placebo-controlled studies are needed to assess the efficacy and safety of topiramate.

8.3.4 Clinical evidence summary for anticonvulsants

No evidence was identified for the use of anticonvulsants for behaviour management in adults with autism or in adults with intellectual disability. All of the available evidence comes from children with autism and thus is indirect. This evidence was also downgraded on the basis of inconsistency. The majority of the placebo-controlled trials of anticonvulsants for behaviour management in children with autism compare valproate with placebo. However, no clear conclusions can be drawn based on the best available evidence as mixed results were found both between-studies and within-study. For instance, HELLINGS2005 found no evidence for significant treatment effects on challenging behaviour, whereas HOLLANDER2010 found evidence for a positive treatment effect on irritability. However, while HOLLANDER2010 found significant treatment effects of valproate on a dichotomous measure of irritability (as assessed by the Clinical Global Impressions ratings of irritability), significant treatment effects were not replicated

on the continuous outcome measure (Aberrant Behaviour Checklist-Irritability subscale) in the same study. As with all other biomedical interventions it is also important to bear in mind that the evidence is concerned with the use of medication as an adjunctive therapeutic intervention aimed at behaviour management and not the core symptoms of autism.

8.3.5 Health economics evidence for anticonvulsants

No studies assessing the cost effectiveness of anticonvulsants 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.

8.3.6 From evidence to recommendations

The evidence for the use of anticonvulsants for behaviour management in autism is indirect (extrapolating from child data), of only very low to low quality, and is inconsistent with mixed results reported. On this basis, the GDG concluded that there is no good evidence to recommend the use of anticonvulsants for either core autistic symptoms or for managing challenging behaviour in adults with autism.

8.3.7 Recommendations for anticonvulsants

8.3.7.1 Do not use anticonvulsants for the treatment of core symptoms of autism or for the routine management of challenging behaviour in adults with autism.

8.4 DRUGS AFFECTING COGNITION FOR BEHAVIOUR MANAGEMENT

8.4.1 Introduction

Post-mortem analysis of the brains of individuals with pervasive developmental disorders have revealed limbic system abnormalities, including decreased neuronal size and increased cell packing density of the hippocampus, amygdala, mammillary bodies, septum, and anterior cingulate cortex (Kemper & Bauman, 1993). These interrelated structures are known to be involved in memory processes and the neuropathological findings suggest neurodevelopmental immaturity in these brain regions in autism. Another disease process in which memory processes are affected and related structures are involved is Alzhemier's disease. There are several competing hypotheses concerning the neurochemical mechanisms underpinning the changes in memory function observed in Alzheimer's disease. The oldest of these theories is the cholinergic hypothesis (Francis *et al*., 1999) which proposes that the memory problems seen in Alzheimer's disease are caused by reduced synthesis of the neurotransmitter acetylcholine. Based on this hypothesis, drugs used to treat dementia include acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) which reduce the rate at which acetylcholine is broken down and consequently increase the concentration of acetylcholine in the brain to combat the loss of acetylcholine caused by the death of cholinergic neurons (Stahl, 2000). There is some evidence for the efficacy of these drugs in treating Alzheimer's disease (Birk, 2006; Birks & Harvey, 2006; Birks *et al*., 2009). For instance, donepezil hydrochloride, which belongs to this class of drugs, has been found to improve executive function deficits in dementia. On this basis it has been hypothesised that acetylcholinesterase inhibitors have a role in treating executive function deficits in autism (see Yoo *et al*., 2007). However, acetylcholinesterase inhibitors have also been associated with adverse events with common side effects (occurring in approximately 10-20% of cases) including nausea and vomiting (linked to cholinergic excess), and less common side effects including muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.

Another class of drugs used in the treatment of Alzheimer's disease are N-methyl-D-aspartate (NMDA) blockers (memantine). NMDA blockers are thought to be effective through prevention of a phenomenon called 'excitotoxicity' (Kemp & McKernan, 2002) which may account for the changes observed in Alzheimer's disease whereby persistent activation of NMDA receptors by the excitatory amino acid glutamate leads to excessive calcium entry and subsequent neuronal death (Lipton, 2006). There is evidence for the efficacy of memantine in treating moderate to severe Alzheimer's disease (Reisberg *et al*., 2003). In addition, there is some evidence of glutamatergic abnormalities in autism (Fatemi *et al*., 2002; Jamain *et al*., 2002; Shuang *et al*., 2004), and it has been proposed that NMDA blockers may enhance frontal lobe function and translate to an autistic population (Chez *et al*., 2007). Reported evidence for side effects of memantine in Alzheimer's disease are

infrequent and mild, but include hallucinations, confusion, dizziness, headache, and fatigue (based on prescribing information).

Finally, amantadine, a compound structurally similar to memantine which has known non-competitive glutamate NMDA antagonist activity (Kornhuber *et al*., 1994), has been used to treat influenza, herpes zoster and Parkinson disease, and has also been identified as having a possible role in the treatment of autism due to reports of its efficacy in treating behavioural disturbance in traumatic brain injury (Gualtieri *et al*., 1989) and hyperactivity and irritability in attention deficit hyperactivity disorder (Masters, 1997).

8.4.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence for drugs affecting cognition for behaviour management in adults with autism. Due to the lack of primary data, and based on GDG expert judgement, a decision was made to extrapolate from children with autism. Two RCTs (N=82) were found which provided relevant clinical evidence, met extrapolation eligibility criteria and were included. In addition, four observational studies were included in a narrative synthesis (N=196). All of these studies were published in peer-reviewed journals between 2001 and 2007. Further information about included studies can be found in Appendix 14.

Of the two included RCT trials in children with autism (see Table 87), one involved a comparison of donepezil hydrochloride with placebo (Chez *et al*., 2003 [CHEZ2003]), and one involved a comparison of amantadine hydrochloride with placebo (King *et al*., 2001 [KING2001]).

Of the four observational studies (see Table 88), three examined the effects of memantine (Chez *et al*., 2007 [CHEZ2007]; Erickson *et al*., 2007 [ERICKSON2007]; and Owley *et al*., 2006 [OWLEY2006]), and one of galantamine (Nicolson *et al*., 2006 [NICOLSON2006]).

Table 87: Summary study characteristics of included placebo-controlled trials of drugs affecting cognition for behaviour management in children with autism

	Donepezil hydrochloride	Amantadine hydrochloride
No. trials (Total participants)	1 (43)	1 (39)
Study IDs	CHEZ2003	KING2001
N/% female	8/19	5/13
Mean age	7	7
IQ	Not reported	Not reported
Axis I/II disorders	100% autism	100% autism
Dose	1.25-2.5mg/day	5mg/kg per day
Comparator	Placebo	Placebo
Length of treatment	6 weeks	4 weeks
Length of follow-up	6 weeks	5 weeks

Table 88: Summary study characteristics of included observational studies of drugs affecting cognition for behaviour management in children with autism

	Memantine	Galantamine
No. trials (Total participants)	3 (183)	1 (13)
Study IDs	(1) CHEZ2007* (2) ERICKSON2007* (3) OWLEY2006*	NICOLSON2006*
N/% female	(1) 22/15 (2) Not reported (3) 0/0	3/23
Mean age	(1) 9 (2) 11 (3) 8	9
IQ	(1) Not reported (2) Not reported (3) Nonverbal IQ mean 96.8	Not reported
Axis I/II disorders	(1) 100% autism (70% autism; 30% PDD-NOS) (2) 100% autism (72% autistic disorder; 17% Asperger syndrome; 11% PDD-NOS); 61% ID (3) 100% autism (71% autistic disorder; 14% Asperger syndrome; 14% PDD-NOS)	100% autism; 54% ID
Dose	(1) final dose 2.5-30mg/day, mean dose 12.67mg/day (2) 2.5-20mg/day, mean 10.1mg/day (3) 5-20mg/day	2-24mg/day, mean final dose 18.4mg/day
Comparator	(1) No comparator (2) No comparator (3) No comparator	No comparator
Length of treatment	(1) 1-20 months (mean 9.27 months) (2) 1.5-56 weeks (mean 19.3 weeks) (3) 8 weeks	12 weeks
Length of follow-up	(1) 1-20 months (mean 9.27 months) (2) 1.5-56 weeks (mean 19.3 weeks) (3) 8 weeks	12 weeks

*Efficacy data not extractable

8.4.3 Clinical evidence for drugs affecting cognition

Donepezil hydrochloride versus placebo for autistic behaviours

There were no RCT, quasi-experimental, or observational studies comparing donepezil hydrochloride with placebo in adults with autism. Based on the rules for extrapolation, data were included from a population of children with autism. Of the

two included RCTs examining drugs affecting cognition for behaviour management in children with autism, one compared donepezil hydrochloride with placebo (see Table 89). CHEZ2003 found no evidence for a significant treatment effect on autistic behaviours (test for overall effect: Z=0.15, p=0.88), with no statistically significant difference in scores on the Childhood Autism Rating Scale between children receiving donepezil hydrochloride and children receiving placebo. To conclude, this single trial failed to find evidence for a significant treatment effect of donepezil hydrochloride on autistic behaviours.

Table 89: Summary evidence profile for donepezil hydrochloride versus placebo in children with autism

Outcome	Autistic behaviours
Study ID	CHEZ2003
Effect size	MD = 0.40 (-4.88, 5.68)
Quality of evidence (GRADE)	Low[1,2]
Number of studies/participants	1 (34)
Forest plot	1.2.3, Appendix 15

[1]Downgraded for indirectness as extrapolating from children with autism
[2]Downgraded for imprecision as the sample size is small

Amantadine hydrochloride versus placebo for behaviour management

The second included RCT of drugs affecting cognition in children with autism, compared amantadine hydrochloride with placebo (see Table 90). KING2001 examined the effects of amantadine hydrochloride on behaviour management as assessed by the parent-rated Aberrant Behaviour Checklist-Community Version (ABC-C). Dichotomous data were extracted for the ABC-C, with responders categorised on the basis of a reduction of at least 25% in irritability and/or hyperactivity subscale scores at the end of treatment. This trial failed to find evidence for a significant treatment effect (test for overall effect: Z=0.65, p=0.51), suggesting that participants receiving amantadine hydrochloride were no more likely to show a treatment response for challenging behaviour than participants receiving placebo.

Table 90: Summary evidence profile for amantadine hydrochloride versus placebo in children with autism

Outcome	Challenging behaviour
Study ID	KING2001
Effect size	RR = 1.29 (0.60, 2.74)
Quality of evidence (GRADE)	Low[1,2]
Number of studies/participants	1 (38)
Forest plot	1.2.3, Appendix 15

[1]Downgraded for indirectness as extrapolating from children with autism
[2]Downgraded for imprecision as the sample size is small

Open-label memantine for behaviour management

There were no RCT, quasi-experimental, or observational studies comparing memantine with placebo in adults with autism. Based on the rules for extrapolation, data were included from a population of children with autism. However, again there were no RCTs comparing memantine with placebo which met extrapolation eligibility criteria in children with autism. There were, however, three observational studies (of the four observational studies included) which examined the effects of memantine on behaviour management in children with autism without a control group (CHEZ2007; ERICKSON2007; OWLEY2006). Efficacy data could not be extracted for these studies, however, they are considered within a narrative synthesis.

Both CHEZ2007 and OWLEY2006 examined the effects of memantine on challenging behaviour in children with autism and both studies report statistically significant change-from-baseline scores on the Clinical Global Impression scale focusing on behaviour (71% improvement, $p<0.001$ [CHEZ2007]) and for the Aberrant Behaviour Checklist-Community Version (ABC-CV) Irritability subscale ($p=0.027$ [OWLEY2006]).

CHEZ2007 also examined the effects of memantine on the core autistic symptom of communication as measured by the Clinical Global Impression Improvement scale based on both receptive language skills and expressive utterances (70% improvement, $p<0.001$ [CHEZ2007]). However, there are some concerns with regards to the precision of the outcome measurement as the CGI scale is more commonly used to rate global symptom severity/improvement, and it is not clear whether it is a precise enough measure to evaluate and differentiate language and behaviour scores as used in this study.

Both ERICKSON2007 and OWLEY2006 use the CGI scale to rate symptom severity (as it is more commonly used). However, here there is inconsistent evidence for the effects of memantine in children with autism with ERICKSON2007 reporting a significant change from baseline in scores on the CGI-Severity scale ($p=0.008$) and OWLEY2006 failing to find a statistically significant pre-to-post test difference in symptom severity ($p=0.165$).

