PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE

THE NICE GUIDELINE ON RECOGNITION AND MANAGEMENT

NATIONAL COLLABORATING CENTRE FOR MENTAL HEALTH

PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE

RECOGNITION AND MANAGEMENT

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October 2016: this guideline has been partially updated: recommendation 1.3.19 and Table 1 were updated to remove reference to hip circumference percentile charts.

Minor changes since publication

December 2021: Following a surveillance review we have updated recommendations on monitoring for antipyschotic medication and the supplementary information table to say that either glycosylated haemoglobin (HbA1c) or fasting blood glucose may be used to test for diabetes. We have also added a link to NICE's guideline on babies, children and young people's experience of healthcare.

These changes can be seen in the short version of the guideline at www.nice.org.uk/guidance/CG155

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1 PREFACE

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

Although the evidence base is rapidly expanding, there are a number of major gaps. The guideline makes a number of research recommendations specifically to address gaps in the evidence base. In the meantime, it is hoped that the guideline will assist clinicians, and children and young people with psychosis and schizophrenia and their parents and carers, by identifying the merits of particular treatment approaches where the evidence from research and clinical experience exists.

1.1 NATIONAL GUIDELINE

1.1.1 What are clinical guidelines?

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

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

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

1.1.2 Uses and 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 children and young people with psychosis and schizophrenia. However, there will always be some children and young people and situations where clinical guideline recommendations are not readily applicable. This guideline does not, therefore, override the individual responsibility of healthcare professionals to make appropriate decisions in the circumstances of the individual, in consultation with the child or young person with psychosis or schizophrenia or their parents or carers.

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

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

1.1.3 Why develop national guidelines?

The National Institute for Health and Care Excellence (NICE) 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 From national clinical guidelines to local protocols

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

1.1.5 Auditing the implementation of clinical guidelines

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

1.2 THE NATIONAL *PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE* GUIDELINE

1.2.1 Who has developed this guideline?

This guideline has been commissioned by NICE and developed within the National Collaborating Centre for Mental Health (NCCMH). The NCCMH is a collaboration

of the professional organisations involved in the field of mental health, national service user and carer organisations, a number of academic institutions and NICE. The NCCMH is funded by NICE and is led by a partnership between the Royal College of Psychiatrists and the British Psychological Society's Centre for Outcomes Research and Effectiveness, based at University College London.

The GDG was convened by the NCCMH and supported by funding from NICE. The GDG included people with psychosis and schizophrenia and their carers, and professionals from psychiatry, clinical psychology, general practice and nursing.

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 user and carer representatives received training and support from the NICE Public Involvement Programme. The NICE Guidelines Technical Adviser provided advice and assistance regarding aspects of the guideline development process.

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of 11 times throughout the process of guideline development. It met as a whole, but key topics were led by a national expert in the relevant topic. The GDG was supported by the NCCMH technical team, with additional expert advice from special advisers where needed. The group oversaw the production and synthesis of research evidence before presentation. All statements and recommendations in this guideline have been generated and agreed by the whole GDG.

1.2.2 For whom is this guideline intended?

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

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 recognition and management of psychosis and schizophrenia in children and young people. It aims to:

- improve access and engagement with treatment and services for children and young people with psychosis and schizophrenia

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

1.2.4 The structure of this guideline

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide an introduction to guidelines, to the topic of psychosis and schizophrenia and to the methods used to develop them. Chapters 4 to 8 provide the evidence that underpins the recommendations about the treatment and management of psychosis and schizophrenia in children and young people.

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 evidence 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 13. Where meta-analyses were conducted, the data are presented using forest plots in Appendix 14 (see Table 1 for details).

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

Table 1: Appendices on the CD-ROM

Search strategies for the identification of clinical studies	Appendix 8
Search strategies for the identification of health economic evidence	Appendix 10
Clinical evidence study characteristics tables	Appendix 13
Clinical evidence forest plots	Appendix 14
Economic evidence: completed methodology checklists	Appendix 15
Economic evidence: evidence tables of published studies	Appendix 16
Clinical and economic evidence profiles	Appendix 17

2 PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE

This guideline is concerned with the recognition and management of psychosis and schizophrenia in children and young people up to the age of 18. The term 'psychosis' is used in this guideline to refer to the group of psychotic disorders that includes schizophrenia, schizoaffective disorder, schizophreniform disorder and delusional disorder as identified by the *International Classification of Diseases* – 10th revision (ICD-10; World Health Organization, 1992). This guideline also addresses the population of children and young people considered clinically to be at high risk or prodromal for psychosis and schizophrenia. It does not address the identification and management of other psychotic disorders, such as bipolar disorder and unipolar psychotic depression, or schizophrenia in adults, because they are covered by other NICE guidelines.

2.1 THE DISORDER

2.1.1 Symptoms, presentation and patterns

Psychosis and the specific diagnosis of schizophrenia in children and young people represent a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms that alter the child or young person's perception, thoughts, mood and behaviour. The symptoms of psychosis are usually divided into 'positive symptoms', including hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms' (such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect). Children and young people who develop psychosis will have their own unique combination of symptoms and experiences, the precise pattern of which will be influenced by their circumstances and stage of development.

Typically, in child and adolescent-onset psychosis and schizophrenia there is a prodromal period characterised by some deterioration in personal functioning, which may follow an acute period of stress, a distressing experience or physical illness (Garralda, 1984a). The prodromal period includes negative symptoms such as concentration and memory problems, unusual or uncharacteristic behaviour and ideas, unusual experiences, bizarre perceptual experiences, disturbed communication and affect, social withdrawal, apathy and reduced interest in daily activities. This period can last up to 1 year (Werry *et al*., 1994) and negatively affect school performance. The insidious pattern of onset can delay the diagnosis of psychosis and schizophrenia in children.

The prodromal period is typically followed by an acute episode marked by the positive symptoms of hallucinations and delusions, and behavioural disturbance.

These symptoms are usually accompanied by agitation and distress (NCCMH, 2010). A wide range of anomalous perceptual experiences may occur at the onset of an episode of psychosis leading to a sense of fear or puzzlement, which may constitute a delusional mood and herald a full psychotic episode. These anomalous experiences may include the sense that familiar places and people and their reactions have changed in some subtle way. These experiences may result from a breakdown between perception and memory (for familiar places and people) and associated affective responses (salience given to these perceptions). These experiences may be frightening, confusing and distressing for the child or young person. For example, a child or young person at the onset of illness may study their reflection in the mirror for hours because it looks strangely unfamiliar, misattribute threatening intent to an innocuous comment or experience family members or friends as being unfamiliar, leading to a secondary delusional belief that they have been replaced by doubles or aliens. In summary, some clinical phenomena in psychosis and schizophrenia can be understood in terms of a loss of normal contextualisation and coordination of cognitive and emotional processing. Following resolution of the acute episode, commonly after pharmacological and psychological interventions, the positive symptoms diminish and disappear for many children and young people, although a number of negative symptoms may remain. This phase, which can last for years, may be interrupted by recurrent acute episodes that may need additional intervention. Persisting symptoms appear to be especially common when the condition starts in pre-adolescent children (Eggers & Bunk, 1997).

2.1.2 At risk mental states

In recent years there has been a growing emphasis on early detection and intervention in order to delay or possibly prevent the onset of psychosis and schizophrenia. This focus on very early intervention and prevention has stimulated an interest in identifying, and potentially intervening in, the so-called 'at risk mental states' (or prodrome) which may precede the onset of the disorder (see Section 2.8.4).

At risk or 'ultra-high risk' mental states, are characterised by help-seeking behaviour and the presence of attenuated (subclinical) positive psychotic symptoms, brief limited intermittent psychotic symptoms or a combination of genetic risk indicators, such as the presence of schizotypal disorder, with recent functional deterioration. Although the risk for schizophrenia emerging over a 12-month period appears to be increased in these children and young people (between one in five to one in ten may be expected to develop a schizophrenic disorder, Ruhrmann *et al.,* 2010), it remains the case that prediction of schizophrenia based on at risk or ultra-high risk mental states is modest given that the majority of those identified do not become psychotic. Furthermore, most children and young people identified with at risk mental states have a mixture of other mental health problems (for example, depression, anxiety, substance-use disorders or emerging personality disorder) requiring a range of targeted interventions. In addition, the potential use of a clinical label that conveys a future risk of psychosis or schizophrenia raises ethical issues and may itself be perceived

as stigmatising. It may be that at risk or ultra-high risk mental states are best viewed as a dimension rather than a diagnostic category, including at one extreme children and young people with non-specific symptoms and at the other those on the cusp of psychosis. Finally, given the low rate of transition to psychosis, any interventions used must benefit (and not harm) the majority of children and young people (false positives) who do not develop psychosis.

2.1.3 Impairment and disability

Impairments associated with psychosis and schizophrenia include the consequences of living with disabling psychotic symptoms, the adverse effects of drug treatments and poor physical health (see Section 2.1.6) and stigma (see Section 2.6). Impairment can affect a child or young person's psychological, social and educational development and functioning. While about one fifth of children and young people with schizophrenia have a good outcome with only mild impairment, at the other extreme about a third are severely impaired requiring intensive social and psychiatric support (Hollis, 2000). The onset of schizophrenia in childhood and adolescence results in greater impairment than when schizophrenia first presents in adulthood (see Section 2.1.4). This is in part because the nature of the disorder is more severe in children and young people, but also because the onset of schizophrenia during childhood disrupts social and cognitive development. Social functioning, in particular the ability to form friendships and love relationships, appears to be very impaired in early-onset schizophrenia. Impairment affecting families can also be considerable, creating distress and disharmony in social interactions and relationships. For young adults, impairment is also seen in their working lives. Since children and young people with psychosis and schizophrenia have greater cognitive, psychological and social impairments, early recognition and intervention is crucial.

2.1.4 Prognosis, course and recovery

Schizophrenia in children and young people characteristically runs a chronic course, with only a minority making a full symptomatic recovery from the first psychotic episode. The short-term course for schizophrenia is worse than for other psychotic disorders in children and young people, with only 12% in full remission at discharge compared with 50% of children and young people with affective psychoses (Hollis & Rapoport, 2011). The short-term outcome for schizophrenia presenting in early life appears to be worse than that for adults with a first episode of psychosis (Robinson *et al*., 1999a). If full recovery does occur then it is most likely to happen within the first 3 months of onset of psychosis. Early recovery appears important in determining outcome. Young people with schizophrenia who have psychotic symptoms after 6 months have only a 15% chance of their symptoms achieving full remission, while over half of all those who make a full recovery have active psychotic symptoms for less than 3 months (Hollis & Rapoport, 2011).

A recent Israeli whole population study found that people with schizophrenia who were younger than 17 years had a poorer outcome overall, with longer length of initial hospital stay, more readmissions and more hospital days per year than young people aged 18 or older (Rabinowitz *et al.*, 2006). Schizophrenia is also frequently associated with significant impairments in many aspects of life including social, educational, vocational and familial. It is also associated with increased morbidity and mortality through both suicide and natural death.

The predictors of poor outcome in child and adolescent-onset psychoses include premorbid social and cognitive impairments, a prolonged first psychotic episode, extended duration of untreated psychosis (DUP) and the presence of negative symptoms. Premorbid functioning and negative symptoms at onset of psychosis provide better prediction of long-term outcome than categorical diagnosis (Hollis & Rapoport, 2011) using ICD-10 or *Diagnostic and Statistical Manual of Mental Disorders* – 4th edition (American Psychiatric Association, 1994; DSM-IV).

Even though some children and young people never experience a complete recovery from their psychotic illness, they still manage to sustain an acceptable quality of life if given adequate support and help. Recovery is a fundamentally personal process that involves finding a new sense of self and feeling of hope, and it also requires appropriate external, material and psychosocial conditions that can facilitate the process (Kogstad *et al.*, 2011).