CHEZ007 found no evidence for serious side effects and this is the largest study considered in this review. However, ERICKSON2007 and OWLEY2006 narratively report results suggestive of adverse events with memantine. For instance, in ERICKSON2007 there was a high attrition rate with 39% of participants experiencing adverse events including irritability, rash, emesis, increased seizure frequency, and excessive sedation and 22% of participants dropping out of the trial because of these adverse events. While in OWLEY2006, 36% of participants experienced hyperactivity associated with memantine, and for 14% of participants in this observational trial the hyperactivity was severe enough for carers to withdraw their children from the study.

To summarise, these observational trials provide suggestive evidence for beneficial effects of memantine on challenging behaviour and the core autistic symptom of communication in children with autism. However, the evidence for treatment effects on symptom severity is inconsistent. In addition, there are concerns regarding side effects, imprecision of outcome measures, indirectness, and because efficacy data cannot be extracted further placebo-controlled trials of memantine are needed.

Open-label galantamine for behaviour management

Finally, one open-label observational study examined the effects of galantamine in children with autism without a control group (NICOLSON2006). Efficacy data could not be extracted. Narrative review of the results suggests significant change from baseline scores for irritability (t=2.5, p=0.03), autistic behaviours (t=4.3, p=0.001) as measured by the autism factor of the Children's Psychiatric Rating Scale, and symptom severity/improvement (t=2.3, p=0.04). To conclude, this single observational study reports evidence suggestive of a treatment effect for galantamine in children with autism. However, the small sample size and low grade of the evidence suggest caution in interpreting these results.

8.4.4 Clinical evidence summary for drugs affecting cognition

There were no RCTs examining the effects of drugs affecting cognition on behaviour management in adults with autism. Based on the rules for extrapolation the GDG extrapolated from data on children with autism. However, even with the inclusion of child data there were only two RCT studies included. These placebo-controlled trials failed to find evidence for statistically significant treatment effects of donepezil hydrochloride on autistic behaviours or for amantadine hydrochloride on challenging behaviour. Conversely, the open-label observational trials on memantine and galantamine in children with autism provide some evidence suggestive of beneficial effects on challenging behaviour, core autistic symptoms, autistic behaviours and symptom severity/improvement.

8.4.5 Health economics evidence for drugs affecting cognition

No studies assessing the cost effectiveness of drugs affecting cognition 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.

8.4.6 From evidence to recommendations

The evidence for drugs affecting cognition is of very low quality, indirect, inconclusive, and includes a number of studies with small sample sizes. There were only two placebo-controlled trials, both of which failed to find evidence for significant treatment effects for donepezil hydrochloride or amantadine hydrochloride in children with autism. The observational studies report more positive results, however, it is not possible to extract efficacy data from these studies, the methodology has an inherent risk of bias, and the results reported are far from

conclusive. In light of this evidence the GDG decided not to recommend the use of drugs to improve cognitive functioning for adults with autism.

8.4.7 Recommendations

8.4.7.1 Do not use drugs specifically designed to improve cognitive functioning (for example, cholinesterase inhibitors) for the routine treatment of core symptoms of autism or associated cognitive or behavioural problems.

8.5 HORMONAL INTERVENTIONS: ANDRENOCORTICOTROPIC HORMONES FOR BEHAVIOUR MANAGEMENT

8.5.1 Introduction

Animal models have associated andrenocorticotropic hormones (ACTH) with a number of functions including, most relevantly to autism, social behaviour. For example, the synthetic ACTH 4-9 analogue ORG 2766 was found to normalise environmentally-induced disturbances of social behaviour in rats (Niesink & Van Ree, 1983). ORG 2766 is a neuropeptide which has lost its peripheral activity on the adrenal cortex and exclusively affects the functioning of the brain. Neuropeptides may exert their effects on the nervous system by acting as a neurotransmitter, as a neurohormone, or as a neuromodulator, that is, by modulating the activity of the classic neurotransmitter systems (Gispen, 1980; Versteeg, 1980).

8.5.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence for andrenocorticotropic hormones for behaviour management in adults with autism. Due to the lack of primary data, and through GDG expert judgement, a decision was made to extrapolate from children with autism. Two RCTs (N=68) were found which provided relevant clinical evidence, met extrapolation eligibility criteria and were included. Both of these studies were published in peer-reviewed journals between 1992 and 1996. In addition, one study was excluded because the sample size was fewer than ten participants per arm for analysis as it was a crossover study. Further information about both included and excluded studies can be found in Appendix 14.

Both of the included RCT trials in children with autism (see Table 91) involved a comparison of ORG 2766 with placebo (Buitelaar *et al*., 1992 [BUITELAAR1992]; and Buitelaar *et al*., 1996 [BUITELAAR1996]).

Table 91: Summary study characteristics of included placebo-controlled trials of ORG 2766 for behaviour management in children with autism

	ORG 2766
No. trials (Total participants)	2 (68)
Study IDs	(1) BUITELAAR1992 (2) BUITELAAR1996
N/% female	(1) 4/19 (2) 15/32
Mean age	(1) 10 (2) 10-11
IQ	(1) Range and mean not reported (19% in IQ range 22-40; 19% in IQ range 40-55; 15% in IQ range 55-70; and 48% in IQ range 70-85) (2) Range not reported (means 77 & 80)

Axis I/II disorders	(1) 100% autism (autistic disorder) (2) 100% autism (autistic disorder)
Dose	(1) 40mg/day (2) 40mg/day
Comparator	(1) Placebo (2) Placebo
Length of treatment	(1) 8 weeks per intervention (2) 6 weeks
Length of follow-up	(1) 36 weeks (2) 6 weeks

8.5.3 Clinical evidence for andrenocorticotropic hormones

ORG 2766 versus placebo for behaviour management

There were no RCT, quasi-experimental, or observational studies comparing ORG 2766 with placebo in adults with autism. Based on the rules for extrapolation, data were included from a population of children with autism. Of the two included RCTs examining andrenocorticotrophic hormones for behaviour management in children with autism, both compared ORG 2766 with placebo (see Table 92).

Inconsistent results were found for the effects of ORG 2766 on challenging behaviour. For instance, BUITELAAR1992 found modest treatment effects on the social isolation subscale of the General Assessment Parents Scale (GAP) which was designed for this study (test for overall effect: Z=2.01, p=0.04) with superior ratings observed for participants in the ORG 2766 phase relative to the placebo phase. Whereas, BUITELAAR1996 analysed dichotomous data for the Aberrant Behaviour Checklist, with responders classified as participants showing reliable improvement on the ABC social withdrawal subscale either at home or at school or in both contexts, and no significant difference in treatment response was observed between participants receiving ORG 2766 and participants receiving placebo (test for overall effect: Z=0.86, p=0.39).

Conversely, more consistent evidence was found for the effects of ORG 2766 on symptom severity/improvement as measured by the CGI scale and meta-analysis with data from BUITELARR1992 and BUITELAAR1996 combined found a statistically significant treatment effect for ORG2766 on symptom severity/ improvement (test for overall effect: Z=3.69, p=0.0002) with superior ratings for participants receiving ORG 2766 compared with participants receiving placebo.

Table 92: Summary evidence profile for ORG 2766 versus placebo in children with autism

Outcome	Challenging behaviour (social withdrawal)	Challenging behaviour (social isolation)	Symptom severity/ improvement
Study ID	BUITELAAR1996	BUITELAAR1992	BUITELAAR1992 BUITELAAR1996
Effect size	RR = 1.55 (0.57, 4.22)	SMD =	SMD =

		-0.92 (-1.82, -0.02)	-0.97 (-1.48, -0.45)
Quality of evidence (GRADE)	Very low[1,2,3,4]	Very low[2,3,4]	Low[1,3]
Number of studies/participants	(K=1; N=47)	(K=1; N=21)	(K=2; N=68)
Forest plot	1.2.4, Appendix 15	1.2.4, Appendix 15	1.2.4, Appendix 15

[1]Downgraded for risk of bias as randomisation methods were unclear in BUITELAAR1996 (authors state 'randomised in principle') and there was a trend for group differences in age and CARS score at baseline

[2] Downgraded for inconsistency as BUITELAAR1992 found statistically significant treatment effects for challenging behaviour as measured by social isolation on the GAP, whereas BUITELAAR1996 found no significant differences for social withdrawal as measured by ABC

[3]Downgraded for indirectness as extrapolating from children with autism

[4]Downgraded for imprecision as the sample size is small

8.5.4 Clinical evidence summary for andrenocorticotropic hormones

To summarise, the two included placebo-controlled trials provide some evidence for the efficacy of andrenocorticotrophic hormones on symptom severity in children with autism. However, the results are inconsistent with regards to treatment effects for challenging behaviour, and the modest effect sizes in BUITELAAR1992 and small sample sizes contribute to the downgrading of the quality of the evidence to low or very low. The evidence was also downgraded on the basis of methodological concerns with BUITELAAR1996 with regards to the method of randomisation. It is also possible that there may be an overlap of participants across the two studies leading to double counting as both studies were conducted by the same first author and in the same setting. Finally, the data from both studies is indirect as it comes from children with autism.

8.5.5 Health economics evidence for andrenocorticotropic hormones

No studies assessing the cost effectiveness of andrenocorticotropic hormones 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.

8.5.6 From evidence to recommendations

The GDG reached the decision that there is insufficient evidence on which to make a recommendation about the use of andrenocorticotrophic hormones for behaviour management in adults with autism.

8.6 HORMONAL INTERVENTIONS: SECRETIN FOR AUTISTIC BEHAVIOURS

8.6.1 Introduction

Secretin is a gastrointestinal polypeptide that helps digestion and has been used to treat peptic ulcers and in the evaluation of pancreatic function (Tulassay *et al*., 1992; Watanabe *et al*., 1991). Results from animal studies have suggested that secretin affects the central nervous system and may function as a neurotransmitter (Charlton *et al*., 1983; Fremeau *et al*., 1983). The use of secretin for the treatment of autistic behaviours in individuals with autism has gained interest in recent years for several reasons (Parikh *et al*., 2008) including the increased incidence of gastrointestinal problems in children with autism (Horvath & Perman, 2002). In addition, a nonblinded, uncontrolled case series of children with autism reported improvements in social, cognitive and communication domains following synthetic intravenous secretin during a routine endoscopy evaluation for gastrointestinal problems (Horvath *et al*., 1998).

8.6.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence for secretin for autistic behaviours in adults with autism. Due to the lack of primary data, and through GDG expert judgement, a decision was made to extrapolate from children with autism. Three RCTs (N=182) were found which provided relevant clinical evidence, met extrapolation eligibility criteria and were included. All of these studies were published in peer-reviewed journals between 2000 and 2003. In addition, ten studies were excluded from the analysis. These studies were excluded on the basis that efficacy data could not be extracted in order to enter into either a meta-analysis or narrative review, or the sample size was less than ten participants per arm. Further information about both included and excluded studies can be found in Appendix 14.

There were three included RCTs in children with autism (see Table 93) which involved a comparison of secretin with placebo (Chez *et al*., 2000 [CHEZ2000]; Dunn-Geier *et al*., 2000 [DUNNGEIER2000]; and Levy *et al*., 2003 [LEVY2003]).

Table 93: Summary study characteristics for included placebo-controlled trials of secretin for autistic behaviours in children with autism

	Secretin
No. trials (Total participants)	3 (182)
Study IDs	(1) CHEZ2000 (2) DUNNGEIER2000 (3) LEVY2003
N/% female	(1) 3/12 (2) 7/7 (3) 12/19
Mean age	(1) 6

	(2) 5 (3) 6
IQ	(1) Not reported (2) Not reported (3) Not reported
Axis I/II disorders	(1) 100% autism (2) 100% autism (3) 100% autism
Dose	(1) single dose 2 IU/kg (2) single dose injection of 2 CU/kg to a maximum of 75 CU (3) single dose injection of 2 CU/kg to a maximum of 75 CU
Comparator	(1) Placebo (2) Placebo (3) Placebo
Length of treatment	(1) Single dose (2) Single dose (3) Single dose
Length of follow-up	(1) 8 weeks (2) 3 weeks (3) 8 weeks

8.6.3 Clinical evidence for secretin

Secretin versus placebo for autistic behaviours

There were no RCT, quasi-experimental, or observational studies comparing secretin with placebo in adults with autism. Based on the rules for extrapolation, data were included from a population of children with autism. Three RCT studies compared secretin with placebo in children with autism and met extrapolation eligibility criteria (see Table 94).

LEVY2003 and DUNNGEIER2000 both examined treatment effects of single-dose secretin on the core autistic symptom of communication in children with autism. However, neither trial found evidence for a statistically significant treatment effect on communication (test for overall effect: Z=1.15, p=0.25), and the non-significant treatment effects across the two studies were also in opposite directions.

CHEZ2000 and LEVY2003 also examined the effects of secretin on autistic behaviour as measured by the Childhood Autism Rating Scale or the Real Life Ritvo Behaviour Scale. However, again the meta-analysis revealed no evidence for a significant treatment effect of secretin (test for overall effect: Z=1.13, p=0.26).

Finally, LEVY2003 examined the effects of secretin on challenging behaviour as measured by the parent-rated Global Behaviour Rating Scales (GBRS) developed for this study. As for the other outcome measures there was no statistically significant difference between participants receiving secretin and participants receiving placebo (test for overall effect: Z=0.54, p=0.59).

Table 94: Summary evidence profile for secretin versus placebo in children with autism

Outcome	Core autistic symptom (communication)	Autistic behaviours	Challenging behaviour
Study ID	LEVY2003 DUNNGEIER2000	CHEZ2000 LEVY2003	LEVY2003
Effect size	SMD = -0.29 (-0.77, 0.20)	SMD = -0.24 (-0.67, 0.18)	SMD = -0.14 (-0.64, 0.36)
Quality of evidence (GRADE)	Very low[1,2,3]	Low[1,3]	Low[1,3]
Number of studies/participants	(K=2; N=157)	(K=2; N=86)	(K=1; N=62)
Forest plot	1.2.5, Appendix 15	1.2.5, Appendix 15	1.2.5, Appendix 15

[1]Downgraded for risk of bias as in LEVY2003 there was a significant difference between the groups in baseline CARS total score

[2]Downgraded for inconsistency as the studies found modest (but non-significant) effect sizes in different directions

[3]Downgraded for indirectness as extrapolating from children with autism

8.6.4 Clinical evidence summary for secretin

All three of the included RCT studies in children with autism failed to find significant treatment effects for single-dose secretin on autistic behaviours, the core autism symptom of communication, or challenging behaviour. Moreover, the data were indirect due to extrapolation from children with autism, and there is some risk of bias conferred by baseline differences between groups, small sample sizes, and short follow-up periods.

8.6.5 Health economics evidence for secretin

No studies assessing the cost effectiveness of secretin 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.

8.6.6 From evidence to recommendations

There was no evidence for secretin in adults with autism, and all three of the included RCT studies from an extrapolation population of children with autism failed to find positive beneficial effects of this gastrointestinal hormone and neurotransmitter on autistic behaviours. Consequently, the GDG judged that secretin should not be recommended for the treatment of the core symptoms of autism.

8.6.7 Recommendations

8.6.7.1 Do not use secretin for the treatment of core symptoms of autism in adults.

8.7 HORMONAL INTERVENTIONS: OXYTOCIN FOR CORE AUTISM SYMPTOMS

8.7.1 Introduction

Oxytocin is a hormone synthesised in the hypothalamus, and is best known for its role in female reproduction. Synthetic oxytocin, also known as 'pitocin' and 'syntocinon', has been widely used for inducing labour, postpartum care and for enhancing lactation (Gimpl, 2008). In addition to peripheral affects, oxytocin also acts as a neurotransmitter in the brain and appears to play a key role in social behaviour and social understanding with receptors distributed in various brain regions including the limbic system and amygdala (Andari *et al*., 2010). Mammalian research suggests that oxytocin reduces anxiety through amygdala-dependent mechanisms and enhances reward via dopamine-dependent mesolimbic reward pathways (Donaldson & Young, 2008). In addition, research in humans is consistent with an anxiolytic effect of oxytocin. Oxytocin has been found to reduce levels of anxiety (Heinrichs *et al*., 2003) and amygdala activation to social stimuli (Domes *et al*., 2007; Kirsch *et al*., 2005), and increase levels of trust (Kosfeld *et al*., 2005), gaze to the eyes (Guastella *et al*., 2008) and accurate emotion processing (Di Simplicio *et al*., 2009; Fischer-Shofty *et al*., 2010). It is postulated that oxytocin may have a role in treating autism because the amygdala and face-processing regions have been implicated in emotion recognition deficits in autism (Baron-Cohen *et al*., 2000). In addition, Gregory and colleagues (2009) found genomic and epigenetic evidence for a reduced function of the oxytocin receptor in autism. While, Modahl and colleagues (1998) found evidence for significantly lower levels of plasma oxytocin in children with autism and a significant correlation between oxytocin levels and social impairment in a subgroup with severe social cognition impairments. In addition to the social domain, some evidence from animals has been found for significant effects of oxytocin on repetitive behaviours. For instance, intravenous oxytocin has been found to induce stereotypic behaviours in mice (Drago *et al*., 1986; Insel & Winslow, 1991; Meisenberg & Simmons, 1983; Nelson & Alberts, 1997), and to inhibit extinction and promote perseverative behaviours (de Wied *et al*., 1993). However, it is important to apply caution when making analogies between animal and human behaviour.

Current safety information regarding the use of intranasal oxytocin with humans largely comes from research into the use of oxytocin by mothers to promote lactation and not in clinical trials where oxytocin is used to target psychological problems. However, MacDonald and colleagues (2011) systematically reviewed 38 RCTs conducted between 1990 and 2010 that investigated the central effects of intranasal oxytocin in mostly typically developing samples and found no evidence for reliable side effects or adverse outcomes when oxytocin was delivered in doses of 18-40 IU for short term use in controlled research settings. However, comprehensive product information describing possible side effects associated with the use of oxytocin for promoting lactation is accessible from Novartis Pharmaceuticals (Novartis, 2011) and reports that cardiovascular changes can be common including tachycardia and

bradycardia. Nausea, vomiting and headaches have also been reported to occur with intravenous infusion, and less frequent reactions from intravenous infusion also include water intoxication and associated neonatal hyponatraemia, skin rashes and anaphylactoid reactions (Novartis, 2011). Safety information regarding the use of intranasal oxytocin is available from European countries such as the Netherlands where it is marketed for improving lactation (see MacDonald *et al.*, 2011), and this product information lists headaches, nausea and allergic dermatitis occurring rarely, and abnormal uterine contractions known to occur sometimes.

It is important to note that assuming oxytocin was to prove efficacious and safe there are potential practical problems with delivering oxytocin as a routine treatment for the core symptoms of autism. Oxytocin is destroyed in the gastrointestinal tract and therefore must be administered as an injection or intranasal spray. However, oxytocin has a half-life of about three minutes in the blood when administered intravenously (MacDonald *et al*., 2011).

8.7.2 Studies considered

Four placebo-controlled oxytocin trials were found for review. All four were published in peer-reviewed journals between 2003 and 2010, and were in an adult population with autism. However, all of these studies were excluded on the basis of failing to meet sample size eligibility criteria. For all four studies the sample size was fewer than ten participants per arm for analysis due to the crossover design. These studies will, however, be narratively reviewed below in order to provide background to the GDG recommendation regarding the use of oxytocin in adults with autism. Further information about these excluded studies can be found in Appendix 14.

8.7.3 Clinical evidence for oxytocin

All of the placebo-controlled studies examining oxytocin in adults with autism were excluded on the basis that the sample sizes were insufficient to be entered into meta-analysis because they were crossover studies and failed to meet the eligibility criteria of at least ten participants per arm. The results of these studies will, however, be described as the GDG felt that a recommendation should be made with regards to the use of oxytocin in adults with autism due to the recent interest in this intervention. Four crossover RCT studies examined the effects of oxytocin on core autistic symptoms in adults with autism, three of these trials examined effects of oxytocin on social behaviour and one study examined treatment effects on repetitive behaviour.

The authors of the studies examining the effects of oxytocin on social cognition in adults with autism report results suggestive of potential benefits. For instance, ANDARI2010 found that oxytocin inhalation produced more appropriate social behaviour in the context of a computer-based social ball tossing game ($z=1.99$, $p<0.047$). GUASTELLA2010 found that oxytocin inhalation improved performance on the Reading of the Mind in the Eyes Test with 60% of participants demonstrating improvement ($t=2.43$, $p=0.03$). In addition, HOLLANDER2007 found that

intravenous oxytocin increased the retention of affective speech comprehension in autism, but not for participants who received placebo first, as demonstrated by the statistically significant three-way interaction of time by treatment by order (z=-2.134, p=0.033).

The single trial which examined the effects of oxytocin on repetitive behaviours in adults with autism also suggested potential benefits. HOLLANDER2003 found a significant reduction in repetitive behaviour following oxytocin infusion compared with placebo infusion as demonstrated by the statistically significant time by treatment interaction (F=3.487, p=0.027).

However, it was not possible to extract efficacy data for these studies due to the small sample sizes. The statistical analysis reported by the authors implies that the treatment effects although statistically significant were modest in size. The results from these studies also imply that the response to oxytocin may be inconsistent. For instance, ANDARI2010 state that inspection of individual performances revealed that some participants responded strongly to oxytocin, others more weakly, and some not at all. While, the results from GUASTELLA2010 suggest that oxytocin did not improve performance on a measure of social cognition for 40% of participants, and HOLLANDER2007 found that the order of administration affected the treatment response to oxytocin.

8.7.4 Clinical evidence summary for oxytocin

Although the review identified and described above a number of placebo-controlled trials for oxytocin in adults with autism, efficacy data could not be extracted from these studies due to insufficient sample sizes. Moreover, these studies could be described as proof of concept studies rather than standard placebo-controlled RCTs and as a result the ecological validity and generalisability of results is unknown. Moreover, the results of the studies which are reported are suggestive of modest treatment effects, inconsistent responses and have methodological limitations (see HOLLANDER2007).

8.7.5 Health economics evidence for oxytocin

No studies assessing the cost effectiveness of oxytocin 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.

8.7.6 From evidence to recommendations

The studies reviewed above suggest that oxytocin may be beneficial in helping to reduce repetitive behaviours, and to improve some aspects of communication, in some adults with autism. Based on the absence of any included RCT studies and the practical issues with regards to the half-life of oxytocin and the barriers that this might present to routine administration, the GDG judged that further evidence would be needed in order for oxytocin to be recommended for the treatment of core

autistic symptoms in adults with autism. Given the current mode of delivery and the half-life of the drug it is unlikely to beneficial to people with autism.

8.7.7 Recommendations

8.7.7.1 Do not use oxytocin for the treatment of core symptoms of autism in adults.

8.8 HORMONAL INTERVENTIONS: MELATONIN FOR COEXISTING CONDITIONS

8.8.1 Introduction

Melatonin is a hormone and neurotransmitter which regulates the biological clock and which has been used to treat insomnia. Melatonin induces sleep by inhibiting the wakefulness generating system (Arendt, 2003; Cajochen *et al*., 2003; Sachs *et al*., 1997).

Melatonin has been used successfully to promote sleep in children with neurodevelopmental disorders (Miyamoto *et al*., 1999; Wheeler *et al*., 2005; Zhdanova *et al*., 1999). Most studies have not found evidence for serious adverse side effects or development of tolerance (Jan *et al*., 1999; Saebra *et al*., 2000). A few studies have reported side effects of tiredness, dizziness and headache associated with melatonin treatment (for example, Paavonen *et al*., 2003; Palm *et al*., 1997). However, these side effects immediately disappeared after discontinuation (Arendt, 1997; Jan & O'Donnel, 1996).

Sleep problems are common in autism with prevalence rates ranging from 43% to 83% in children with autism (Miano & Ferri, 2010; Richdale & Schreck, 2009). It has been proposed that because prefrontal cortex functions are particularly prone to the deficits induced by sleep deprivation, and individuals with autism may already have compromised function of the prefrontal cortex, poor sleep may impair the daytime functioning of adults with autism more than for neurotypical adults (Tani *et al*., 2003). Sleep problems in autism may be caused by a circadian rhythm disturbance (see Guénolé *et al*., in press), and melatonin regulation has been found to be abnormal in children with autism, with reports of a daytime elevation in melatonin, as well as decreased amplitude and lack of night time elevation (Jan *et al*., 1999; Nir *et al*., 1995; Richdale *et al*., 1999; Ritvo *et al*., 1993). Rossignol and Frye (2011) reviewed nine studies reporting melatonin or melatonin metabolite concentrations in autism and found that all but one of these studies found evidence for abnormal melatonin levels. Moreover, correlations have been found between levels of melatonin or melatonin metabolites and autistic symptoms or clinical findings (Leu *et al*., 2010; Melke *et al*., 2008; Nir *et al*., 1995; Tordjman *et al*., 2005). There is also evidence for abnormalities in genes which code for melatonin receptors or enzymes involved in melatonin synthesis in autism. For instance, the acetylserotonin methyltranserase (ASMT) gene, which codes for the last enzyme involved in melatonin synthesis has been found to be abnormal in autism (Cai *et al*., 2008; Jonsson *et al*., 2010; Melke *et al*., 2008; Toma *et al*., 2007).