2.1.5 Diagnosis

This guideline is concerned with both the broader category of psychosis (including schizoaffective disorder, schizophreniform disorder, delusional disorder and schizophrenia) and with the narrower diagnosis of schizophrenia in children and young people. However, as a full discussion of the issues of the diagnosis of psychosis and schizophrenia is outside the scope of this guideline, specific issues relating to children and young people are described here.

The experience of a psychotic disorder challenges an individual's fundamental assumption that they can rely upon the reality of their thoughts and perceptions. This is often both frightening and emotionally painful for both the person with psychosis and for those close to them. Having this experience classified as a disorder, and acquiring a diagnostic label, may either be helpful in facilitating understanding or may be experienced as yet a further assault upon their identity and integrity. Professionals need to be aware of both the positive and negative impacts of discussing a diagnosis, especially in children and young people. This has led to some professionals and service user/carer groups questioning the usefulness of the diagnosis and instead preferring to emphasise a narrative formulation of the individual's experiences.

The current concept of schizophrenia in children and young people evolved from a different perspective held during much of the 20th century. Until the early 1970s the term 'childhood schizophrenia' was applied to children who would now be diagnosed with autism. Kolvin's landmark studies distinguished early onset (autistic)

children from those with a relatively 'late onset' psychosis that closely resembled schizophrenia (Kolvin, 1971; Kolvin *et al.*, 1971). Importantly, in DSM-III (American Psychiatric Association, 1980) and ICD-9 (World Health Organization, 1975) the separate category of childhood schizophrenia was removed, and the same diagnostic criteria for schizophrenia were applied across the age range. Major additional evidence for the validity of the diagnosis of schizophrenia in childhood and adolescence comes from the Maudsley Child and Adolescent Psychosis Follow-up Study (Hollis, 2000). A DSM-III-R (American Psychiatric Association, 1987) diagnosis of schizophrenia in childhood and adolescence predicted a significantly poorer adult outcome compared with other non-schizophrenic psychoses and a diagnosis of schizophrenia showed a high level of stability—80% had the same diagnosis at adult follow-up (Jarbin *et al.*, 2003).

Both ICD-10 and DSM-IV describe similar symptom clusters necessary for a diagnosis of schizophrenia (see Section 2.1.1). ICD-10 requires that these be present for 1 month while DSM-IV requires a total duration of 6 months. But this difference is less marked when one considers that ICD-10 refers to acute positive symptoms only, while DSM-IV includes any period of non-specific impairment or attenuated (subclinical) symptoms that may precede an acute episode. In both DSM-IV and ICD-10, evidence of deteriorating and impaired functioning in addition to persistent psychotic symptoms is essential for a diagnosis. Isolated psychotic symptoms (typically auditory hallucinations) without functional impairment are surprisingly common in children (definite psychotic symptoms are found in 6% of 11 year olds in the general population) (Horwood *et al.*, 2008) and should not be confused with a diagnosis of psychosis or schizophrenia, which is very rare in prepubertal children.

The majority of children and young people for whom a diagnosis of psychosis or schizophrenia is being considered will be in their first episode of illness. The future natural history and diagnostic stability of an initial psychotic episode shows much variation. However, when an ICD-10 or DSM-IV diagnosis of schizophrenia can be made (particularly when accompanied by insidious onset and early presentation of negative symptoms) the greater is the likelihood of diagnostic stability (Hollis, 2000). There is therefore a tension between not wishing to be precipitately deterministic in diagnosis and prognosis but also wishing to give as accurate a prediction of likely future course as possible.

While the much less specific umbrella term 'psychosis' has therefore found increasing favour by some professionals and by some service user and carer groups, it should only be used in those instances where criteria for more specific ICD-10 and DSM-IV diagnoses of schizophrenia or schizophreniform psychosis are not fulfilled. Indeed recent findings suggest that a formal diagnosis of schizophrenia can be made in a large proportion of children and young people presenting with multiple features of a psychotic illness (Coentre *et al.*, 2011). Stigma towards schizophrenia among clinicians, together with overly pessimistic views of outcome and the likelihood of recovery, may prevent clinicians from openly and honestly sharing a diagnosis with young people and their families.

2.1.6 Physical healthcare

Children and young people with psychosis and schizophrenia can expect poorer physical health than the general population as they get older, with life expectancy reduced by 16 to 25 years (Brown *et al.*, 2010; Parks *et al.*, 2006). While suicide or injury cause a third of these premature deaths, two thirds result from cardiovascular, pulmonary and infectious diseases (Brown *et al.*, 2010). These issues are discussed in the *Schizophrenia* guideline for adults (NCCMH, 2010). However schizophrenia in children and young people tends to be a more disabling and persistent disorder (Hollis, 2003), bringing with it greater vulnerability to physical harm from both the condition and its treatments.

Given that cardiovascular disease is the main cause of reduced life expectancy, the question arises whether there are potentially modifiable precursors operating in children and young people with schizophrenia? The major candidates are smoking, obesity, dyslipidaemias, glucose intolerance and hypertension. These factors are interdependent. For example, the link between childhood obesity, dyslipidaemias, glucose intolerance, hypertension and vascular abnormalities is conclusive (Weiss *et al.*, 2004), explaining why childhood obesity increases coronary heart disease in adulthood (Baker *et al.*, 2007).

Evidence that children and young people with schizophrenia are exposed to these risks comes mainly from antipsychotic treatment studies where such impacts may be even more important given that these drugs are prescribed for lengthy periods over a critical developmental phase. Only one paediatric cohort study has examined this issue in children and young people treated for the first time with antipsychotics (Correll *et al.*, 2009). This revealed high prevalence and rapid onset (within 12 weeks) of weight gain in all antipsychotics investigated (aripiprazole, olanzapine, quetiapine and risperidone). Metabolic disturbances were also observed in olanzapine, quetiapine and risperidone, but not aripiprazole. Changes in weight gain in those taking risperidone were dose related, whereas only adverse metabolic effects were dose related with olanzapine, and no dose relationship was observed with aripiprazole and quetiapine. This landmark study included children and young people aged 4 to 19 years with various mental disorders including schizophrenia and its findings have been reinforced by two systematic reviews (De Hert *et al.*, 2011; Fedorowicz & Fombonne, 2005). A systematic review confined to schizophrenia in children and young people observed that while antipsychotics had similar efficacy, adverse effects varied between drugs (Kumra *et al.*, 2008b). Overall, children and young people appear more vulnerable than adults to side effects of antipsychotic medication (weight gain, extrapyramidal symptoms [EPS], metabolic problems, prolactin elevation and sedation).

Studies of first episode psychosis provide insights into a treatment-naïve young group, mostly in their late teens and 20s, and encompassing the under 18s (for example, Kirkbride *et al.*, 2006). A systematic review of weight gain and cardiometabolic abnormalities (Foley & Morley, 2011) revealed that there was no difference in weight gain, blood pressure (BP) and cardiometabolic indices between people with a first episode and controls before starting antipsychotics. However, within 8 weeks of first exposure, heightened cardiovascular risk was apparent and worsened over the next 12 months.

No significant differences separated first- and second-generation antipsychotics but variance in adverse effects was evident within each class of drugs. For instance, weight gain after 12 months with olanzapine far exceeded ziprasidone among the second-generation 'atypical' antipsychotics. Over a third of those with a first episode experienced metabolic disturbance within 8 months of commencing treatment (Curtis *et al.*, 2011). It should also be noted that occasionally diabetes and dyslipidaemia have been observed in the absence of weight gain, which underlines the clinical importance of being alert to the possibility of serious metabolic disturbance in those taking antipsychotic medication who have not gained weight (McIntyre *et al.*, 2001).

The association between antipsychotics and weight gain is well established and a substantial number of children and young people with emerging psychosis experience aggressive early changes in weight and cardiometabolic risk. Their vulnerability to future physical ill health is further explained by concomitant lifestyle issues, particularly tobacco use.

While smoking rates in the UK general population fell from 39% in 1980 to 25% in 2004, rates for people with schizophrenia continued at about 70%, suggesting they have failed to benefit from the effective prevention of the most potent cause of premature death (Brown *et al.*, 2010). Understanding how smoking develops is vital to reducing harm. Myles and colleagues (2012) found that 59% of people with first-episode schizophrenia used tobacco at presentation, a rate six times higher than that in comparable non-psychiatric populations. Furthermore, in the general population 66% of current and past tobacco users started smoking before the age of 18 (Health and Social Care Information Centre, Lifestyles Statistics, 2010) while very few commence smoking after their early 20s (Amos *et al.*, 2009). Thus tobacco use in children and young people with psychosis and schizophrenia is a substantial problem which continues into adult life.

Poor physical health is not just experienced through illness or premature death. Severe weight gain may lower self-esteem, contribute to discrimination and lead to treatment non-compliance, already problematic in the adolescent population (Hack & Chow, 2001). Other metabolic side effects such as hyperprolactinaemia (causing menstrual disturbances, sexual dysfunction and galactorrhoea) can similarly distress young people (Fedorowicz & Fombonne, 2005). Although antipsychotic selection may mitigate such effects, the distress evoked requires sensitive clinical practice.

In summary, precursors of future cardiovascular disease threaten substantial numbers of children and young people with emerging psychosis and schizophrenia. Previously unexposed to antipsychotics, this group are particularly vulnerable to weight gain and cardiometabolic disturbances (Correll *et al.*, 2009; Foley & Morley, 2011; Álvarez -Jiménez *et al.*, 2008). Although antipsychotics vary in their propensity to induce weight gain and cardiometabolic disturbance, these effects may be caused by any antipsychotic, whether typical or atypical, occur frequently and appear within weeks of starting treatment (Correll *et al.*, 2009; Foley & Morley, 2011). Notwithstanding the adverse metabolic effects of antipsychotics, children and young people with psychosis and schizophrenia often experience multiple cardiovascular risk factors, including poor nutrition, inadequate exercise and problematic tobacco and substance use, compounded by poor healthcare (Varley & McClennan, 2009).

2.2 INCIDENCE AND PREVALENCE

Schizophrenia is very rare in pre-pubertal children (Burd *et al.*, 1987; Gillberg, 1984; Gillberg & Steffenburg, 1987) and there is limited epidemiological knowledge on this early onset disorder. From the information available it has been estimated that the prevalence of childhood schizophrenia may be 1.6 to 1.9 per 100,000 child population (Burd & Kerbeshian, 1987; Gillberg, 1984 and 2001; Hellgren *et al.*, 1987). However, its prevalence increases rapidly from age 14 onwards (Gillberg *et al.,* 1986; Thomsen, 1996) with a peak incidence in the late teens and early 20s. In an Australian sample of first episode psychosis, a third of those newly diagnosed were aged between 15 and 19 years old (Amminger *et al.*, 2006). While male gender predominance has been described in pre-adolescent children (Russell *et al.,* 1989), an equal gender ratio is more commonly reported in adolescence (Hollis, 2000).

2.3 POSSIBLE CAUSES OF SCHIZOPHRENIA

Psychosis and schizophrenia in children and young people appears clinically and biologically continuous with the adult-onset disorder. In common with schizophrenia in adults, the possible causes of schizophrenia in children and young people are not well understood. No single cause has been identified. Increasingly, it is thought that schizophrenia results from a complex interaction of genetic, biological, psychological and social factors, as described briefly below.

Much of the research into the causes of schizophrenia has been based on adult populations and is consistent with a stress-vulnerability model (Zubin & Spring, 1977). This model suggests that anyone could experience psychotic symptoms if placed under sufficient stress, but that people vary in their level of vulnerability to developing psychosis due to individual differences, which may be genetic, social, physiological or psychological. The model proposes that whether or not an individual develops psychosis is dependent on the interaction between their pre-existing vulnerability and stressful events. There is good reason to think that such a model can be applied to children and young people as well as adults. Research has attempted to determine what kinds of vulnerability and what types of stressors are most closely linked to the development of schizophrenia and other psychoses.

Twin studies have shown that schizophrenia results from interplay of genetic and environmental factors. Parental schizophrenia increases the risk in children, especially if both parents are affected (Gottesman *et al.,* 2010) and/or if children grow up in poor rearing environments within suboptimally functioning or otherwise disturbed families (Wahlberg *et al.,* 1997). However, we still know relatively little about which specific genes or environmental factors are involved and how these factors interact and actually cause psychotic symptoms. Because there are likely to be multiple genes involved, the genetics of schizophrenia is moving away from the notion of finding a single major gene for the disorder, towards a search for genes that confer susceptibility or vulnerability traits. Studies of pre-pubertal children with schizophrenia have also found a high rate (up to 10%) of various cytogenetic abnormalities including

small structural deletions or duplications that disrupt genes (Eckstrand *et al.,* 2008; Rapoport *et al*., 2005; Walsh *et al.,* 2008).

The search for environmental factors includes perinatal risk factors (for example, birth complications, nutrition, infections, child abuse and neglect, early cannabis use in adolescence and stressful life events. Read and Sanders (2010) propose that the vulnerability described in the stress-vulnerability model need not be the result of a genetic vulnerability but can be caused by difficult childhood events. They point to numerous studies illustrating that factors like urban living, poverty and child abuse are highly predictive of later psychotic symptoms with or without a genetic predisposition (Read *et al.,* 2008). There is evidence of a dose–response association between childhood trauma and psychosis, which suggests a causal relationship with childhood trauma. Therefore in order for effective treatment and recovery to occur it is imperative to routinely enquire about traumatic experiences and offer psychosocial treatments to those who report such events (Larkin & Read, 2008).

Cannabis use in adolescence has been shown to have a strong association with onset of psychosis and schizophrenia in adult life (Arseneault *et al.,* 2002). It has not been directly implicated in child and adolescent onset schizophrenia, possibly because of the relatively lower prevalence of cannabis use in younger adolescents and a short duration between exposure and psychotic outcome. However, cannabis use is associated with earlier age of onset of schizophrenia in adults (Arendt *et al*., 2005). Current thinking suggests that cannabis may enhance the risk of schizophrenia in vulnerable individuals during a critical period of adolescent brain development.

2.4 ASSESSMENT

2.4.1 Pre-pubertal children

The prevalence of psychosis and schizophrenia in pre-pubertal children is very low (Burd *et al*., 1987; Gillberg, 1984; Gillberg & Steffenburg, 1987), which means that only those clinicians working in specialist tertiary centres are likely to see sufficient numbers of children to have developed skills in assessment and diagnosis. The diagnosis of schizophrenia is to a large extent based on the effective communication by the child to others of a mixture of unusual subjective mental experiences, poor integration of sensory, emotional and cognitive experiences and bizarre behaviour. Young children's ability to integrate and communicate these experiences develops gradually before puberty, making the diagnosis of psychosis more difficult than in young people or adults and is more likely to be based on behaviour than subjective experiences.

Very early onset schizophrenia shows a high rate of insidious development (Ropcke & Eggers, 2005) over 6 months (Gordon *et al*., 1994), with a mean age at onset of 6.9 years (range of 3 to 11 years). The majority of children display pre-morbid psychiatric disturbance (Russell *et al.*, 1989), most commonly attention deficit hyperactivity disorder (ADHD), conduct problems (with aggression, truancy and firesetting) and developmental abnormalities within the autistic spectrum (present in 1 in 4, 26%). Early diagnostic stages can take some time to resolve; in children presenting

with a possible diagnosis of psychosis and schizophrenia, the latter is confirmed in about half (Remschmidt *et al*., 2007). Services need to be configured to facilitate early detection and treatment.

A mental health assessment helps in the formulation of the problem, identifying strengths and weaknesses, risks and needs. The assessment of a child should provide an understanding of the presenting problem within the social context of their life, both past and present, and facilitate the development of a care plan that addresses their broad range of needs, including social, educational and health needs. Assessment should include mental state, physical examination and a detailed developmental history, paying particular attention to pre-morbid functioning (Hollis, 2008). Abnormal premorbid functioning is more common than in adult onset disorder or non-schizophrenic psychoses starting in childhood and adolescence (Hollis, 2003; Hollis, 1995; Jacobsen & Rapoport, 1998) and is associated with negative symptoms (Hollis, 2003) and may be a predictor for poor prognosis (Hollis, 2000; Werry & McClellan, 1992; Vyas *et al.,* 2007).

The child's cognitive level will influence their ability to both express and understand complex psychotic symptoms and subjective experiences like hallucinations (Hollis, 2008; Ropcke & Eggers, 2005). An understanding of the child's cognitive functioning and whether they have speech or language problems will aid the clinician in teasing out the developmental issues from core psychotic phenomenon. Hallucinations in children are more frequently described as being internally located making it difficult to distinguish such experiences from inner speech or thoughts (Garralda, 1984a & b). The clinician needs to distinguish true hallucinations from normal subjective phenomena such as dreams or imaginary friends (Hollis, 2008).

Delusions are less frequent than in adolescent or adult schizophrenia and are likely to be less systematised. Formal thought disorder may be difficult to distinguish from immature language development with apparent loosening of associations and illogical thinking. Negative symptoms can appear very similar to non-psychotic language and social impairments, and can be confused with anhedonia or depression (Hollis, 2008).

Assessing a child's mental state can be a complex process. Understanding the child's development and whether they have speech and language problems or a learning disability will affect this assessment and what conclusions can be drawn from it. Clinicians may need to observe the child in a variety of settings to help clarify the diagnosis. Inpatient or day care services provide an opportunity to observe the child over a period of time, which can assist in providing a comprehensive and detailed mental state assessment. Engagement with the child and gaining their confidence may require a number of meetings. Assessment should also include a full mental health assessment to identify comorbid conditions— onset of schizophrenia in childhood can coexist with pervasive developmental disorder (Rapoport *et al.,* 2009). Multidisciplinary assessment is beneficial in providing a holistic view of the child's needs. Baseline psychometric testing can be helpful in assessment and for future educational planning.

Given the rarity of very early onset psychosis and schizophrenia it is important that organic illness is excluded. Physical healthcare and baseline investigations

should include detailed physical examination and blood tests. Magnetic resonance imaging (MRI) brain scanning may be considered in more complex presentations, electroencephalogram (EEG) if seizures are suspected and referral for a neurological opinion if neurodegenerative disorders are indicated (Hollis, 2008). Genetic testing (including consultation with a clinical geneticist) could be considered given reports of genetic abnormalities in one cohort of childhood-onset schizophrenia reaching 10% (Eckstrand et al., 2008). A careful differentiation needs to be made between children with psychotic states and those with what is sometimes called multiple complex developmental disorder or multiple developmental impairment, when children present with brief psychotic symptoms, inappropriate affect and mood lability, poor interpersonal skills in spite of normal social skills, thought disorder (bizarre, disorganised thinking) and impaired sensitivity to social stimuli (Kumra et al., 1998), but not the full schizophrenic presentation. While the long-term risk for development of schizophrenia is increased in these children, the majority will not develop the disorder in the short term.

2.4.2 Young people

The assessment of young people thought to be experiencing an emerging or frank psychotic disorder will vary according to the route they have taken to the healthcare professional. Some young people will present themselves seeking help for their distress, impairment or abnormal experiences, while others will be unwilling participants who are referred or presented for assessment by someone else (a parent or carer or possibly a teacher). In either scenario engagement of the young person is crucial both to assessment and to subsequent intervention.

The assessment needs to flexible and adapted to the young person's age and developmental level in terms of setting, language and the style of interviewing. Empathic and curious enquiry regarding the young person's current life situation, concerns and predicaments should usually be the starting point. However, this will need to progress to a more comprehensive account of a young person's global functioning and developmental history in order to reach any formulatory or diagnostic understanding.

Assessment needs to encompass careful enquiry about core symptomatology, particularly of abnormal belief systems, perceptions, thoughts and experiences. Physical health factors and a physical examination should not be overlooked (see Section 2.1.6). The role of substance use as both a causative and a comorbid or exacerbating factor requires careful exploration (see Section 2.3). Risks both to the individual and to others need to be assessed but also placed carefully within the developmental stage of adolescence where a degree of risk taking is both normal and necessary for individuation.

Psychosis in childhood or adolescence may result from an organic neuropsychiatric cause such as encephalitis, temporal lobe epilepsy, cerebral lupus, drug intoxication and rare neurodegenerative conditions such as Wilson's disease and adrenoleukodystrophy. The index of suspicion of an organic cause is increased when there are positive neurological signs, autonomic disturbance and fluctuating levels of consciousness. In

such cases physical investigations such as blood tests, EEG and an MRI or computed tomography (CT) scan may be helpful in reaching a diagnosis.

Physical investigations are also indicated before starting antipsychotic drug treatment. These include measuring height, weight, pulse, blood pressure and depending, on the drug, an electrocardiogram (ECG) and baseline lipids, prolactin and glycosylated haemoglobin (HbA_1c).

Collateral information from parents and carers (particularly historical information) and from schools also forms an important part of assessment. The failure of a young person to make expected progress (personal, social or academic) is as significant a marker of impairment and deterioration as is the loss of previously gained skills or competencies by an adult.

Semi-structured interview tools can be a useful adjunct to clinical assessments, providing prompts for less commonly experienced symptoms and setting a benchmark for future improvement (or deterioration) in symptoms or functioning.

2.5 ENGAGEMENT, CONSENT AND THERAPEUTIC ALLIANCE

Children and young people with schizophrenia and psychosis, together with their families and those close to them, can face times of significant distress. This can be especially so during acute phases, when the individual might exhibit fear, agitation, suspicion or anger in ways that can be confusing and alarming. Successful engagement in both the short and long term is the foundation of subsequent psychosocial and pharmacological interventions and interventions aimed at addressing physical health. Early engagement is crucial as delays in receiving treatment have been shown to have a detrimental effect on longer term outcomes (The NHS Confederation, 2011).

Engaging a child or a young person with these experiences may at times require considerable persistence and flexibility from professionals. *The Early Psychosis Declaration* highlights the need to 'reduce the long delays and coercive engagements that many families experience by services working better together and much earlier to meet the specific needs of young people and their families'(Rethink, 2004). Engaging the child or young person and their parents or carers may be made more challenging if they do not share the professionals' view of what the main problems are, the nature of the diagnosis and the need for treatment.

One barrier to engagement might be the potential challenge of an implied or future diagnosis for individuals considered to be 'at risk' of developing psychosis or schizophrenia (see Section 2.1.2) and offered or receiving services from an early intervention in psychosis (EIP) team.[1] Given that the development of psychosis in these circumstances is a possibility rather than a certainty, the clinical value of focusing on an at risk mental state needs to be balanced against the need to address the presenting problems in order to create a therapeutic alliance.

[1]At time of publication, EIP services are only available in England

Psychosis can have a profound effect on an individual's judgment and their capacity to understand their situation and consent to specific interventions. To support the child or young person in giving informed consent with regards to decisions about their care, the *Mental Capacity Act 2005* (Her Majesty's Stationery Office [HMSO], 2005; Department for Constitutional Affairs, 2007) can be used as a guide for those aged 16 and over, and 'Gillick competence' can be used for those aged under 16. However, depending on the level of risk, refusal to accept treatment in those under 16 may be overruled by parental authority or at any age by the *Mental Health Act 2007*[2] (HMSO, 2007).

An important consideration is the requirement to manage children and young people with psychosis and schizophrenia in low-stigma and age-appropriate settings (The NHS Confederation, 2011), and to provide information that is age appropriate (Department of Health, 2010) and supports the individual and their family in making informed decisions about treatment (Department of Health, 2011a).