In evaluating the treatment of coexisting conditions like insomnia in individuals with autism it is important to consider the extent to which modifications need to be made to the routine treatment of these conditions as a consequence of the autism.

Current practice

Rossignol and Frye (2011) reviewed studies reporting the prevalence of melatonin usage in autism and report three survey studies (Aman *et al*., 2003; Green *et al*., 2006; Polimeni *et al*., 2005), which estimate a mean prevalence of 7.2% (95% CI 5.6-8.7%) for melatonin use in autism.

8.8.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence for melatonin for the coexisting condition of sleep disorder in adults with autism. Due to the lack of primary data, and following the rules for extrapolation, a decision was made to extrapolate from children with autism. No RCTs which met the extrapolation eligibility criteria were found for children with autism. One observational open-label trial (N=15) was found. This study was published in a peer-reviewed journal in 2003. In addition, two observational studies were excluded from the analysis because no data was reported for the statistical analysis of treatment effects. Further information about both included and excluded studies can be found in Appendix 14.

The included observational before-and-after trial in children with autism (Paavonen *et al*., 2003 [PAAVONEN2003]) examined the effects of melatonin on sleep in children with autism with no control group (see Table 95).

Table 95: Summary study characteristics of included observational open-label trials of melatonin for coexisting conditions in children with autism

	Melatonin
No. trials (Total participants)	1 (15)
Study IDs	PAAVONEN2003*
N/% female	2/13
Mean age	10
IQ	Not reported
Axis I/II disorders	100% autism (Asperger's syndrome); 7% ADHD
Dose	3mg/day 30 minutes prior to bedtime
Comparator	No comparator
Length of treatment	2 weeks
Length of follow-up	5 weeks

*Efficacy data not extractable

8.8.3 Clinical evidence for melatonin

Open-label melatonin for coexisting sleeps disorders

There were no included RCT, quasi-experimental, or observational studies comparing melatonin with placebo, or examining open-label melatonin with no control group, in adults with autism. Based on the rules for extrapolation, data were

included from a population of children with autism. There were also no included RCT studies for melatonin in children with autism. However, one open-label observational trial was included (PAAVONEN2003). Efficacy data could not be extracted for this study. However, PAAVONEN2003 report results suggestive of a statistically significant change from baseline after melatonin treatment in the form of decreased mean nocturnal activity (p=0.041) and sleep onset latency (p=0.002) as measured by actigraph. However, the authors also reported a significantly greater number of awakenings (p=0.048) post-melatonin treatment which suggests that the effects of melatonin on sleep patterns in children with autism were inconsistent.

8.8.4 Clinical evidence summary for melatonin

This single open-label before-and-after observational study provides some suggestion that melatonin may help with insomnia in children with autism. However, the lack of efficacy data, and the indirectness and inconsistency of the evidence contributed to the GDG judgement that there was insufficient evidence to make a recommendation about the use of melatonin for insomnia in adults with autism.

8.8.5 Health economics evidence for melatonin

No studies assessing the cost effectiveness of melatonin 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.

8.8.6 From evidence to recommendations

No recommendation is made due to lack of evidence for melatonin in people with autism and sleep related problems.

8.9 STIMULANTS FOR COEXISTING CONDITIONS

8.9.1 Introduction

Stimulants (also known as psychostimulants) are psychoactive drugs that affect the action of certain chemicals in the brain and can bring about improvements in attention and behaviour organization. Psychostimulants are predominantly used as the first line of treatment for hyperactivity and inattention in patients diagnosed with attention deficit hyperactivity disorder (ADHD). Prevalence estimates suggest that 11-14% of individuals with autism are treated for ADHD symptoms with stimulant medication (Aman *et al*., 1995b, 2003; Langworthy-Lam *et al*., 2002; Martin *et al*., 1999). The most prescribed and studied stimulant medication in typically developing children is methylphenidate. Methylphenidate is a central nervous system (CNS) stimulant. Its action has been linked to inhibition of the dopamine transporter, with consequent increases in dopamine available for synaptic transmission (Volkow *et al*., 1998). There is some evidence suggesting significant symptom reduction of overactivity and inattention with methylphenidate in children with autism (see Lubetsky & Handen, 2008, for review). However, side effects have been found with higher doses (Handen *et al*., 2000; Quintana *et al*., 1995). In addition, response rates for children with autism have been found to be significantly lower than the 77% response rate reported for children with ADHD (Greenhill *et al*., 2001). It is also important to consider whether individuals with autism may be at higher risk for experiencing the side effects which have been found for stimulant medications including motor tics, social withdrawal, irritability and appetite loss (Handen *et al*., 1991; Posey *et al*., 2004). The review of evidence for the use of stimulants to treat hyperactivity in individuals with autism will need to consider whether any modifications need to be made to the recommendations for the treatment of hyperactivity symptoms and ADHD (NICE, 2009d) as a result of the autism.

Current practice

In the UK, methylphenidate is licensed for the management of ADHD in children and young people, but not for the treatment of ADHD in adults, although it is used off-label for the treatment of adults with ADHD. Methylphenidate is a Schedule 2 controlled drug and is currently licensed for use in children over 6 years old. Both immediate-release (IR) and modified-release (MR) formulations are available in the UK. Methylphenidate is used in the treatment of ADHD and associated symptoms in children with autism; this is unsurprising given the extent of comorbidity between the disorders but we were unable to identify any data on the extent of its use in adults with autism.

8.9.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence for the effects of stimulants on hyperactivity or ADHD symptoms in adults with autism. Due to the lack of primary data, and through the use of the rules on extrapolation, a decision was made to include evidence from children with autism. One RCT (N=66) was found which met the extrapolation eligibility criteria. In addition, this one primary RCT paper was supplemented by two papers reporting secondary analysis of the same data set. These papers were published in peer-reviewed journals between 2005 and 2009. In addition, five studies were excluded from the analysis. Two because data could not be extracted due to the lack of a control group, naturalistic retrospective chart review design, and no reported statistics which could be incorporated into a meta-analysis or narrative synthesis (NICKELS2008; STIGLER2004). The remaining three excluded studies were not included due to insufficient sample size of less than ten participants per arm. Further information about both included and excluded studies can be found in Appendix 14.

The single included RCT trial of stimulants (see Table 96) involved a comparison of methylphenidate with placebo to target coexisting hyperactivity in children with autism (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005 [RUPP2005]). As detailed above, the data from this trial was also reported in secondary analysis papers where methylphenidate was compared with placebo for core autistic symptoms of social interaction and repetitive behaviour and that data is extracted here too (Jahromi *et al.*, 2009 [JAHROMI2009]; Posey *et al.*, 2007 [POSEY2007]).

Table 96: Summary study characteristics for included placebo-controlled trials of stimulants for coexisting conditions in children with autism

	Methylphenidate
No. trials (Total participants)	1 (66)
Study IDs	RUPP2005 (secondary analysis: JAHROMI2009; POSEY2007)
N/% female	7/11
Mean age	8
IQ	16-135 (mean 62.6)
Axis I/II disorders	100% autism; 100% hyperactivity/impulsivity (CGI-S; SNAP-IV)
Dose	low, medium, and high dosage levels of 0.125, 0.250, and 0.500 mg/kg three times a day
Comparator	Placebo
Length of treatment	1 week for each phase (placebo, low dose, medium dose, high dose)
Length of follow-up	12 weeks (including open-label continuation)

8.9.3 Clinical evidence for stimulants

Methylphenidate versus placebo for coexisting hyperactivity

There were no included RCT, quasi-experimental, or observational studies comparing methylphenidate with placebo, or examining open-label methylphenidate with no control group, in adults with autism. Based on the rules for extrapolation, data were included from a population of children with autism. There was a single included crossover RCT trial (RUPP2005) with secondary analysis (JAHROMI2009; POSEY2007) for methylphenidate in children with autism (see Table 97).

RUPP2005 found evidence for significant treatment effects of methylphenidate on the hyperactivity subscale of the Aberrant Behaviour Checklist (test for overall effect: Z=3.50, p=0.0005) with participants receiving optimal dose methylphenidate in the active drug phase exhibiting less hyperactive behaviours than participants in the placebo phase.

However, the secondary analysis papers found no evidence for significant treatment effects of methylphenidate on core autistic symptoms. JAHROMI2009 found no statistically significant differences between scores in the methylphenidate phase and scores in the placebo phase for the social communication measure of joint attention initiation as assessed by observational ratings (test for overall effect: Z=1.36, p=0.17). POSEY2007 also failed to find statistically significant treatment effects for methylphenidate on repetitive behaviour as assessed by the Children's Yale-Brown Obsessive Compulsive Scales-PDD (CYBOCS-PDD)(test for overall effect: Z=0.95, p=0.34). Thus, there is some evidence for the efficacy of methylphenidate in treating hyperactive symptoms but not core autistic symptoms.

There are also safety concerns based on the high rate of discontinuation owing to adverse events in the RUPP2005 trial. 18% of the original participants dropped out owing to intolerable side effects with the symptom of irritability reported as the primary reason for discontinuation (accounting for 46% of the dropouts). This is of particular concern as the rate of adverse events may be underestimated in this trial given the short duration for each dosage level of methylphenidate (1 week each), and the fact that previous adverse response to methylphenidate was an exclusion criterion.

8.9.4 Clinical evidence summary for stimulants

This single placebo-controlled crossover trial and secondary analyses provide some evidence for the efficacy of methylphenidate in treating hyperactive behaviour in children with autism. However, no evidence was found for significant treatment effects of methylphenidate on core autistic symptoms and the high discontinuation rate owing to adverse events provides cause for concern with regards to safety.

Table 97: Summary evidence profile for methylphenidate versus placebo in children with autism

Outcome	Hyperactivity	Core autistic symptoms (social interaction)	Core autistic symptoms (repetitive behaviour)
Study ID	RUPP2005	JAHROMI2009	POSEY2007
Effect size	MD = -8.80 (-13.72, -3.88)	MD = 6.50 (-2.85, 15.85)	MD = -0.92 (-2.82, 0.98)
Quality of evidence (GRADE)	Moderate[1]	Low[1,2]	Moderate[1]
Number of studies/participants	(K=1; N=62)	(K=1; N=34)	(K=1; N=63)
Forest plot	1.2.6, Appendix 15	1.2.6, Appendix 15	1.2.6, Appendix 15

[1]Downgraded for indirectness as extrapolating from children with autism
[2] Downgraded for imprecision as small sample size

8.9.5 Health economics evidence for stimulants

No studies assessing the cost effectiveness of stimulants 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.

8.9.6 From evidence to recommendations

There is evidence from one trial, of moderate quality, for the efficacy of methylphenidate in treating hyperactivity in children with autism. However, the evidence for treatment effects on core autistic symptoms was not statistically significant. The authors conclude that clinicians can feel more confident that methylphenidate targeted at hyperactivity will not exacerbate core autistic symptoms. However, further research examining the effects of stimulants on core autistic symptoms is needed in order to justify targeting these outcomes for treatment. It is also important to note that this evidence is indirect (extrapolating from children) and there are adverse event concerns given the high attrition rate during methylphenidate treatment in the RUPP2005 study. On this basis the GDG concluded that the treatment of hyperactivity in autism should be in line with existing NICE guidance for the management of hyperactivity in ADHD (NICE, 2009d). In coming to this conclusion the GDG were mindful of the data suggesting a high attrition rate in trials of methylphenidate in autism (Murray, 2011) and the possibility of improved retention rates with atomoxitine (Posey *et al.*, 2006)

8.9.7 Recommendations

8.9.7.1 For adults with autism and symptoms of hyperactivity, treatment of the hyperactivity should be informed by 'Attention deficit hyperactivity disorder' (NICE clinical guideline 72). Consider atomoxetine[44] because there is a higher adherence rate in people with autism compared with methylphenidate.