Effective engagement for children and young people with psychosis and schizophrenia might be supported by minimising disruptive, developmentally inappropriate transitions. For example, although EIP patients have to be transitioned after 3 years, it makes little sense to have to transition a young person who entered an EIP service at age 14 to CAMHS at age 17 for 1 year. Services need to adapt to developmental needs as well as targeting specific disorders by supporting mental health across the life cycle, developing youth-focused mental health services stretching from childhood into adulthood, and utilising the expertise of both child and adult services (Rethink, 2011). How this is achieved in practice has particular relevance to this guideline.

2.6 LANGUAGE AND STIGMA

Psychosis and schizophrenia are among the most stigmatised mental health problems and people with these conditions are often stereotyped as dangerous and unpredictable (Thornicroft *et al*., 2009). Studies have shown that the public and mental health staff express a desire for social distance from people with psychosis (Corrigan *et al*., 2002). Stigma has been described by service users as more disabling than the mental health problem itself, resulting in a second 'illness'. Other psychological conditions such as depression, social anxiety and low self-esteem may occur as a direct consequence of stigma. Internalised or 'subjective' stigma encompasses the idea that those with mental health problems internalise public stereotypes and experience both shame of their diagnosis and fear of discrimination. Stigma and discrimination associated with psychosis can discourage people from seeking help, which may delay treatment and lead to social isolation, which can hamper recovery. These issues can also reduce employment and education opportunities and result in poorer physical healthcare,

[2]Mental Health Act Codes of Practice differ in England and Wales. For England, refer to *Code of Practice: Mental Health Act 1983 (*Department of Health, 2008a) and for Wales, refer to *Mental Health Act 1983: Code of Practice for Wales* (Welsh Assembly Government, 2008).

suicidality and higher mortality rates (Thornicroft, 2006). Stigma among professionals towards psychosis and schizophrenia may also delay diagnosis and treatment.

Language is one way in which stigma can be influenced for better or worse. Throughout the guideline the term 'psychosis' is used as a shorthand to describe psychotic disorders that are characterised by experiences that are described by clinicians as 'hallucinations' (hearing voices, seeing, feeling or tasting things that others cannot) and 'delusions' (believing in things that are not deemed to be based in reality). It is important to note that many people who hear voices would not define their experiences as either 'hallucinations' or 'psychosis', or indeed as pathological, and many individuals who are viewed as having 'delusions' would not identify their beliefs as such or consider their experiences to be 'psychosis'. Part of the difficulty and confusion around terminology in this area may arise because the term 'psychosis' is sometimes used interchangeably to refer to both psychotic symptoms (which may be common and not impairing) and a psychotic disorder (for example, schizophrenia), which is rare and associated with functional impairment. In this guideline the term 'psychosis' is reserved to refer to psychotic disorder.

The experience of being diagnosed can also be a cause of disempowerment for people with psychosis and schizophrenia and lead to the creation of a new identity as a 'schizophrenic', thus promoting social exclusion (Pitt *et al.*, 2009). Diagnostic labels can be particularly divisive, with terminology such as 'schizophrenic' generally being recognised as unacceptable to people with psychosis and schizophrenia. Personal accounts emphasise that the diagnostic 'label' is difficult to shed and can take on a life of its own, dehumanising and devaluing the individual (Bjorklund, 1996). Therefore, when referring to people with such diagnoses, the guideline employs terminology such as 'people who have psychosis and schizophrenia' rather than 'schizophrenic'. The term 'service user' is used for individuals who use mental health services.

2.7 ISSUES FOR PARENTS AND CARERS

As many children and young people offered treatment for psychosis and schizophrenia will still be in the direct care of parents or carers, it is important to consider developing treatments and decision-making processes that involve parents and carers as much as possible. At the same time, however, young service users will also need opportunities for confidential discussion of their concerns, as some of these may relate directly to difficulties with family members or carers.

While developing the most appropriate and effective intervention strategy for psychosis and schizophrenia with children and young people, it is important to remember that this age group, as well as their parents or carers, may have different priorities and preferences for treatment than older service users (see Section 2.5). This includes addressing the normal developmental tasks of adolescence with young people and their parents and carers as well as managing the psychotic disorder. It is also important to consider carefully the effectiveness and safety of particular treatments that have been developed for adults when recommending similar treatments for children and young people, and to offer service users and their parents or carers full

information about the relative costs and benefits of any recommended treatments (for example, long-term side effects of antipsychotics versus potential short-term reduction in psychological distress).

2.8 TREATMENT AND MANAGEMENT OF PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE IN THE NHS

2.8.1 Pharmacological interventions

Medication has formed the mainstay of treatment for psychosis since the introduction of chlorpromazine in the 1950s. Today, antipsychotic medication is considered an important part of a comprehensive package, which should also include psychological treatments and psychoeducation for the service user and their family. Antipsychotics are being prescribed more widely, and in one national survey (Nielsen *et al*., 2010) this was associated with less inpatient use for those with first episode psychosis.

There has been a substantial increase in the prescription of antipsychotic medications for children and young people (Vitiello *et al.,* 2009) with evidence also of a change of use from so-called 'first generation' antipsychotics (FGAs) such as haloperidol to 'second generation' antipsychotics (SGAs) such as olanzapine and risperidone. The latter drugs were introduced and marketed as being more effective and less likely to cause side effects, particularly extrapyramidal movement disorders and parkinsonism. However, recent evidence in this age group indicates there are few advantages of SGAs over FGAs in treating psychosis (Armenteros & Davies, 2006; Kennedy *et al.,* 2007, updated 2012; Sikich *et al.,* 2008). Indeed, weight gain, risk of diabetes, and metabolic problems associated with SGAs raise important public health concerns given the widespread use of these medications (Sikich *et al.,* 2008). Dietary and lifestyle counselling are required when initiating antipsychotic treatment alongside continued monitoring for adverse effects to optimise physical as well as psychiatric outcomes (Correll, 2011). Caution is further heightened by the finding that, generally, side effects in children and young people appear more severe than in adults (Correll, 2011). The lower rate of tardive dyskinesia with SGAs (Correll & Schenk, 2008) is potentially an argument in favour of SGAs over FGAs. With the notable exception of clozapine (Gogtay & Rapoport, 2008), there is no evidence for greater efficacy of one antipsychotic over another in the treatment of psychosis in this age group; choice may, therefore, be guided by the side-effect profile (Correll, 2010). Switching of antipsychotics ideally requires knowledge of the drug safety, efficacy, receptor profile and use of a tapering schedule (Buckley & Correll, 2008).

There is increasing evidence from meta-analyses of RCTs (Armenteros & Davies, 2006; Kennedy *et al*., 2007, updated 2012) confirming the efficacy of antipsychotic medication in children and young people. Antipsychotic medication is effective in reducing the positive symptoms of psychosis (hallucinations, delusions and thought disorder), however, the effect size is modest (0.2 to 0.3) according to Cohen's (1992) criteria. Furthermore, there is limited evidence to suggest efficacy of these medications

against negative symptoms of psychosis (lack of motivation, poverty of thought and so on). The relative lack of efficacy is a concern because early-onset schizophrenia is noted to be more severe, with greater cognitive impairment, increased negative symptoms, and less response overall to treatment than adult-onset schizophrenia (Correll, 2010; Eggers & Bunk, 2009).

Although there is some commonality in the pharmacotherapy of psychosis in adults and younger people, some important differences exist. Children and young people are more sensitive to the effects of medication (Correll, 2011) and therefore what is done during initiation of treatment is particularly important, such as starting with a low dose, whenever possible, and gradually titrating upwards over a period of several days to weeks. Although drug metabolism may be more rapid in young people than in adults (suggesting the possible need for higher doses) the use of higher than *British National Formulary*[3] (BNF) doses of antipsychotics does not appear effective—with only indirect evidence for high-dose olanzapine (Kumra *et al.*, 2008b)—and is not recommended unless guided by drug levels (for example, when treating with clozapine). It is also worth noting that for the most part the use of antipsychotic medication in children and young people is off-licence, therefore when prescribing off-label it is important to make parents and carers and, where appropriate, children and young people aware of this.

Psychoeducation for the child/young person and their family/carers is important, particularly as long-term compliance with medication is generally poor, and likely to be one of the major reasons for relapse. Unfortunately, strategies to enhance compliance have not been shown to be generally effective (Lincoln *et al.,* 2007), although the evidence is limited. Nevertheless, explanation, guidance and involving the family or carers in decisions about medication are important, as is continuity of care, especially across the transition of adolescence to early adulthood.

2.8.2 Psychological and psychosocial interventions

Before the introduction of neuroleptic medication for schizophrenia in the 1950s and 1960s, analytical psychotherapies based on the work of Frieda Fromm-Reichmann (1950) and Harry Stack Sullivan (1947) and others were widely practiced. The concept of rehabilitation grew during this period influenced by the pioneering work of Manfred Bleuler in the Bergholzi clinic in Zurich where patients were engaged in meaningful vocational and occupational endeavour in the context of an 'open door' policy (Bleuler, 1978). In the early 1980s, the publication of the seminal 'Chestnut Lodge' evaluation of exploratory and investigative psychotherapies (McGlashan, 1984) had a major impact: the trial demonstrated no impact of psychotherapy on the core psychotic symptoms contributing to a decline in their use in routine practice with the neuroleptics taking their place as the mainstay of treatment.

[3]http://www.bnf.org/bnf/index.htm

However, as deinstitutionalisation gained ground in the 1970s, psychological and social research into factors that might contribute to relapse in people with psychosis living in community settings, such as stressful life events and communication difficulties in families (high 'expressed emotion'), stimulated the development of family intervention to prevent relapse (Leff *et al*., 1982; Lobban & Barrowclough, 2009). Family intervention often included education for family members about schizophrenia (sometimes called 'psychoeducation') and, in time, research was conducted on the benefits of psychoeducation alone (Birchwood *et al*., 1992).

Meanwhile, the success of CBT in treating affective disorders sparked a renewed interest in 'talking therapies' for psychosis. One of the key progenitor studies was the work of Chadwick and Lowe (1994) showing that it was possible to 'reason' with people about their delusions and to reduce the strength of delusional beliefs. This was followed by the work of a number of groups in the UK developing cognitive models of psychosis (Garety *et al*., 2001; Morrison *et al.,* 2004b) and of specific symptoms such as hallucinations (Chadwick & Birchwood, 1994) and applying the assumptions and techniques of CBT to psychosis (for example, Kingdon & Turkington, 1994; Fowler *et al*., 1995). CBT is a very complex intervention in psychosis, working not only with delusions and hallucinations, but including a broad focus on self-evaluative thinking, which can require up to 25 sessions of treatment. There has been much debate about the future development of the CBT approach including the view (Birchwood & Trower, 2006; Fowler *et al*., 2011) that it needs to focus on the interaction of affect and psychosis and on the high level of affective disturbance seen in psychosis (depression and suicidal thinking, social anxiety and trauma symptoms). CBT has been developed further to reduce the likelihood of relapse, including young people with a first episode of psychosis (Álvarez-Jiménez *et al*., 2011).

Another approach, cognitive remediation therapy (CRT), was also developed in the 1980s and 1990s, and differs from CBT in that it is not directed at distressing symptoms but is instead focused on training in cognitive functions, such as learning, planning, attention or memory (Wykes *et al*., 2011); these have been linked with negative symptoms and general functioning. CRT is, however, rarely available in the NHS. In the mid 1990s a specific cognitive behavioural approach that aims to enhance compliance with medication, now commonly known as 'adherence therapy', was also developed (Kemp *et al*., 1996). Arts therapies that emerged as organised professions in the middle of the last century have in recent years begun to be evaluated formally in trials (Crawford & Patterson, 2007). Finally, there has been a focus on structured approaches to access employment for people with psychosis, particularly 'individual placement and support', which has great relevance for young people with psychosis (Killackey *et al*., 2008).

2.8.3 Factors influencing treatment approaches

Since the 1980s there has been an emerging consensus that schizophrenia in children and young people represents essentially the same disorder as seen in adults. Despite a much more limited evidence-base there is also consensus that psychosis

and schizophrenia in children and young people should generally be treated with the same interventions that are effective in adults. However, there are also a number of important differences between children/young people and adults that influence treatment approaches. These include:

- increased sensitivity of children and young people to adverse effects of antipsychotic medication
- greater severity of schizophrenia and prevalence of treatment resistance in children and young people
- a different pattern of comorbidities, with neurodevelopmental disorders (for example, autism, receptive language disorders and so on) being more common in children and young people with psychosis and schizophrenia
- a greater likelihood of cognitive impairment, negative symptoms and less systematised delusions and hallucinations (possibly limiting the universal applicability of cognitive behavioural therapy [CBT] approaches) in children and young people
- the importance of families in providing care and supporting children and young people with psychosis and schizophrenia (emphasising the importance of family intervention).

2.8.4 Management of at risk mental states and early psychotic symptoms

Reliable and valid criteria are now available to identify help-seeking individuals in diverse settings who are at high risk of imminently developing schizophrenia and related psychoses (see Section 2.1.2). Yung and colleagues (1996) developed operational criteria to identify three subgroups possessing an at risk mental state for psychosis. Two subgroups specify state risk factors, defined by the presence of either transient psychotic symptoms, also called brief limited intermittent psychotic symptoms, or attenuated (subclinical) psychotic symptoms. The other subgroup comprises trait-plus-state risk factors, operationally defined by the presence of diminished functioning plus either a first-degree relative with a history of psychosis or a pre-existing schizotypal personality disorder. All subgroups are within a specified age range known to be at greatest risk for the onset of psychosis.

Effective interventions to prevent or delay transition to psychosis are needed because of the significant personal, social and financial costs associated with it. To date there have been six randomised controlled trials (RCTs) that have reported outcomes associated with antipsychotic medication, omega-3 polyunsaturated fatty acids and/or psychological interventions, each using similar operational definitions of at risk mental states. These studies have been conducted in Australia (McGorry *et al.*, 2002; Yung *et al.*, 2011), North America (Addington *et al.*, 2011; McGlashan *et al.*, 2006), the UK (Morrison *et al.*, 2004a and 2007) and Austria (Amminger *et al.*, 2010).

It is generally agreed that research regarding interventions for at risk mental states and subthreshold psychotic experiences is in a state of clinical equipoise. Existing recommendations promote a clinical staging approach that utilises benign interventions (such as monitoring mental states, case management, social support and psychosocial interventions) before considering those with more significant side effects,

such as antipsychotic medication, or restrictive approaches involving hospitalisation (International Early Psychosis Association Writing Group, 2005; McGorry *et al*., 2006). However, due to local resources and service configurations, clinicians' attitudes and awareness of such recommendations, current clinical practice is likely to be highly variable, which is evident in the recent large international naturalistic cohort studies (Cannon *et al*., 2008; Ruhrmann *et al*., 2010).

2.8.5 Organisation of care

Child and adolescent mental health services (CAMHS) and early intervention in psychosis (EIP) services

Until the 1990s most children and young people with psychosis and schizophrenia were managed in child and adolescent inpatient units. The last decade of the 20th century saw a major change in service delivery with a shift towards community treatment in CAMHS. The first decade of this century saw the development of EIP services, with a policy implementation guide (Department of Health, 2001) recommending that these services should be provided for young people aged 14 to 35. EIP teams are generally managed by adult mental health services (AMHS) although some are embedded within CAMHS.

In 2004 CAMHS were directed by the *National Service Framework for Children, Young People and Maternity Services* (Department of Health, 2004)[4] to provide care for young people up until the age of 18. Prior to this the upper age range for CAMHS could vary according to whether the young person was in receipt of full-time educational provision. A recent report on this subject (Rethink, 2011) illustrates that this continues to be the case despite some models of good practice and recommends an agreed protocol for managing young people with psychosis who are under the age of 18, which should be embedded within everyday practice and based on cross-agency agreement of threshold criteria. Given that the policy implementation guidelines for EIP services in 2001 followed on from the *National Service Framework for Mental Health* in 1999 (Department of Health, 1999), it is strange that these recommendations[5] are still required some 10 years later.

Also in 2004 a group of international experts published a paper with recommendations on the involvement of CAMHS in EIP services (Marshall *et al*., 2004). There was a strong consensus that EIP services should have close links with CAMHS and be supported to prescribe medication to those aged under 16. There was also consensus that EIP services should integrate CAMHS and AMHS, have at least one representative from CAMHS, have designated sessions from child and adolescent psychiatry and employ youth workers. Despite this an audit of EIP services in England in 2005

[4]This refers to the National Service Framework for England. For Wales, refer to the *National Service Framework for Children, Young People and Maternity Services in Wales* (Welsh Assembly Government, 2004a).

[5]In the original policy implementation guideline (HMSO, 2001) there was a recommendation of 0.1 whole time equivalent child and adolescent psychiatrist as part of the EIP service.

(Pinfold *et al*., 2007) found that only 16% of EIP teams had dedicated input from CAMHS or youth workers. A quarter of EIP teams did not see young people under the age of 16.

The Rethink (2011) report found that of staff working in EIP/AMHS, 91% had not received training to work with those aged under 14 years; 67% reported that their staff had not received training to work with 14 to 16 year olds; and 64% reported that their staff had not received training to work with 16 to 18 year olds. Over 50% of EIP teams responded that they were not identifying young people in CAMHS with first episode psychosis or at risk of developing psychosis. One of the most commonly reported explanations was interface problems and role confusion between EIP and CAMHS teams.

In 2006 the Newcastle and North Tyneside EIP team sought to address this issue by appointing a consultant child and adolescent psychiatrist as an integral EIP team member rather than referring to, potentially, eight different CAMHS and consultant psychiatrists. In 2006 this was cited as a model of good practice in a review of the implementation of Part 9 of the *National Service Framework for Children, Young People and Maternity Services* (Department of Health, 2006a) and has been presented as a case study in the Rethink (2011) report. This is not to say that this is the preferred model for integrating EIP and CAMHS. What is likely to be the predominant model nationally is for young people with psychotic symptoms to be referred to CAMHS or EIP services but possibly receiving care that comprises components of both. For example, young people may be most likely to receive care coordination from EIP services but psychiatric input from CAMHS.

Admission to hospital

A child or young person experiencing psychosis or schizophrenia may be admitted to a range of inpatient settings. In part this will depend upon clinical features, for example, age (child or adolescent), the nature or purpose of admission (planned, crisis or emergency), level of disturbance and risk, and intensity of nursing care required. But in part it will also be determined by local service configuration and provision. The 2007 amendments to the *Mental Health Act* (HMSO, 2007) have made it much less likely that that a child or young person will be admitted to an adult mental health ward unless this is clearly appropriate to their very specific needs.

CAMHS inpatient units are characterised by their emphasis on meeting the developmental needs of the individual and minimising the impact of the disorder and the admission on the child or young person's emotional, social and educational development. Such units are likely to have a strong multidisciplinary team including an integrated education provision. The Quality Network for Inpatient CAMHS (QNIC) aims to demonstrate and improve the quality of inpatient child and adolescent psychiatric inpatient care through a system of review against the QNIC service standards (Royal College of Psychiatrists, 2011).

However, demand for age appropriate mental health beds frequently outstrips supply and alternative solutions may be necessary, particularly in a crisis. This can include brief mental health supported admission to a paediatric environment. It should be borne in mind that the range of provision that exists in AMHS for managing acute

presentations in or out of hospital (for example, crisis resolution and home treatment, acute admission and psychiatric intensive care) is less well developed in CAMHS and partnership with, or provision from, other non-NHS providers may be necessary.

Admission to hospital is disruptive to all aspects of a child or young person's life and the gains of admission do need to outweigh the losses. However the experience of psychosis is also extremely disruptive and may require the specialist skills or resources in assessment, risk management or treatment that can only be provided by admission. Admission to hospital should always be seen as one part of a child or young person's pathway through services and never as an end itself. There should be close liaison and collaboration between community services and any inpatient unit throughout the period of admission. The care programme approach (CPA) (Department of Health, 2008b) and care and treatment plans (C&TP)[6] provide the appropriate frameworks within which this should take place.

2.8.6 Pre-pubertal children

Treatment for pre-pubertal children is generally offered within the framework of the consent of those with parental responsibility for the child. However it is good practice to involve and inform the child in a manner that is appropriate to their developmental level and this requires clinicians to be confident in the assessment of the child's level of understanding and competence. Information leaflets using simple language may be helpful. Children may need several discussions and opportunities to ask questions about their condition and the treatments that they are being offered. Parents and carers should be expected to be actively involved in the treatment, which may include family intervention, psychoeducation and CBT targeted at symptoms, as well as pharmacotherapy (Hollis, 2008; Kennedy *et al.,* 2007).

There is some evidence that childhood-onset schizophrenia improves with antipsychotic medication (Kennedy *et al.,* 2009; James, 2010). Children may be more sensitive to the side effects of antipsychotic medication (Correll, 2008; James, 2010; Kumra *et al.,* 1996), therefore physical healthcare, baseline investigations and ongoing monitoring of side effects of drug treatment need to form part of the treatment package (see Chapter 7). For children who have not responded to other medications, clozapine appears to have some benefits in the treatment of psychotic symptoms and improving general functioning (James, 2010; Kennedy *et al.,* 2009; Kumra *et al.,* 1996). Given that many antipsychotic drugs are not licensed for use in younger age groups, children are often treated using licensed medication for an unlicensed indication. It is good practice to inform parents and carers of this fact and give them an opportunity to ask questions.

Children may come to the attention of either paediatric services or community CAMHS, which generally provides the initial treatment package. Inpatient care may

[6]Mental Health (Wales) Measure 2010. See: http://www.assemblywales.org/bus-home/bus-legislation/bus-leg-measures/business-legislation-measures-mhs-2.htm

become necessary for clarification of diagnosis, detailed assessment or risk management—this would usually be provided in a Tier 4 CAMHS specialist inpatient unit. In the absence of suitable CAMHS inpatient provision, children may be admitted to a paediatric ward. Strong links between community CAMHS and the inpatient paediatric service need to be maintained during treatment. Protocols across services may help to clarify lines of responsibility. Occasionally treatment may be required under the *Mental Health Act 2007* (HMSO, 2007).

2.8.7 Primary–secondary care interface

Pathways to specialist care can be particularly problematic for people with psychosis and schizophrenia under the age of 18. A study of first time presentations in young people in central Scotland (study population 1.75 million) reported that 80% were hospitalised, often onto adult wards, suggesting most had reached crisis before engaging specialist services (Boeing *et al*., 2007). Crisis response also featured in a first episode psychosis study in London and Nottingham where 40% of those presenting to generic community services required compulsory admission, rising to 50% for young black men (Morgan *et al*., 2005). This study linked general practitioner (GP) involvement with fewer legal detentions reported previously (Cole *et al*., 1995; Burnett *et al*., 1999), suggesting that it decreases the likelihood of police involvement and compulsory admissions. Moreover, GPs are frequently consulted in a first episode and are the most common final referring agency (Cole *et al*., 1995; Skeate *et al*., 2002).

Although GP participation in the pathway can reduce distress and delay in treatment, GPs may hold negative opinions about providing care for people with psychosis and schizophrenia (Lawrie *et al*., 1998) believing that the prevalence is too low to justify more active involvement (Bindman *et al*., 1997). Rarity of presentation was highlighted by a Swiss study, which found that GPs suspect an emerging psychosis in only 1.4 service users a year (Simon *et al*., 2005) and the proportion under 18 would be fewer still as 20% of people with a first episode are under 20 and 5% are under 16 (Hollis, 2003). Moreover early features may be difficult to distinguish from normal adolescent behaviour and substance misuse (Etheridge *et al*., 2004; Falloon, 2000). Few GPs receive postgraduate mental health training, but evidence of the effects of training is mixed. A study of a GP educational intervention about early presentations of psychosis failed to reduce treatment delay, although the training may have facilitated access to EIP teams (Lester *et al*., 2009). Indeed when asked, GPs prefer better collaboration with specialist services and low-threshold referral services rather than educational programmes (Simon *et al*., 2005).