[44] At the time of publication (date), atomoxetine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

8.10 ANXIOLYTICS FOR COEXISTING CONDITIONS

8.10.1 Introduction

There is considerable evidence that autism coexists with anxiety disorders (Bellini, 2004; Gillott *et al*., 2001; Green *et al*., 2000; Kim *et al*., 2000). Tantam (2000) stated that anxiety is almost universally comorbid with Asperger syndrome and that high trait anxiety is a common feature of individuals across the spectrum of autism, with social anxiety, panic, and obsessive–compulsive rituals being the most common anxiety symptoms shown by individuals with autism. The review of the evidence for the use of anxiolytics to treat anxiety in individuals with autism will need to consider if any autism-specific modifications need to be made to the existing NICE guidance for anxiety disorders (NICE, 2005a; 2005b; 2011c).

8.10.2 Studies considered

Three studies examining the effects of the anxiolytic, busiprone, in the treatment of individuals with autism were found in the initial search (Buitelaar *et al*., 1998; Edwards *et al*., 2006; Realmuto *et al*., 1989). However, all of these studies were excluded at the first sift (on the basis of the abstract) due to a mean sample age of below 15 years old or a sample size of less than ten participants per arm.

8.10.3 Clinical evidence for anxiolytics

As discussed above, there was no clinical evidence for anxiolytics in adults with autism which met the eligibility criteria.

8.10.4 Clinical evidence summary for anxiolytics

There was no clinical evidence for anxiolytics in adults with autism. The GDG were of the view that future placebo-controlled trials of anxiolytics in adults with autism would be required in order to determine whether any adjustment to the usual treatment of anxiety disorders may be required for individuals with autism. The safety and efficacy of anxiolytics where these drugs are targeted at behaviour management in autism also needs to be studied in future placebo-controlled trials of anxiolytics in adults with autism.

8.10.5 Health economics evidence for anxiolytics

No studies assessing the cost effectiveness of anxiolytics 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.

8.10.6 From evidence to recommendations

As detailed above there was no clinical evidence for the use of anxiolytics in adults with autism. However, given the high prevalence of anxiety disorders in autism the GDG consider that anxiolytics may be used to treat coexisting anxiety disorders in individuals with autism and may be considered as a treatment option for the

pharmacological management of challenging behaviour in autism where anxiety was identified as a potential contributory factor in the development or maintenance of the challenging behaviour. Therefore despite the absence of any direct clinical evidence in autism but based on an understanding that the likely mechanisms of action of anxiolytics may well be the same in autistic and non-autistic populations, the GDG decided to recommend the use of anxiolytics in line with existing NICE guidelines for anxiety disorders (NICE, 2005a; 2005b; 2011c). Some adjustment in the dosing of the drugs may be required (for example starting at a lower does and gradually building up the dose if necessary), to take account of the increased sensitivity to drugs found in some people with autism.

8.10.7 Recommendations

8.10.7.1 For adults with autism and a coexisting anxiety disorder, the use of anxiolytic medication should be informed by existing NICE clinical guidelines for the relevant anxiety disorder.

8.11 ANTIDEPRESSANTS FOR AUTISTIC BEHAVIOURS

8.11.1 Introduction

Psychiatric disorders, especially anxiety and depression, are common in people with autism (Gillberg & Billsteadt, 2000; Howlin, 2000). There are a number of antidepressants available, including monamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Results from surveys suggest that 22% of individuals with autism are prescribed antidepressants (Aman *et al*., 2003). As well as being used to treat depressive symptoms in individuals with autism, antidepressant medication has also been targeted at ritualistic and stereotypic behaviours (Hollander *et al*., 1998). There has only been limited systematic evaluation of interventions for depression in children with autism. However, results are suggestive of the efficacy of antidepressants (Ghaziuddin *et al*., 2002; Stewart *et al*., 2006). There is less evidence for the role of antidepressants in treating core symptoms of autism or autistic behaviours. However, these are the target symptoms in the antidepressant trials reviewed here.

Tricyclic antidepressants (including amitriptyline, clomipramine, doxepin, imipramine, and trimipramine) are the oldest class of antidepressant drug. They were thought to exert their therapeutic effect by inhibiting the reuptake of monoamine neurotransmitters into the presynaptic neurone, thus enhancing noradrenergic and serotonergic neurotransmission, but as with other antidepressants, this is no longer accepted as an explanation of their efficacy (Hyman & Nestler, 1996). All tricyclic antidepressants cause, to varying degrees, anticholinergic side effects (dry mouth, blurred vision, constipation, urinary retention, and sweating), sedation, and postural hypotension. Tricyclic antidepressants are also toxic in overdose, with seizures and arrhythmias being a particular concern. This toxicity and the perceived poor tolerability of tricyclic antidepressants in general have led to a decline in their use in the UK over the last decade.

Selective serotonin reuptake inhibitors (SSRIs) are more widely used as they are better tolerated. SSRIs are also the antidepressant drug group which is most often used in individuals with autism (Antochi *et al*., 2003). SSRIs inhibit the reuptake of serotonin into the presynaptic neurone thus increasing neurotransmission. SSRIs are associated with less anticholinergic side effects and are less likely to cause postural hypotension or sedation. They are also less cardiotoxic and much safer in overdose than tricyclic antidepressants. The most problematic side effects of SSRIs are nausea, diarrhoea and headache.

As serotonin has been linked to the mediation of psychological processes which are altered in autism, for instance, mood, social interaction, sleep, obsessive compulsive behaviours and aggression (Saxena, 1995), it has been suggested that inhibition of serotonin reuptake may result in improvement of autistic symptoms (see Williams *et*

al., 2010). In addition, the aggregation of depressive symptoms in certain families affected by autism has suggested possible overlap in genetic influences underlying the two conditions (Bailey *et al*., 1995; Daniels *et al*., 2008; Ghaziuddin & Greden, 1998; Sullivan *et al*., 2000). However, there is also evidence for substantial independence of their respective genetic origins (Constantino *et al*., 2003; Hallett *et al*., 2009).

Prevalence rates for depression in individuals with autism vary widely with estimates ranging from 1.4% (Simonoff *et al*., 2008) to 38% (Lainhart & Folstein, 1994). The reasons for this inconsistency are thought to lie in the phenotypic overlap between the two conditions, for instance, the tendency for autistic symptomatology to mask key features of depression and the fact that symptoms of depression in children with autism may be atypical (see Magnuson & Constantino, 2011). Research has suggested that "higher-functioning" or more socially adjusted individuals with autism may show a heightened risk for depression (Ghaziuddin *et al*., 2002; Simonoff *et al*., 2008). For instance, Vickerstaff and colleagues (2007) found that superior cognitive abilities and greater condition insight was associated with lower self-perceived social competence and subsequently higher rates of depression in children with autism. Similarly, Sterling and colleagues (2008) found that depression in adults with autism was associated with higher cognitive ability, less social impairment, and older age. The review of the evidence for the use of antidepressants to treat depression in individuals with autism will need to consider if any autism-specific modifications need to be made to existing NICE guidance (NICE, 2009a)

8.11.2 Studies considered

Two RCTs (N=66) which examined the effects of antidepressants in individuals with autism were found. One of these studies included an adolescent sample. However, the GDG decided to include this study in line with the rules for extrapolation as the mean age was 16 years of age. Two open-label observational studies with no control groups (N=65) were also included, one of these studies again included an adolescent sample with a mean age of 16 years which the GDG decided to include. All of these studies were published in peer-reviewed journals between 1992 in 2001. In addition, eight studies were excluded from the analysis, predominantly due to the mean age of the sample that was below 15 years old. Further information about both included and excluded studies can be found in Appendix 14.

Of the two RCTs (see Table 98), one compared clomipramine with placebo (Remington *et al*., 2001 [REMINGTON2001]), and one compared fluvoxamine with placebo (McDougle *et al*., 1996 [MCDOUGLE1996]).

Of the two observational before-and-after studies (see Table 99), one examined the effects of fluoxetine with no control group (Cook *et al*., 1992 [COOK1992]), and one examined the effects of sertraline with no control group (McDougle *et al*., 1998b [MCDOUGLE1998B]).

Table 98: Summary study characteristics of included placebo-controlled trials of antidepressants in adolescents and adults with autism

	Clomipramine	Fluvoxamine
No. trials (Total participants)	1 (36)	1 (30)
Study IDs	REMINGTON2001	MCDOUGLE1996
N/% female	6/17	3/10
Mean age	16	30
IQ	Not reported	25-115 (mean 79.9)
Axis I/II disorders	100% autism	100% autism (autistic disorder); 3% fragile x syndrome
Dose	final dose 100-150 mg/day (mean 123 mg/day)	200-300 mg/day (mean dose 276.7 mg/day)
Comparator	Placebo	Placebo
Length of treatment	6 weeks per intervention	12 weeks
Length of follow-up	21 weeks	12 weeks

Table 99: Summary study characteristics of included open-label observational studies of antidepressants in adolescents and adults with autism

	Fluoxetine	Sertraline
No. trials (Total participants)	1 (23)	1 (42)
Study IDs	COOK1992*	MCDOUGLE1998B*
N/% female	5/22	15/36
Mean age	16	26
IQ	Not reported but with ID	25-114 (mean 60.5)
Axis I/II disorders	100% autism (autistic disorder); 96% ID; 13% OCD; 26% impulse control disorder NOS with SIB; 22% impulse control disorder NOS without SIB; 4% cyclothymia; 4% bipolar disorder NOS; 4% eating disorder	100% autism (52% autistic disorder; 14% Asperger's disorder; 33% PDD-NOS); 67% ID
Dose	dose range from 20mg every other day to 80mg/day	50-200 mg/day
Comparator	No comparator	No comparator
Length of treatment	11-426 days (mean: 189 days)	12 weeks
Length of follow-up	11-426 days (mean: 189 days)	12 weeks

*Efficacy data not extractable

8.11.3 Clinical evidence for antidepressants

Clomipramine versus placebo for autistic behaviours

Of the two RCTs examining antidepressants in adolescents and adults with autism, one involved a comparison of clomipramine with placebo (see Table 100). REMINGTON2001 found no evidence for a statistically significant treatment effect of clomipramine on autistic behaviours as measured by the Childhood Autism Rating Scale (test for overall effect: Z=0.57, p=0.57). This trial also found no statistically significant difference between participants receiving clomipramine and participants receiving placebo in global side effects as measured by the Dosage Treatment

Emergent Symptom Scale (test for overall effect: Z=1.43, p=0.15). However, the attrition rate in this study does give cause for concern with regards to adverse events associated with clomipramine. For instance, 34% of the clomipramine group dropped out due to side effects of fatigue or lethargy, tremors, tachycardia, insomnia, diaphoresis, nausea or vomiting, or decreased appetite. Whereas, only 3% of the placebo group dropped out due to side effects, in this case, nosebleeds. To summarise, this single trial provides no evidence for significant beneficial effects of clomipramine on autistic behaviours and the attrition rate provides grounds for safety concerns.

Table 100: Summary evidence profile for clomipramine versus placebo in adolescents with autism

Outcome	**Autistic behaviours**	**Global side effects**
Study ID	REMINGTON2001	REMINGTON2001
Effect size	MD = -1.60 (-7.07, 3.87)	MD = 1.20 [-0.45, 2.85]
Quality of evidence (GRADE)	Very low[1,2,3]	Very low[1,2,3]
Number of studies/participants	(K=1; N=32)	(K=1; N=32)
Forest plot	1.2.7, Appendix 15	1.2.7, Appendix 15

[1]Downgraded for risk of attrition bias due to high drop out in the clomipramine group
[2]Downgraded for indirectness as the sample includes children and adolescents with autism and mean age is 16 years
[3]Downgraded for imprecision as the sample size is small

Fluvoxamine for autistic behaviours

The remaining included RCT for antidepressants in adults and adolescents with autism compared fluvoxamine with placebo (see Table 101). MCDOUGLE1996 found evidence for statistically significant treatment effects on the core autistic symptom of repetitive behavior (test for overall effect: Z=2.81, p=0.005), autistic behaviours (test for overall effect: Z=2.15, p=0.03), reduction in aggression and maladaptive behaviour (test for overall effect: Z=2.40, p=0.02, and Z=3.83, p=0.0001, respectively) and symptom severity/improvement (test for overall effect: Z=2.01, p=0.04 for dichotomous measure, and Z=4.37, p<0.0001 for continuous measure). So to summarise, this study found evidence for significant treatment effects with participants receiving fluvoxamine showing superior scores to those receiving placebo. Moreover, the authors report that fluvoxamine was well tolerated and all participants completed the trial. However, the quality of this study was downgraded due to the small sample size and there may be reliability and validity issues with the measure of the core autistic symptom of repetitive behavior as this is measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and although the Y-BOCS scale is valid and reliable for assessing the severity of obsessive-compulsive symptoms in individuals with OCD, the reliability and validity for assessing repetitive thoughts in autism is unknown.