The other major interface difficulty concerns the management of associated physical disorders due to poor organisation of health services and an ongoing failure by medical doctors in primary and specialist care to agree responsibility (Leucht *et al*., 2007; *The Lancet*, 2011). Despite numerous published screening recommendations, monitoring rates remain poor in adults (Mackin *et al*., 2007; Buckley *et al*., 2005; Morrato *et al*., 2009; Nasrallah *et al*., 2006) and children (Morrato *et al*., 2010). European screening and monitoring guidelines for diabetes and cardiovascular risk in

schizophrenia offered no specific guidance on the risks in children and young people (De Hert *et al.*, 2009). A recent systematic review concluded that good collaboration among child and adolescent psychiatrists, GPs and paediatricians is essential for the monitoring and management of severe adverse effects of antipsychotics (De Hert *et al.*, 2011).

GPs are more likely to accept physical healthcare as a core role (Lester *et al.*, 2005). The Quality and Outcomes Framework (QOF) (BMA & NHS Employers, 2011) has incentivised GPs to undertake annual physical health checks in people with psychosis and schizophrenia since 2004, reinforced by the NICE *Schizophrenia* guideline for adults (NICE, 2009a) which allocates overall responsibility to primary care for managing physical healthcare. However, the QOF and the NICE guideline do not prioritise the physical needs of young people with early psychosis. What is perhaps lacking is recognition of a group of many thousands of young people in adolescence and early adulthood, at ages primary care would not normally consider for active cardiovascular prevention, who are at high risk of dying prematurely. Whether from primary or specialist clinicians, these young people require clear and consistent information, particularly about the benefits and risks of antipsychotic medication to help them and their families or carers understand and balance improved mental health symptoms against increased risks to physical health.

Given that 'modifiable cardiovascular risk' appears within months of starting treatment with antipsychotics (Foley & Morley, 2011) the onus should arguably shift towards prevention and early intervention by those specialist services responsible for the critical early phase (Phutane *et al.*, 2011). However, simply issuing more guidance, for instance, to EIP services, is unlikely to change clinical practice without investing in systematic approaches to analysing and understanding the barriers to routine monitoring, organisational commitment to overcoming these, and clinical leadership (Hetrick *et al.*, 2010).

2.9 SUPPORTING CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS AND SCHIZOPHRENIA IN SCHOOL

2.9.1 Recognising psychosis and schizophrenia in schools

It is estimated that up to three out of 1000 secondary school pupils might be expected to be at risk of developing psychosis. Staff in secondary schools should be aware that some of their pupils are likely to develop early–onset psychosis and schizophrenia particularly around times of stress such as examinations. There are a number of signs that can indicate that a young person is becoming unwell and possibly developing psychosis. These prodromal symptoms may include social withdrawal, increasingly bizarre ideas and perceptual experiences, deteriorating concentration and academic performance (see Section 2.1.1). Those staff with a greater knowledge of individual pupils, such as form tutors, year heads or others with pastoral responsibilities, need to be alert to persistent changes in mood or demeanour (lasting for more than 3 weeks).

If these changes are persistent, school staff may consult with pupils, parents and carers and share their concerns. As a consequence, it may be necessary to discuss the matter further with other professionals working in schools (such as educational psychologists, school doctors or school nurses) who may well carry out further structured observations. If there is no improvement, they may well ask if the pupil and their parents or carers would accept referral to CAMHS or an EIP team.

2.9.2 Supporting children and young person in school

Children and young people will often feel distressed and frightened by their psychotic symptoms. They will be aware that other people do not experience the world in the same way that they do. This is disturbing in itself, however the experiences of a young person with psychosis can be worsened by the responses of those around them. If, for example, the young person is mocked or bullied for their different view of reality, this will exacerbate their fear and isolation. All schools now have anti-bullying policies and it is essential that they are operational and function effectively in order to best support all young people including those with psychosis and schizophrenia.

If school staff are inexperienced or concerned about supporting a child or a young person with psychosis or schizophrenia they have a responsibility to seek support themselves through a supervisory process perhaps from the school educational psychologist or other mental health workers.

As the condition progresses it may become increasingly difficult for the child or young person to continue in full-time education. They may be unable to sustain long periods of academic work and cope with the many interactions that comprise a school day. In these circumstances alternatives to full-time education may need to be considered. It is beneficial if alternatives can be planned for and discussed by those supporting the child or young person in advance. Breakdown of school placement and consequent emergency admission to some alternate provision will only add to the fear felt by the child or young person.

2.9.3 Returning to full-time education

When the child or young person is recovering, it is appropriate that in time they should be able to return to full-time education. School staff need to prepare for re-admission and be quietly welcoming. Environments with high levels of expressed emotion are known to increase the likelihood of a relapse into psychosis and schizophrenia, and it might be beneficial if pastoral staff who are aware of such environments within the school structure a timetable to avoid or minimise exposure to such classes, in consultation with the child or young person. At the same time it may be appropriate to provide opportunities for quiet and limited social interaction as part of each day. It is important to remember that a young person with psychosis or schizophrenia is experiencing an illness as devastating in its impact as leukaemia and they deserve the same levels of care, respect and support from those in educational settings.

2.10 THE ECONOMIC COST OF PSYCHOSIS AND SCHIZOPHRENIA

In 1990 the World Health Organization ranked schizophrenia as the ninth leading cause of disability. Assessment indicators of disability-adjusted life years (DALYs), such as non-fatal health outcomes as well as the premature mortality ratio for the condition, rank it as the 26th leading cause of global economic burden and the ninth leading cause of DALYs for people aged 15 to 44 years (Murray & Lopez, 1996).

The reported total cost of schizophrenia in the US amounted to US $62.7 billion in 2002 (Wu *et al.*, 2005). Over 50% of this cost was attributed to productivity losses, caused by unemployment, reduced workplace productivity, premature mortality as a result of suicide and family care. An average of 36% of the cost has been linked to direct healthcare service use, while 12% has been incurred by non-healthcare services. Several national studies conducted in Europe in the 1990s revealed schizophrenia 'was associated with a significant and long-lasting health, social, and financial burden, not only for patients but also for families, other caregivers, and the wider society'. (Knapp *et al.*, 2004).

The cost of treatment of people with schizophrenia is incredibly high, especially for those who require inpatient treatment and other psychiatric care facilities. In England approximately £2 billion of the estimated societal cost for schizophrenia of £6.7 billion (2004–2005 prices; Mangalore & Knapp, 2007) was accounted for by direct costs of treatment and care. The remaining £4.7 billion constituted indirect costs borne by society. Other costs, including the lost cost of productivity owing to unemployment, absence from work and premature mortality have been estimated at £3.4 billion and the cost of carers has been estimated roughly at £32 million. Other unanticipated costs include the cost of informal care and private expenditure borne by families, which has been estimated at roughly £615 million. In addition, the cost attributed to the criminal justice system amounts to nearly £1 million. The costs associated with administration relating to all of the above payments also need to be factored in – so far, these have been calculated at £14 million. Based on these estimates, the annual average cost borne by a person with schizophrenia in England can easily exceed £55,000.

There is a necessary distinction to be made when allocating economic costs to people with schizophrenia. Traditionally, newly diagnosed schizophrenia is of a considerably lower financial burden than chronic schizophrenia. According to Davies and Drummond (1994), the lifetime total direct and indirect financial costs borne by people with schizophrenia who have had a single episode can range from £8,000; for those experiencing multiple episodes, lasting more than 2.5 years, the estimated cost is nearly £535,000, factoring in long-term care in hospitals, private psychiatric facilities and/or intensive community programmes (1990/1991 prices). Guest and Cookson (1999) revised this estimate after taking into account the estimated average costs borne by a newly diagnosed patient at around £115,000 over the first 5 years following diagnosis. This amounts to nearly £23,000 annually, where 49% of the cost is directly attributed to indirect losses owed to lost productivity.

A recent review reported that the rate of unemployment among people with schizophrenia in the UK was between 4 and 27%. Stigmatisation has been cited as a

leading barrier to employment for this population. Unemployment rates were higher for those who were newly diagnosed compared with those living with established schizophrenia, however, a majority of people presenting to services for the first time were already unemployed (Marwaha & Johnson, 2004). According to Guest and Cookson (1999) between 15 and 30% of people with schizophrenia are unable to work at the diagnosis stage and this figure is expected to rise to approximately 67% following a second episode. Overall, the estimates of total indirect costs for patients in the UK range from between £412 million for newly diagnosed patients over the first 5 years to £1.7 billion annually for chronic patients (Davies & Drummond, 1994).

The use of inpatient care is often significant and in the financial year 2006–2007, 34,407 admissions were reported for schizophrenia and related disorders in England. This resulted in 2,232,724 inpatient bed days and amounted to 16% of all admissions and 34% of all bed days for psychiatric inpatient care (NHS, Information Centre, 2008). Inpatient care is by far the most costly healthcare component in treating schizophrenia. Kavanagh and colleagues (1995) found that in short- or long-stay psychiatric hospitals the cost accounted for 51% of the total public expenditure for the condition. Lang and colleagues (1997) reported that providing inpatient care amounted to 59% of the total cost of health and social care for people with schizophrenia.

Perhaps the cost that is most often overlooked and the hardest to allocate is that associated with informal care. Family members and friends often provide care for people with psychosis and schizophrenia, including children, and this places a substantial burden on their health, time, finances and employment status. Guest and Cookson (1999) estimated that at least 1.2 to 2.5% of carers in the UK stop working to look after dependents with schizophrenia. Measuring this cost in exact financial terms is difficult, however, it does form a significant component of the total economic costs associated with the condition. Based on Office for National Statistics (ONS) figures, the Sainsbury Centre for Mental Health (2003) estimated that in 2002/2003 the aggregate value of informal care by family members and friends in the UK for people with mental health problems amounted to £3.9 billion.

It is clear that apart from the emotional and mental strain borne by people with schizophrenia and their family there is a substantial economic burden that individuals, the healthcare system and society need to contend with. Efficient use of available healthcare resources is essential to maximise benefits for this population and could go a long way to reduce the emotional stress and other implications that people with schizophrenia, including children and young people, inevitably face.

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, 2009b]). A team of healthcare professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from NCCMH staff, undertook the development of a person-centred, evidence-based guideline. There are seven basic steps in the process of developing a guideline:

1. Define the scope, which lays out exactly what will be included in the guideline.
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 reviews and apply to the evidence recovered by search.
5. Synthesise and (meta-) analyse data retrieved, guided by the review questions, and produce evidence profiles including quality assessments and summaries.
6. Consider the implications of the research findings for clinical practice and reach consensus decisions on areas where evidence is not found.
7. Answer review questions with evidence-based recommendations for clinical practice.

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

3.2 THE SCOPE

Topics are referred by the Secretary of State and the letter of referral defines the remit, which defines the main areas to be covered (see *The Guidelines Manual* [NICE, 2009b] for further information). The NCCMH developed a scope for the guideline based on the remit (see Appendix 1). The purpose of the scope is to:

- provide an overview of what the guideline will include and exclude
- 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 NCCMH and NICE reviewed the scope in light of the comments received. The revised scope was signed off by NICE.

3.3 THE GUIDELINE DEVELOPMENT GROUP

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

3.3.1 Guideline development group meetings

Eleven GDG meetings were held between March 2011 and September 2012. 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 (see Appendix 2), and service user and carer concerns were routinely discussed as a standing agenda item.