Open-label fluoxetine for behaviour management

Of the two open-label before-and-after observational studies with no control group, one examined the effects of fluoxetine on behaviour management in adolescents with autism (COOK1992). It was not possible to extract efficacy data from this study. However, the authors report statistically significant change from baseline scores for Clinical Global Impression (CGI) ratings of overall clinical severity ($t=4.03$, $p<0.002$) and for CGI ratings of severity of perseverative or compulsive behavior ($t=3.13$, $p<0.005$). However, the authors also report evidence for adverse events associated with fluoxetine with 26% of participants showing side effects that significantly interfered with function or outweighed therapeutic effects. Side effects included hyperactivity, insomnia, elated affect, decreased appetite, behavioural problems, and maculopapular rash. Thus, these results provide limited evidence of possible beneficial treatment effects of fluoxetine for behavior management in adolescents with autism. However, there is some evidence for adverse events. In addition, the efficacy and safety evidence is of very low quality having been downgraded on the basis of very serious risk of bias (due to no control and lack of extractable efficacy data), indirectness (due to coexisting psychiatric diagnoses and age of the sample), and imprecision (as a result of the small sample size).

Table 101: Summary evidence profile for fluvoxamine versus placebo in adults with autism

Outcome	**Core autistic symptom (repetitive behaviour)**	**Autistic behaviours**	**Challenging behaviour (aggression; change-from-baseline)**	**Maladaptive behaviour (change-from-baseline)**	**Symptom severity/ improvement (dichotomous)**	**Symptom severity/ improvement (continuous)**
Study ID	MCDOUGLE1996	MCDOUGLE1996	MCDOUGLE1996	MCDOUGLE1996	MCDOUGLE1996	MCDOUGLE1996
Effect size	MD = -8.20 (-13.92, -2.48)	SMD = -0.82 (-1.56, -0.07)	SMD = -0.92 (-1.68, -0.17)	SMD = -1.61 (-2.43, -0.79)	RR = 17.00 (1.07, 270.41)	SMD = -1.94 (-2.80, -1.07)
Quality of evidence (GRADE)	Low[1,2]	Moderate[1]	Moderate[1]	Moderate[1]	Moderate[1]	Moderate[1]
Number of studies/participants	(K=1; N=30)	(K=1; N=30)	(K=1; N=30)	(K=1; N=30)	(K=1; N=30)	(K=1; N=30)
Forest plot	1.2.7, Appendix 15	1.2.7, Appendix 15	1.2.7, Appendix 15	1.2.7, Appendix 15	1.2.7, Appendix 15	1.2.7, Appendix 15

[1]Downgraded for imprecision as the sample size is small

[2]Downgraded for imprecision as Y-BOCS scale valid and reliable for assessing severity of obsessive-compulsive symptoms in individuals with OCD but reliability and validity for assessing repetitive thoughts in autism is unknown

Open-label sertraline for autistic behaviours

Finally, the remaining open-label before-and-after observational study with no control group examined the change-from-baseline effects of sertraline on autistic behaviours in adults with autism (MCDOUGLE1998B). It was not possible to extract efficacy data for this study. However, the authors report statistically significant main effects of time in their one-way ANOVA analysis for the core autistic symptom of repetitive behaviour as measured by the Yale-Brown Obsessive Compulsive Scale (F=4.78, p=0.000), autistic behaviours as measured by the Ritvo-Freeman Real-Life Rating Scale (F=10.74, p=0.0001), maladaptive behavior as measured by the Vineland Adaptive Behaviour Scale (F=18.52, p=0.0001), and symptom severity/improvement as measured by the Clinical Global Impression scale (F=15.78, p=0.0001) with participants showing superior scores post-sertraline treatment. This study provides evidence suggestive of beneficial treatment effects of sertraline on autistic behaviours in adults with autism. However, the evidence is of a very low quality due to the lack of a control group and the fact that efficacy data cannot be extracted and the very small sample size. In addition, there are concerns with the Y-BOCS scale as a measure for repetitive thoughts in autism.

8.11.4 Clinical evidence summary for antidepressants

The two placebo-controlled trials examining the use of antidepressants for autistic behaviours in adolescents and adults with autism provide inconsistent results, with the single trial of clomipramine providing no evidence for efficacy and the attrition rate raising safety concerns and the single trial of fluvoxamine providing evidence for tolerability and significant beneficial treatment effects. Thus, there is some evidence to suggest that fluvoxamine may be effective for treating the core autistic symptom of repetitive behaviour and autistic behaviours and for reducing challenging and maladaptive behaviour. However, this evidence is only of a low to moderate quality due to concerns with the reliability and validity of the Y-BOCS as a measure of repetitive behaviour in autism and the small sample size.

8.11.5 Health economics evidence for antidepressants

No studies assessing the cost effectiveness of antidepressants 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.

8.11.6 From evidence to recommendations

There is evidence from one trial, of moderate quality, for the efficacy of fluvoxamine in treating autistic behaviours in adults with autism. This study also found fluvoxamine to be well tolerated with all participants completing the trial. However, the GDG concluded that further research examining the efficacy and safety of fluvoxamine and other potent and selective serotonin uptake inhibitors was necessary in order to provide evidence for clinically important treatment effects. At present the GDG concluded that there was not sufficient evidence to recommend

antidepressants targeted at core symptoms of autism in adults with autism. There was also no evidence for autism-specific modifications to antidepressant treatment of coexisting depression and consequently the GDG concluded that treatment of coexisting depression should be in accordance with existing NICE guidance with some account taken of the increased sensitivity to drugs in some people with autism.

8.11.7 Recommendations

8.11.7.1 Do not use antidepressant medication for the routine treatment of core symptoms of autism in adults.

8.11.7.2 For adults with autism and coexisting depression, the use of antidepressant medication should be informed by 'Depression' (NICE clinical guideline 90) and 'Depression in adults with a chronic physical health problem' (NICE clinical guideline 91).

8.12RESTRICTIVE DIETS, VITAMINS, MINERALS AND SUPPLEMENTS FOR AUTISTIC BEHAVIOURS

8.12.1 Introduction

There has been increasing interest in dietary interventions for individuals with autism, which has been motivated by findings of increased incidence of gastrointestinal problems in children with autism (Horvath & Perman, 2002; White, 2003). For instance, a gluten- and casein-free diet has been proposed as a therapeutic intervention for autism. This restrictive diet, as the name suggests, eliminates the dietary intake of gluten (found most often in wheat, barley, and rye) and casein (found most often in milk). The gluten- and casein-free diet is based on the hypothesis that the intestinal barrier is abnormally permeable in individuals with autism and as a result the digestion products of gluten or casein are able to enter the blood through a 'leaky' small intestinal mucosa and induce antigenic responses which directly affect the central nervous system (White, 2003). There is some evidence for increased intestinal permeability in children with autism (D'Eufemia *et al*., 1996). It has been proposed that peptides from gluten and casein may have an aetiological role in the pathogenesis of autism (Reichelt *et al*., 1981), and that the physiology and psychology of autism may be explained by excessive opioid activity linked to these peptides (Israngkun *et al*., 1986). The 'opioid excess' theory of autism postulates that autistic behaviours mimic the influence of opioids on human brain function (White, 2003). Anecdotal reports and limited single-blind studies have claimed to demonstrate improvements in social, communication, and cognitive skills in individuals with autism using gluten-and-casein-free diets (White, 2003). However, a Cochrane review of gluten- and/or casein-free diets for individuals with autism found that the efficacy evidence for these diets is poor and larger scale good quality RCTs are needed (Millward *et al*., 2008).

An alternative restrictive diet which has been proposed as a treatment for autism is the ketogenic diet. The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that was originally introduced as a therapeutic intervention for epileptic seizures (Wilder, 1921). The low carbohydrate contained in the diet mimics a state of starvation and leads the liver to convert fats into fatty acids and ketone bodies. The ketone bodies pass into the brain and replace the glucose (which would normally be extracted from carbohydrates) as an energy source. An elevated level of ketone bodies in the blood, a state known as ketosis, leads to a reduction in the frequency of epileptic seizures (see Freeman *et al*., 2007). However, this diet lost popularity as a standard treatment for epilepsy with the advent of modern anticonvulsant drugs. The diet has, however, been applied to epilepsy in slightly more recent years, and it has been suggested that it may be beneficial for behaviour and hyperactivity when it was applied to control seizures in Rett's syndrome (Haas *et al*., 1986). More recently the ketogenic diet has been proposed as a potential therapeutic intervention for autism based on the hypothesis that individuals with autism may have deficient glucose oxidation which a ketogenic diet would address by allowing ketone bodies to be used as an alternative energy source in the brain

(Evangeliou *et al*., 2003). Evidence has been found for deficient glucose oxidation in autism (Siegel *et al*., 1995). However, the question of how this diet works and how it might specifically impact on autistic behaviours remains to be answered.

In addition to restrictive diets, dietary supplements including vitamins and minerals, such as magnesium-vitamin B6, have been proposed for autism and are based on the hypothesis that individuals with autism have nutritional deficiencies and that these deficiencies may be the cause of some of the symptoms of autism.
Dietary supplements as an adjunct or alternative to restrictive diets have also been put forward as a treatment for autism. For instance, digestive enzyme supplementation has been suggested as an alternative or supplement to the gluten-and-casein-free diet. This digestive enzyme supplementation uses peptidase enzymes to break down exorphins into smaller peptides which do not have opioid activity, and there is pilot data from a non-controlled study suggesting improvements in autistic symptoms post dietary supplementation with peptidase enzymes (Brudnak *et al*., 2002).

Other supplements have targeted brain regions of dysfunction in autism. For instance, supplementation with the amino acid L-carnosine which has been described as accumulating in the enterorhinal subfrontal cortex and is believed to act on the frontal lobe system. The theory that frontal lobe abnormalities may play a role in autism is not a new idea (Damasio & Maurer, 1978; see Mundy, 2003) and is based on findings for the role of the frontal regions in higher-order cognitive, language, social and emotional functions (Stuss & Knight, 2002) which are known to be deficient in autism (Baron-Cohen, 1991; Kanner, 1943; Ozonoff *et al*., 1991). However, the mechanism of action of carnosine is not well understood. For instance, an alternative mode of action is related to the chelation properties of the dipeptide. Zinc and copper are endogenous transition metals that can be synaptically released during neuronal activity. These transition metals are required for normal functioning in the nervous system. However, they can also be neurotoxic and carnosine may act as an endogenous neuroprotective agent by modulating the neurotoxic effects of zinc and copper (Horning *et al*., 2000). These hypotheses are speculative and there has been very little research into the use of L-carnosine as an intervention in autism.

Finally, dietary supplements have also been proposed to target coexisting conditions in individuals with autism. For instance, iron supplementation targeted at sleep problems. There is some evidence for low serum ferritin concentration levels in children with autism (Dosman *et al*., 2006; Latif *et al*., 2002) which suggests iron deficiency as ferritin is an intracellular protein that stores iron and releases it in a controlled fashion and thus the amount of ferritin stored reflects the amount of iron stored. Research has suggested a relationship between low ferritin and restless legs syndrome (Connor *et al*., 2003; Earley, 2003; Earley *et al*., 2000), the symptoms of which are relieved by activity and worsen at night resulting in delayed sleep onset (Walters, 1995). The sleep problems experienced by children with autism, such as longer sleep latency, muscle twitches, and increased muscle activity during rapid eye movement sleep (Elia *et al*., 2000; Patzold *et al*., 1998; Thirumalai *et al*., 2002),

along with the finding of low ferritin levels, may suggest an association between sleep disturbance in autism and restless legs syndrome and thus iron supplementation may be hypothesized to have beneficial effects for sleep in individuals with autism.

To summarise the previous literature, there is very little evidence with regards to safety and efficacy for restrictive diets, vitamins, minerals or supplements for the treatment of autism. Moreover, it is important to bear in mind that, unlike drugs, dietary supplements do not go through rigorous safety and efficacy testing by bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA), and some dietary supplements can be associated with adverse side effects and/or interact and perhaps interfere with the action of other supplements or prescribed drugs.

8.12.2 Studies considered

There were no RCTs, quasi-experimental, observational, or case series studies providing relevant clinical evidence and meeting eligibility criteria for diets, vitamins, minerals or supplements in adults with autism. Due to the lack of primary data, and in line with the rules for extrapolation a decision was made to extrapolate from children with autism. Three RCTs (N=94) which met the extrapolation eligibility criteria were found for children with autism. Five observational studies (N=195), including one case-control study were also found. All of these studies were published in peer-reviewed journals between 1988 in 2010. In addition, 15 studies were excluded from the analysis, predominantly due to small sample sizes of less than ten participants per arm, or because data which could be entered into meta-analysis or included in a narrative synthesis could not be extracted. Further information about both included and excluded studies can be found in Appendix 14.

Of the three RCTs (see Table 102), one compared a gluten-and-casein-free diet with a treatment as usual control group (Knivsberg *et al*., 2003 [KNIVSBERG2003]), one compared a digestive enzyme supplementation with placebo (Munasinghe *et al*., 2010 [MUNASINGHE2010]); and one compared L-Carnosine with placebo (Chez *et al*., 2002 [CHEZ2002]).

Of the five observational studies (see Table 103), the case-control study compared micronutrients with standard medication (Mehl-Madrona *et al*., 2010 [MEHLMADRONA2010]) and of the four before-and-after observational studies, two examined the effects of magnesium-vitamin B6 supplement (Martineau *et al*., 1988 [MARTINEAU1988]; Mousain-Bosc *et al*., 2006 [MOUSAINBOSC2006]), one examined the effect of iron supplementation (Dosman *et al*., 2007 [DOSMAN2007]), and one examined the effects of a ketogenic diet (Evangeliou *et al*., 2003 [EVANGELIOU2003]).

Table 102: Summary study characteristics of included placebo-controlled or treatment-as-usual-controlled trials of diet, vitamins, or supplements in children with autism

	Gluten-and-casein free diet	Digestive enzyme supplementation	L-Carnosine
No. trials (Total participants)	1 (20)	1 (43)	1 (31)
Study IDs	KNIVSBERG2003	MUNASINGHE2010	CHEZ2002
N/% female	Not reported	7/16	10/32
Mean age	7	6	7
IQ	Range not reported (means 81 & 85)	Not reported	Not reported
Axis I/II disorders	100% autism	100% autism (88% Autistic disorder; 12% PDD-NOS)	100% autism
Dose	Not reported	1/2-9 capsules per day according to manufacturer's recommended dose	400mg twice daily
Comparator	Treatment-as-usual control	Placebo	Placebo
Length of treatment	1 year	3 months	8 weeks
Length of follow-up	1 year	6 months	8 weeks

Table 103: Summary study characteristics of included observational trials of diet, vitamins, or supplements in children with autism

	Micronutrients	Magnesium-vitamin B6	Iron supplement	Ketogenic diet
No. trials (Total participants)	1 (88)	2 (44)	1 (33)	1 (30)
Study IDs	MEHLMADRONA2010	(1) MARTINEAU1988* (2)MOUSAINBOSC2006*	DOSMAN2007*	EVANGELIOU2003*
N/% female	20/23	(1) 6/55 (2) 12/36	6/18	14/47
Mean age	8-9	(1) 6 (2) 4	7	Median=7
IQ	Range not reported (means 89 & 91)	(1) 30-80 (mean 50) (2) Not reported	Not reported	Not reported
Axis I/II disorders	100% autism	(1) 100% autism (2) 100% autism	100% autism	100% autism
Dose	Not reported	(1) 30mg/kg per day pyridoxine hydrochloride and 10mg/kg per day magnesium lactate (2) 6mg/kg/day Mag; 0.6mg/kg/day vit. B6	oral preparation 6mg elemental iron/kg/day N=23; sprinkles 2 sachets total of 60mg/day N=10	John Radcliffe diet, which distributes daily energy intake as follows: 30% of energy as medium-chain triglyceride oil, 30% as fresh cream, 11% as saturated fat, 19% as carbohydrates, and 10% as protein
Comparator	Standard medication management	(1) No comparator (2) No comparator	No comparator	No comparator
Length of treatment	3-98 months (means: experimental group mean: 24 months; control group mean: 18 months)	(1) 8 weeks (2) Mean 8 months	8 weeks	6 months (with continuous administration for 4 weeks at a time, interrupted by 2-week intervals that were diet free)
Length of follow-up	3-98 months (means: experimental group mean: 24 months; control group mean: 18 months)	(1) 14 weeks (2) 24 months	8 weeks	6 months

*Efficacy data not extractable

8.12.3 Clinical evidence for restrictive diets, vitamins, minerals and supplements

Restrictive diets for autistic behaviours

There were no included RCT, quasi-experimental, or observational studies comparing restrictive diets with treatment as usual, or examining restrictive diets with no control group, in adults with autism. Based on GDG expert judgement, data were included from a population of children with autism. One RCT study compared a gluten- and casein-free diet to treatment as usual (see Table 104); and one observational before-and-after study examined the effects of a ketogenic diet on autistic behaviours (EVANGELIOU2003) and this will be narratively described below.

KNIVSBERG2003 found evidence for a significant treatment effect of a gluten- and casein-free diet compared to treatment-as-usual (test for overall effect: Z=3.19, p=0.001), with less autistic behaviours (as assessed by the social isolation and bizarre behaviour subscale of the Diagnose of Psykotisk Adferd hos Børn [Diagnosis of Psychotic Behaviour in Children]) observed in children following a gluten- and casein-free diet relative to the control group. However, there was a high risk of performance bias in this study as it is unclear if the control group received the same care apart from the intervention, and participants receiving care and individuals administering care were not blind to group allocation.

EVANGELIOU2003 examined the effects of a ketogenic diet on autistic behaviours in an observational before-and-after study. However, there was no control group and efficacy data could not be extracted for this study. The authors report evidence suggestive of an overall improvement in autistic behaviour as measured by the Childhood Autism Rating Scale post-ketogenic diet intervention (t=5.347, p<0.001).

Thus, in summary these studies provide data suggestive of significant positive treatment effects of restrictive diets on autistic behaviours. However, this evidence is of very low quality and the addition of attention-placebo control groups would be important in order to reduce the risk of bias in these studies.

Table 104: Summary evidence profile for gluten-free and casein-free diet versus control in children with autism

Outcome	**Autistic behaviours**
Study ID	KNIVSBERG2003
Effect size	MD = -5.60 (-9.04, -2.16)
Quality of evidence (GRADE)	Very low[1,2,3]
Number of studies/participants	(K=1; N=20)
Forest plot	1.2.8, Appendix 15

[1]Downgraded for risk of performance bias as unclear if intervention groups received same care apart from treatment, and non-blind

[2]Downgraded for indirectness as extrapolating from children with autism
[3]Downgraded for imprecision as the sample size is small

Vitamins, minerals and supplements for autistic behaviours

There were no included RCT, quasi-experimental, or observational studies comparing vitamins, minerals or supplements with treatment as usual or placebo, or examining dietary supplements with no control group, in adults with autism. Based on the rules for extrapolation, data were included from a population of children with autism. A range of supplements have been examined in children with autism. One RCT examined the effects of a digestive enzyme supplementation compared with placebo (see Table 105). One placebo-controlled study compared an amino acid (L-Carnosine) supplementation with placebo (see Table 106**).** Of the observational studies which will be narratively reviewed below, one open-label before-and-after study with no control group examined the effects of iron supplementation (DOSMAN2007); two open-label before-and-after studies examined the effects of a magnesium-vitamin B6 supplement (MARTINEAU1988; MOUSAINBOSC2006); and one observational case-control study compared a vitamin and mineral supplementation (micronutrient) with standard medication management in children with autism (MEHLMADRONA2010).

MUNASINGHE2010 compared a digestive enzyme supplement (Peptizyde™) with placebo in children with autism. Peptizyde™ is a combination of three plant-derived proteolytic enzymes (Peptidase, Protease 4.5 and Papain) and is designed as a supplement or alternative to the gluten- and casein-free diet. This study failed to find evidence for significant treatment effects of Peptizyde™ on the core autistic symptom of communication as assessed by the vocabulary scale of a parent-completed Language Development Survey (test for overall effect: Z=0.16, p=0.88), challenging behaviour as measured by parent-rated Global Behaviour Rating Scale (test for overall effect: Z=0.78, p=0.44), or for parent-rated gastrointestinal symptoms (test for overall effect: Z=0.84, p=0.40).

CHEZ2002 compared L-carnosine supplementation with placebo. This study failed to find evidence for a statistically significant treatment effect on autistic behaviours as measured by the Childhood Autism Rating Scale (test for overall effect: Z=1.56, p=0.12) or on symptom severity/improvement of autism as assessed by the Clinical Global Impressions Scale (test for overall effect: Z=1.34, p=0.18). Thus, this study found no evidence for significant differences between children with autism who received L-carnosine supplementation and those who received placebo. In addition, this study is downgraded for risk of bias due to baseline group differences in autistic behaviours as measured by the Gilliam Autism Rating Scale (GARS).

Table 105: Summary evidence profile for digestive enzyme supplementation versus placebo in children with autism

Outcome	**Autistic core symptom (communication)**	**Challenging behaviour**	**Gastrointestinal symptoms**

Study ID	MUNASINGHE2010	MUNASINGHE2010	MUNASINGHE2010
Effect size	MD = 1.36 (-15.74, 18.46)	MD = 0.18 (-0.27, 0.63)	MD = 0.14 (-0.19, 0.47)
Quality of evidence (GRADE)	Low[1,2]	Low[1,2]	Low[1,2]
Number of studies/participants	(K=1; N=43)	(K=1; N=43)	(K=1; N=43)
Forest plot	1.2.8, Appendix 15	1.2.8, Appendix 15	1.2.8, Appendix 15

[1]Downgraded for indirectness as extrapolating from children with autism
[2]Downgraded for imprecision as the sample size is small

Table 106: Summary evidence profile for L-carnosine versus placebo in children with autism

Outcome	**Autistic behaviours**	**Symptom severity/ improvement**
Study ID	CHEZ2002	CHEZ2002
Effect size	MD = -4.01 (-9.03, 1.01)	MD = 2.14 (-0.99, 5.27)
Quality of evidence (GRADE)	Very low[1,2,3]	Very low[1,2,3]
Number of studies/participants	(K=1; N=31)	(K=1; N=31)
Forest plot	1.2.8, Appendix 15	1.2.8, Appendix 15

[1]Downgraded for risk of bias due to baseline group differences in autistic behaviours as measured by the Gilliam Autism Rating Scale (GARS)
[2]Downgraded for indirectness as extrapolating from children with autism
[3]Downgraded for imprecision as the sample size is small

One open-label observational study with no control group examined the effects of iron supplementation on coexisting sleep problems in children with autism (DOSMAN2007). However, efficacy data could not be extracted for this study. The authors reported evidence suggestive of a statistically significant treatment effect of iron supplementation on coexisting sleep problems with the restless sleep score showing improvement between pre- and post-iron supplementation (p=0.04). However, no significant change-from-baseline treatment effect was found for challenging behaviour (as measured by Clinical Global Impression ratings of irritability; p=0.11).

Two observational open-label studies with no comparators (MARTINEAU1988; MOUSAINBOSC2006) examined the effects of a magnesium-vitamin B6 supplement on autistic behaviours and, although efficacy data could not be extracted, both studies reported results suggestive of statistically significant change-from-baseline scores after magnesium-vitamin B6 supplementation. MARTINEAU1988 reported a significant change-from-baseline for symptom severity (t=3.28, p<0.01). While,

MOUSAINBOSC2006 found improved post-treatment scores on core autistic symptoms of communication, social interaction, and stereotyped behaviour ($p<0.0001$) as assessed by DSM-IV clinical evaluation. However, although this data is suggestive of significant positive treatment effects of magnesium-vitamin B6 supplements, this evidence is of very low quality having been downgraded for risk of bias (due to the lack of a control group and because efficacy data cannot be extracted), for indirectness (extrapolating from children with autism), and for imprecision (due to small sample sizes). In addition MARTINEAU1988 was also downgraded for risk of bias as the sample was selected for their previous sensitivity to the treatment and the age of the study calls the generalisability of findings into question.