3.3.2 Topic group

A subgroup of GDG members who were service users and carer representatives formed a small topic group to undertake work in the area of experience of care (Chapter 4).

All service user and carer representatives within the GDG were asked to participate in the topic group. The principal aims of the topic group were:

- to identify key issues and areas of concern for children and young people with psychosis and schizophrenia using NHS mental health services
- review the underlying evidence and recommendations from *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a) and the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) for their relevance to children and young people with psychosis and schizophrenia, bearing in mind the identified key issues and areas of concern.

The topic group discussion was fed back to the GDG in a plenary session. The GDG took into account the key issues and areas of concern and the recommendations from *Service User Experience in Adult Mental Health* (NICE, 2011a) and *Schizophrenia* (NICE, 2009a) identified by the topic group as being relevant to children and young people with psychosis and schizophrenia, and adapted the recommendations for use in the context of the current guideline using the method set out in Section 3.7. Topic group members also assisted the review team in drafting the section of the guideline relevant to the area of improving service user experience.

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 service user and carer representatives from service user and carer organisations. They contributed as full GDG members to writing the review questions, providing advice on outcomes most relevant to service users and carers, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service user research to the attention of the GDG. In drafting the guideline, they contributed to writing the guideline's introduction (Chapter 2) and to the process of incorporation and adaptation of existing guideline recommendations (see Section 3.7) for improving experience of care (see Chapter 4).

3.3.4 Special advisers

Special advisers, who had specific expertise in one or more aspects of recognition and management of psychosis and schizophrenia relevant to the guideline, assisted the GDG, commenting on specific aspects of the developing guideline and making presentations to the GDG. Appendix 3 lists those who agreed to act as special advisers.

3.3.5 National and international experts

National and international experts in psychosis and schizophrenia were identified through the literature search and through the experience of the GDG members. These

experts were contacted to identify unpublished or soon-to-be published studies, to ensure that up-to-date evidence was included in the development of the guideline. They informed the GDG about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 5 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 the review questions were prepared by NCCMH staff based on the scope (and an overview of existing guidelines) and discussed with the guideline Chair. The draft review questions were then discussed by the GDG at the first two meetings and amended as necessary. Where appropriate, the 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 most common reason for not including additional questions was when these fell outside of the scope and would generate a volume of work not possible to complete in the time available. The final list of review questions can be found in Appendix 6.

For questions about interventions, the PICO (Population, Intervention, Comparison and Outcome) framework was used (see Table 2).

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.

Table 2: 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?

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.

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of review question of relevance to NICE guidelines. These are listed in Table 3. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'. However, in all cases, a well-conducted systematic review (of the appropriate type of study) is likely to always yield a better answer than a single study. 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.

3.5 SYSTEMATIC CLINICAL LITERATURE REVIEW

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

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

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

(NICE, 2009b), and after considering recommendations from a range of other sources. These included:

- 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, 2004)
- 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.

3.5.2 The review process

Scoping searches

A broad preliminary search of the literature was undertaken in October 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 (HTA) reports, key systematic reviews and RCTs, and conducted in the following databases and websites:

- BMJ Clinical Evidence
- Canadian Medical Association Infobase (Canadian guidelines)
- Clinical Policy and Practice Program of the New South Wales Department of Health (Australia)
- Clinical Practice Guidelines (Australian Guidelines)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews (CDSR)
- Excerpta Medica Database (Embase)
- Guidelines International Network (G-I-N)
- Health Evidence Bulletin Wales
- Health Management Information Consortium (HMIC)
- HTA database (technology assessments)
- Medical Literature Analysis and Retrieval System Online MEDLINE/ MEDLINE In-Process
- National Health and Medical Research Council
- New Zealand Guidelines Group
- NHS Centre for Reviews and Dissemination
- Organizing Medical Networked Information Medical Search
- SIGN
- Turning Research Into Practice

- United States Agency for Healthcare Research and Quality
- Websites of NICE – including NHS Evidence - and the National Institute for Health Research (NIHR) HTA Programme for guidelines and HTAs in development.

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

Systematic literature searches

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

- Allied and Complementary Medicine Database (AMED)
- Applied Social Services Index and Abstracts (ASSIA)
- Australian Education Index (AEI)
- British Education Index (BEI)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- CDSR
- CENTRAL
- Education Resources in Curriculum (ERIC)
- DARE
- Embase
- HMIC
- HTA database (technology assessments)
- International Bibliography of Social Sciences (IBSS)
- MEDLINE / MEDLINE In-Process
- PsycBOOKS
- PsycEXTRA
- Psychological Information Database (PsycINFO)
- Social Sciences Citation Index (SSCI)
- Social Services Abstracts (SSA)
- Sociological Abstracts.

The search strategies were initially developed for MEDLINE before being translated for use in other databases/interfaces. Embase, MEDLINE, MEDLINE In-Process and PsycINFO were included in searches for all review questions, and will herein be described as 'core databases'. The remaining databases searched fall under umbrella headings for 'topic specific databases' or 'grey literature databases'. (Although PsycINFO is topic-specific by design, the resource forms an integral component for searches on all mental health conditions and disorders, and has thus been included under the heading of 'core databases'.) 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 psychosis and schizophrenia in

children and young people were kept purposely broad to help counter dissimilarities in database indexing practices and thesaurus terms, and imprecise reporting of study populations by authors in the titles and abstracts of records. The search terms for each search are set out in full in Appendix 8.

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 eligibility criteria of the reviews before being quality appraised (see the section 'Study selection and quality assessment' on page 49). 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, study design filters were used to limit the number of searches to systematic reviews, RCTs, and where necessary, observational studies. The search filters for systematic reviews and RCTs are adaptations of filters created by the Health Information Research Unit of McMaster University. The observational study filter was 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 May 2011 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in May 2012 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 or they appeared in English language systematic reviews.

Date restrictions were not applied except for searches of systematic reviews. Searches for systematic reviews were limited to 1996 onwards as older reviews were thought to be less useful.

Other search methods

Other search methods involved: (a) scanning the reference lists of all eligible publications (systematic reviews 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 5); (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; (e) conducting searches in ClinicalTrials.gov for

unpublished trial reports; (f) contacting included study authors for unpublished or incomplete datasets. Other relevant guidelines were assessed for quality using the AGREE instrument (AGREE Collaboration, 2003). The evidence base underlying high-quality existing guidelines was utilised and updated as appropriate.

Full details of the search strategies and filters used for the systematic review of clinical evidence are provided in Appendix 8.

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 an Excel database for study information. 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, using NICE methodology checklists (NICE, 2009b).

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 GDG 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 the GDG 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

Authors and principle investigators were approached for unpublished evidence (see Appendix 5). 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

Quantitative analysis

Study characteristics, methodological quality and outcome data were extracted from all eligible studies that met the minimum quality criteria, using Review Manager

(version 5.1; Cochrane Collaboration, 2011) and Excel-based and Word forms (see Appendix 13). This included aspects of the NICE methodology checklists that assess and address study bias.

For a given outcome (continuous or dichotomous), no studies were excluded from the analysis due to missing or incomplete data. However, if more than 20% of the number randomised were missing, this was taken into account when grading the quality of the evidence.

Where possible, outcome data from an intention-to-treat analysis (ITT) (that is, a 'once-randomised-always-analyse' basis) were used. For dichotomous efficacy outcomes the effect size was recalculated 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.[7]

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.

Consultation with another reviewer or members of the GDG was used to overcome difficulties with coding. Data from studies included in existing systematic reviews were extracted independently by one reviewer and cross-checked with the existing dataset. Where possible, two independent reviewers extracted data from new studies. Where double data extraction was not possible, data extracted by one reviewer 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).

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

3.5.4 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; also called a risk ratio) with the associated 95% confidence interval (CI) (see Figure 1 for an example of a forest plot displaying dichotomous data). An RR 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 Figure 1, 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 of the control intervention or, in other words, the RR reduction is 27%.

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

Continuous outcomes were analysed using the mean difference or SMD when different measures were used in different studies to estimate the same underlying effect (see Figure 2 for an example of a forest plot displaying continuous data). If reported by study authors, ITT data, using a valid method for imputation of missing data, were preferred over data only from people who completed the study. In addition, mean endpoint data were preferred over mean change scores. If mean endpoint data were not available, change scores and endpoint data were included in a single analysis, pooled using SMDs and the robustness of the findings checked using sensitivity analysis.

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 following way based on Higgins and Green (2011):

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

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 CI for I^2).

Publication bias

It was not possible to draw funnel plots to explore the possibility of publication bias because there was an insufficient number of included studies for any one outcome. Therefore fixed effects and random effects models were compared for differences.

Figure 1: Example of a forest plot displaying dichotomous data

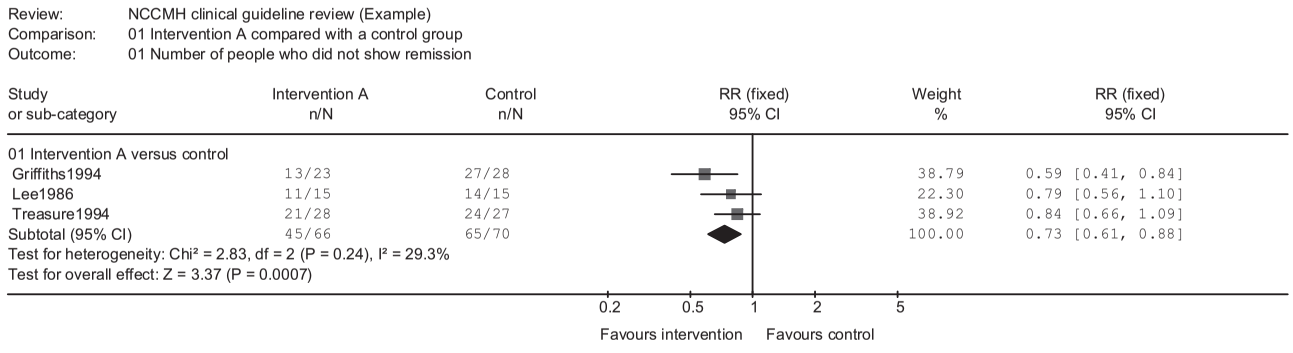
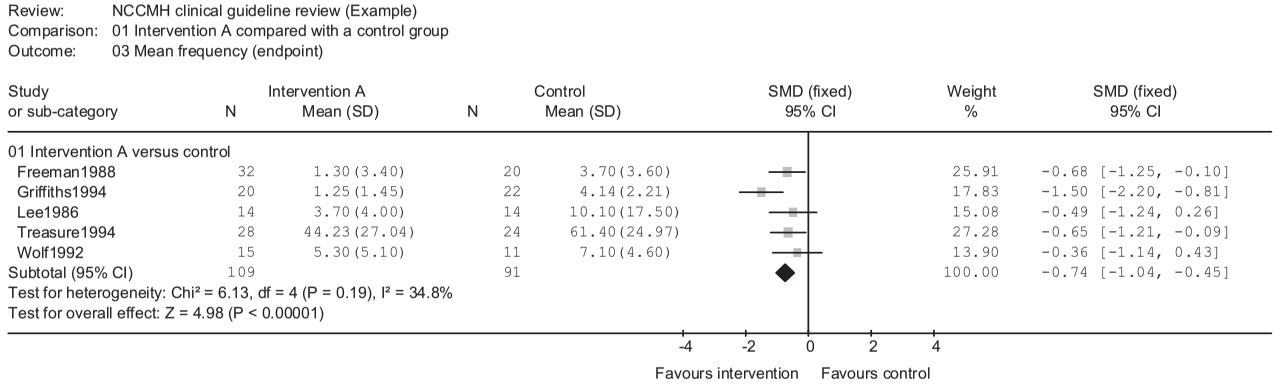


Figure 2: Example of a forest plot displaying continuous data



3.5.5 Grading the quality of the evidence

For questions about interventions, the GRADE approach[8] was used to grade the quality of evidence for each outcome. The technical team produced evidence profiles using Word forms, following advice set out in the GRADE handbook (Schünemann *et al*., 2009).