Finally, an observational case-control study compared micronutrients with standard medication management in children with autism (see Table 107). The experimental group were given a broad-based micronutrient supplement, EMPowerplus, which consisted of all 14 of the known vitamins, 16 dietary minerals, 3 amino acids, and 3 antioxidants. MEHLMADRONA2010 found no evidence for a statistically significant treatment effect on autistic behaviours as measured by the Childhood Autism Rating Scale (test for overall effect: $Z=0.16$, $p=0.87$). However, there was evidence for statistically significant treatment effects on challenging behaviour as measured by the irritability subscale of the Aberrant Behaviour Checklist (test for overall effect: $Z=5.77$, $p<0.00001$) and for symptom severity/improvement as measured by the Clinical Global Impressions Scale (test for overall effect: $Z=4.11$, $p<0.0001$). Thus, the evidence from this study suggests that the children with autism receiving micronutrients showed less challenging behaviour, and less severe symptoms than participants receiving standard medication. However, this study was downgraded to very low quality based on the indirectness of the evidence and the high risk of bias as a result of the lack of randomisation and blinding.

Table 107: Summary evidence profile for micronutrients versus standard medication in children with autism

Outcome	**Autistic behaviours**	**Challenging behaviour (irritability)**	**Symptom severity**
Study ID	MEHLMADRONA2010	MEHLMADRONA2010	MEHLMADRONA2010
Effect size	MD = 0.50 (-5.62, 6.62)	MD = -7.40 (-9.91, -4.89)	MD = -1.38 (-2.04, -0.72)
Quality of evidence (GRADE)	Very low[1,2]	Very low[1,2]	Very low[1,2]
Number of studies/participants	(K=1; N=88)	(K=1; N=88)	(K=1; N=88)
Forest plot	1.2.8, Appendix 15	1.2.8, Appendix 15	1.2.8, Appendix 15

[1]Downgraded for risk of bias as this is a non-randomised and non-blinded study
[2]Downgraded for indirectness as extrapolating from children with autism

8.12.4 Clinical evidence summary for restrictive diets, vitamins, minerals and supplements

No studies examining restrictive diets, vitamins, minerals or supplements in adults with autism could be included, and therefore, all the data reviewed is indirect involving extrapolating from studies of children with autism. The single RCT study examining the effects of restrictive diets in children with autism found limited evidence for a positive effect of a gluten- and casein-free diet on autistic behaviours. In addition, an observational before-and-after study examining the effects of a ketogenic diet on autistic behaviours in children with autism reported limited evidence suggestive of beneficial effects for this restrictive diet as well. However, the quality of this evidence was downgraded due to high risk of bias as a consequence of the lack of blinding. This is an issue that has not yet been addressed but could be effectively done so through the inclusion of an attention-placebo control group.

The evidence for vitamins, minerals, and supplements is more mixed. The two RCTs examining the effects of supplements in children with autism, one of which compared an amino acid supplement (L-carnosine) with placebo and one compared a digestive enzyme supplementation with placebo, both failed to find evidence for statistically significant treatment effects on autistic behaviours. The observational studies of vitamins, minerals and supplements, were on the whole more positive. For instance, the only case-controlled observational study compared micronutrients with standard medication for children with autism and found evidence for significant treatment effects on challenging behaviour and symptom severity/improvement although no significant treatment effects were observed for autistic behaviours as assessed by the Childhood Autism Rating Scale. The observational before-and-after studies (with no control group) present results suggestive of improvements in coexisting sleep problems as a result of iron supplementation, and for symptom severity and core autistic symptoms post-magnesium-vitamin B6 supplementation.

To summarise, the evidence for restrictive diets in children with autism is promising. However, the risk of bias and indirectness of the data results in a very low quality evidence base. While, the evidence for vitamins, minerals, and supplements is inconsistent with some suggestion of beneficial effects of micronutrients for challenging behaviour, iron supplementation for coexisting sleep problems, and magnesium-vitamin B6 supplementation for autistic behaviours. However, further randomised placebo-controlled studies are required to corroborate the existing low to very low quality evidence for diets, vitamins, minerals and supplements in individuals with autism.

8.12.5 Health economics evidence for restrictive diets, vitamins, minerals and supplements

No studies assessing the cost effectiveness of restrictive diets, vitamins, minerals or supplements 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.

8.12.6 From evidence to recommendations

The evidence for the use of restrictive diets, vitamins, minerals and supplements in autism is indirect (extrapolated from child data), and of only low to very low quality. Of the four trials that efficacy data could be extracted from, two suggested positive treatment effects, one for a restrictive diet (gluten-free and casein-free diet) and one for a dietary supplement (micronutrients). However, two trials failed to find significant treatment effects of supplements for either the amino acid L-carnosine or for a digestive enzyme supplementation, and the latter of these studies is of a relatively higher quality than the other trials and is the only blinded trial, although it is important to note that this study is still low quality. On the basis of this evidence the GDG concluded that there was insufficient evidence for the safety and efficacy of restrictive diets or vitamins, minerals or supplements and that further randomised and blinded placebo-controlled trials would be required before the use of diets, vitamins, minerals or supplements could be recommended to treat autistic behaviours in adults with autism.

8.12.7 Recommendations

8.12.7.1 Do not use the following for the treatment of core symptoms of autism in adults:

- restrictive diets (such as gluten- and casein-free or ketogenic diets)
- vitamins, minerals and dietary supplements (such as vitamin B6 or iron supplementation).

8.13 CHELATION FOR AUTISTIC BEHAVIOURS

8.13.1 Introduction

Chelation, also known colloquially as detoxification, involves using one or more substances (chelating agents) to remove materials that are toxic, including heavy metals such as mercury, from the body. There are a wide range of chelating agents which are associated with different efficacy and side effects. These include alpha lipoic acid; cysteine, DMSA (dimercaptosuccinic acid); DMPS (sodium dimercaptopropanesulfonate); EDTA (ethylenedinitrilotetraacetic acid); NDF (nanocolloidal detox factors); TTFD (thiamine tetrahydrofurfuryl disulfide); and zeolite. There is currently no clinical evidence that chelation is an effective treatment for individuals with autism (see Research Autism, 2011b) and there are safety concerns associated with this treatment (see Fombonne, 2008).

8.13.2 Studies considered

Three studies examining the effects of chelation agents, meso-2, 3-dimercaptosuccinic acid (DMSA) or thiamine tetrahydrofurfuryl disulfide (TTFD), in the treatment of individuals with autism were found in the initial search (Adams *et al*., 2009a, 2009b; Geier & Geier, 2006; Lonsdale *et al*., 2002). However, all of these studies were excluded at the first sift (on the basis of the abstract) due to a mean sample age of below 15 years old.

8.13.3 Clinical evidence for chelation

As discussed above, there was no clinical evidence for chelation in adults with autism which met the eligibility criteria.

8.13.4 Clinical evidence summary for chelation

There was no clinical evidence for chelation in adults with autism.

8.13.5 Health economics evidence for chelation

No studies assessing the cost effectiveness of chelation 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.

8.13.6 From evidence to recommendations

As detailed above there was no clinical evidence for the use of chelation in adults with autism. However, discussion of the GDG highlighted that chelation was highly controversial, was actively sought out by people with autism or their families or carers and in the view of the GDG posed a potential serious risk to health. On the basis of the lack of evidence and the GDG concerns with regards to safety the decision was taken that chelation should not be recommended for the treatment of autism.

8.13.7 Recommendations

8.13.7.1 Do not use chelation (for example, zinc chelation) for the treatment of core symptoms of autism or for the management of challenging behaviour in adults with autism.

8.14 TESTOSTERONE REGULATION FOR AUTISTIC BEHAVIOURS

8.14.1 Introduction

Testosterone regulation involves using a drug, such as leuprolide, to reduce the amount of testosterone and oestrogen in the body. Geier and Geier (2005) suggested that this drug may be effective for the treatment of autism, with the proposed mode of action being that excess testosterone may increase the toxicity of mercury, and it is mercury which is believed to be the primary cause of autism. However, the link between autism and tetosterone, and between autism and vaccines containing the mercury-based preservative thimerosal which were hypothesized to be the cause of autism, has since been discredited (see Allen, 2007; Parker *et al*., 2004). There is no evidence for the efficacy of testosterone regulation as a treatment for autism (see Research Autism, 2011c). In addition, if used on children or adolescents leuprolide could cause significant and irreversible damage to sexual development and functioning.

8.14.2 Studies considered

One study examining the effects of testosterone regulation, using anti-androgen therapy in the treatment of individuals with autism was found in the initial search (Geier & Geier, 2006). However, his study was excluded at the first sift (on the basis of the abstract) due to a mean sample age of below 15 years old.

8.14.3 Clinical evidence for testosterone regulation

As discussed above, there was no clinical evidence for testosterone regulation in adults with autism that met the eligibility criteria.

8.14.4 Clinical evidence summary for testosterone regulation

There was no clinical evidence for testosterone regulation in adults with autism.

8.14.5 Health economics evidence for testosterone regulation

No studies assessing the cost effectiveness of testosterone regulation 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.

8.14.6 From evidence to recommendations

As detailed above there was no clinical evidence for the use of testosterone regulation in adults with autism. However, discussion of the GDG highlighted that testosterone regulation was highly controversial and may be offered to people with autism or their families or carers. In view of the serious risk to health and the lack of any evidence of benefit the decision was taken that testosterone regulation should not be recommended for the treatment of autism.

8.14.7 Recommendations

8.14.7.1 Do not use testosterone regulation for the treatment of core symptoms of autism in adults or for the management of challenging behaviour in adults with autism.

8.15 HYPERBARIC OXYGEN THERAPY FOR AUTISTIC BEHAVIOURS

8.15.1 Introduction

Hyperbaric oxygen therapy describes the medical use of oxygen at a level higher than atmospheric pressure. During this therapy oxygen is administered to an individual in a pressurized chamber. The goal of the therapy is that oxygen absorption will be increased in bodily tissue. Hyperbaric oxygen therapy has been used at high pressures (over 2.0 atmosphere absolute [ATA]) for the treatment of conditions such as decompression sickness, arterial gas embolism, carbon monoxide poisoning (Leach *et al*., 1998), amyotrophic lateral sclerosis (Steele *et al*., 2004), and complex regional pain syndrome (Kiralp *et al*., 2004). When used to treat standard medical conditions, hyperbaric oxygen therapy is generally safe providing conditions of proper installation, trained administration, and availability of expert advice are met (see Research Autism, 2011d). Hyperbaric oxygen therapy has also been used at lower pressures (1.5ATA or less) to treat fetal alcohol syndrome (Stoller, 2005) and ischemic brain injury (Neubauer *et al*., 1992). Hyperbaric oxygen has been proposed as a treatment for autism on the basis that neuroimaging results have suggested that there may be hypoperfusion to several areas of the autistic brain in particular to temporal regions, and hyperbaric oxygen therapy can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues, thus hyperbaric oxygen therapy may improve symptoms in individuals with autism (Rossignol & Rossignol, 2006).

8.15.2 Studies considered

Six studies examining the effects of hyperbaric oxygen therapy for individuals with autism were found in the initial search (Bent *et al*., 2011; Chungpaibulpatana *et al*., 2008; Granpeesheh, *et al*., 2010; Jepson *et al*., 2011; Rossignol *et al*., 2007, 2009). However, these studies were excluded at the first sift (on the basis of the abstract) due to a mean sample age of below 15 years old.

8.15.3 Clinical evidence for hyperbaric oxygen therapy

As discussed above, there was no clinical evidence for hyperbaric oxygen therapy in adults with autism that met the eligibility criteria.

8.15.4 Clinical evidence summary for hyperbaric oxygen therapy

There was no clinical evidence for hyperbaric oxygen therapy in adults with autism.

8.15.5 Health economics evidence for hyperbaric oxygen therapy

No studies assessing the cost effectiveness of hyperbaric oxygen therapy 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.

8.15.6 From evidence to recommendations

As detailed above there was no clinical evidence for the use of hyperbaric oxygen therapy in adults with autism. However, discussion of the GDG highlighted that there are risks in using this treatment for adults with autism, which may not be justified if the efficacy of the treatment for autistic behaviours has not been established. On the basis of the lack of evidence the GDG decided that hyperbaric oxygen therapy should not be recommended for the treatment of autism.

8.15.7 Recommendations

8.15.7.1 Do not use hyperbaric oxygen therapy for the treatment of core symptoms of autism or for the management of challenging behaviour in adults with autism.

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