Evidence profiles
A GRADE evidence profile was used to summarise both the quality of the evidence and the results of the evidence synthesis for each 'critical' and 'important' outcome (see Table 4 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 grading the quality of evidence, the following is used as a starting point:

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

For each outcome, quality may be reduced depending on five factors: limitations, inconsistency, indirectness, imprecision and publication bias. For the purposes of the guideline, each factor was evaluated using criteria provided in Table 5.

For observational studies without any reasons for downgrading, the quality may be upgraded if there is a large effect, all plausible confounding would reduce the demonstrated effect (or increase the effect if no effect was observed), or there is evidence of a dose-response gradient (details would be provided under the 'other 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. Under the GRADE approach, the overall quality for each outcome is categorised into one of four groups, with the following meaning:

- **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** We are very uncertain about the estimate.

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

Table 4: Example of an evidence profile

Outcome or subgroup	Study ID	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	Insert Study ID	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[5]	K = 4; N = 516	– 0.32 [–0.52, –0.13] *	Low	Link to Appendix
Global state (SMD)	Insert Study ID	RCT	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	Reporting bias[5]	K = 3; N = 400	– 0.38 [–0.58, –0.18]*	Very low	Link to Appendix
Response (RR)	Insert Study ID	RCT	Serious[1]	No serious inconsistency	Serious[3]	Serious[4]	Reporting bias[5]	K = 1; N = 98	1.43 [0.95, 2.17]	Very low	Link to Appendix

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.

* Favours intervention.

[1] High risk of bias (including unclear sequence generation, allocation concealment and blinding procedures; missing outcomes data; participants excluded if they had a previous non-response to study treatment; treatment exposure different between groups in one study).

[2] $I^2 > 50\%$, $p < 0.05$.

[3] Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

[4] Optimal information size (OIS) (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

[5] Serious risk of reporting bias.

Table 5: Factors that decrease quality of evidence

Factor	Description	Criteria
Limitations	Methodological quality/ risk of bias.	In the studies that reported a particular outcome, serious risks across most studies. The evaluation of risk of bias was made for each study using NICE methodology checklists (see Section 3.5.3).
Inconsistency	Unexplained heterogeneity of results.	Moderate or greater heterogeneity (see Section 3.5.4 for further information about how this was evaluated).
Indirectness	How closely the outcome measures, interventions and participants match those of interest.	If the comparison was indirect, or if the question being addressed by the GDG was substantially different from the available evidence regarding the population, intervention, comparator, or an outcome.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide CIs around the estimate of the effect.	If either of the following two situations were met: • the OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) was not achieved • the 95% CI around the pooled or best estimate of effect included both (1) no effect and (2) appreciable benefit or appreciable harm.
Publication bias	Systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.	If there was evidence of selective publication. This may be detected during the search for evidence, or through statistical analysis of the available evidence.

3.5.6 Presenting the data to the Guideline Development Group

Study characteristics tables, forest plots (where appropriate) generated with Review Manager (version 5.1; Cochrane Collaboration, 2011) and summary of findings tables were presented to the GDG. Summary of findings tables were used to summarise the evidence for each outcome and the quality of that evidence (see Table 6). Where

Table 6: Example of a summary of findings table

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	Study ID	K = 4; N = 516	−0.32 [−0.52, −0.13] *	(P = 0.31); I^2 = 16%	Low[1,5]	Link to Appendix
Global state (SMD)	Study ID	K = 3; N = 400	−0.38 [−0.58, −0.18]*	(P = 0.44); I^2 = 0%	Very low[1,2,5]	Link to Appendix
Response (RR)	Study ID	K = 1; N = 98	1.43 [0.95, 2.17]	N/A	Very low[1,3,4,5]	Link to Appendix

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours intervention.
[1] High risk of bias (including unclear sequence generation, allocation concealment and blinding procedures; missing outcomes data; participants excluded if they had a previous non-response to study treatment; treatment exposure different between groups in one study).
[2] I^2 >50%, $p < 0.05$.
[3] Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).
[4] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Serious risk of reporting bias.

meta-analysis was not appropriate and/or possible, this was reported in the relevant included study characteristics table.

3.5.7 Extrapolation

When answering review questions, it may be necessary to consider extrapolating from another dataset where direct evidence from a primary dataset[9] is not available. In this situation, the following principles were used to determine when to extrapolate:

- primary data are absent, of low quality or judged to be not relevant to the review question under consideration
- a review question is deemed by the GDG to be important, such that in the absence of direct evidence, other data sources should be considered
- a non-primary data source is in the view of the GDG available, which may inform the review question.

[9] A primary dataset is defined as one that contains evidence on the population and intervention under review.

When the decision to extrapolate was made, the following principles were used to inform the choice of the non-primary dataset:

- the population under consideration shares the same diagnosis as the population under review (either at risk for or diagnosed with psychosis and schizophrenia) but differs in age; specifically, studies included individuals younger and older than 18 years, but the mean age of the study sample had to be under 25 years to be eligible for extrapolation
- the interventions under consideration in the view of the GDG have one or more of the following characteristics:
  - share a common mode of action (for example, the pharmacodynamics of a drug or a psychological model of change)
  - be feasible to deliver in both populations (for example, in terms of the required skills or the demands of the healthcare system)
  - share common side effects or harms in both populations
- the context or comparator involved in the evaluation of the different datasets shares some common elements that support extrapolation
- the outcomes involved in the evaluation of the different datasets shares some common elements that support extrapolation (for example, improved symptoms or a reduction in hospitalisations).

When the choice of the non-primary dataset was made, the following principles were used to guide the application of extrapolation:

- the GDG should first consider the need for extrapolation through a review of the relevant primary dataset and be guided in these decisions by the principles for the use of extrapolation
- in all areas of extrapolation datasets should be assessed against the principles for determining the choice of datasets; in general the criteria in the four principles set out above for determining the choice should be met
- in deciding on the use of extrapolation, the GDG will have to determine if the extrapolation can be held to be reasonable, including ensuring that:
  - the reasoning behind the decision can be justified by the clinical need for a recommendation to be made
  - the absence of other more direct evidence, and by the relevance of the potential dataset to the review question can be established
  - the reasoning and the method adopted is clearly set out in the relevant section of the guideline.
  - methods used to answer a review question in the absence of appropriately designed, high-quality research.

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 an informal consensus process was adopted. The starting point for the process of informal consensus was that the systematic reviewer identified, where available, a narrative review that most directly

addressed the review question. This existing narrative review was used as a basis for beginning an iterative process to identify lower levels of evidence relevant to the review question and inform GDG discussion. The process involved a number of steps:

1. A description of what is known about the issues concerning the review question was presented to the GDG by one of the members who had special expertise in the area.
2. Evidence from the existing narrative review was presented 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, where available, added to the information collected. This might include studies that did not directly address the review question but were thought to contain relevant data.
4. Recommendations were then developed and, where necessary, sent for external peer review.

After this final stage of comment, recommendations were again reviewed and agreed upon by the GDG. Within each evidence chapter, the informal consensus process is captured in the 'Evidence to recommendations' sections, which demonstrate how the GDG moved from the evidence obtained to the recommendations made (see Section 3.8).

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 psychosis and schizophrenia in children and young people covered in the guideline. This was achieved by systematic literature review of existing economic evidence

Systematic reviews of economic literature were conducted in all areas covered in the guideline. However, the evidence on psychosis and schizophrenia in children and young people is very limited or not robust. Therefore, no economic model is developed in this guideline. In order to make recommendations the guideline used economic considerations of family intervention, CBT and pharmacological interventions from the adult *Schizophrenia* guideline (NCCMH, 2010).

The rest of this section describes the methods adopted in the systematic literature review of economic studies.

3.6.1 Search strategy for economic evidence

Scoping searches

A broad preliminary search of the literature was undertaken in October 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 HTA reports, and conducted in the following databases:

- Embase
- HTA database (technology assessments)

- 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 HTA reports, and conducted in the following databases:

- EconLit (the American Economic Association's electronic bibliography)
- Embase
- HTA database (technology assessments)
- MEDLINE / MEDLINE In-Process
- NHS EED
- PsycINFO.

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

The search strategies were initially developed for MEDLINE before being translated for use in other databases/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 psychosis and schizophrenia in children and young people were kept purposely broad to help counter dissimilarities in database indexing practices and thesaurus terms, and imprecise reporting of study populations by authors in the titles and abstracts of records.

For standard mainstream bibliographic databases (Embase, MEDLINE and PsycINFO) search terms for psychosis and schizophrenia in children and young people were combined with a search filter for health economic studies. For searches generated in topic-specific databases (EconLit, HTA and NHS EED) search terms for psychosis and schizophrenia in children and young people 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. The search terms are set out in full in Appendix 10.

Reference Manager

Citations from each search were downloaded into Reference Manager 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 the Centre for Reviews and Dissemination at the University of York (2007). The search filter is designed to retrieve records of economic evidence (including full and partial economic evaluations) from the vast amount of literature indexed to major medical databases such as MEDLINE. The filter, which comprises a combination of controlled vocabulary and free-text retrieval methods, maximises sensitivity (or recall) to ensure that as many potentially relevant records as possible are retrieved from a search. A full description of the filter is provided in Appendix 10.

Date and language restrictions

Systematic database searches were initially conducted in May 2011 up to the most recent searchable date. Search updates were generated on a 6-monthly basis, with the final re-runs carried out in May 2012 ahead of the guideline consultation. After this point, studies were included only if they were judged by the GDG to be exceptional (for example, the evidence was likely to change a recommendation).

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

Other search methods

Other search methods involved scanning the reference lists of all eligible publications (systematic reviews 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 10.

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 were included in the review, as well as costing analyses that compared only costs between two or more interventions.

- Economic studies were included if they used clinical effectiveness data from an RCT, a prospective cohort study, or a systematic review and meta-analysis of clinical studies. Studies that had a mirror-image or other retrospective design were excluded from the review.
- Studies were included only if the examined interventions were clearly described. This involved the dosage and route of administration and the duration of treatment in the case of pharmacological therapies; and the types of health professionals involved as well as the frequency and duration of treatment in the case of psychological interventions. Evaluations in which medications were treated as a class were excluded from further consideration.
- Studies that adopted a very narrow perspective, ignoring major categories of costs to the NHS, were excluded; for example, studies that estimated exclusively drug acquisition costs or hospitalisation costs were considered non-informative to the guideline development process.

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, 2009b), the template for which is shown in Appendix 11 of this guideline. All studies that fully or partially met the applicability and quality criteria described in the methodology checklist were considered during the guideline development process. The completed methodology checklists for all economic evaluations considered in the guideline are provided in Appendix 15.

3.6.4 Presentation of economic evidence

The economic evidence considered in the guideline is provided in the respective evidence chapters, following presentation of the relevant clinical evidence. The references to included studies and the respective evidence tables with the study characteristics and results are provided in Appendix 16. Characteristics and results of all economic studies considered during the guideline development process are summarised in economic evidence profiles following the respective GRADE clinical evidence profiles in Appendix 17.

3.6.5 Results of the systematic search of economic literature

The titles of all studies identified by the systematic search of the literature were screened for their relevance to the topic (that is, economic issues and information on health-related quality of life [HRQoL] in children and young people with psychosis and schizophrenia). References that were clearly not relevant were excluded first.

The abstracts of all potentially relevant studies (95 references) were then assessed against the inclusion criteria for economic evaluations by the health economist. Full texts of the studies potentially meeting the inclusion criteria (including those for which eligibility was not clear from the abstract) were obtained. Studies that did not meet the inclusion criteria, were duplicates, were secondary publications of one study, or had been updated in more recent publications were subsequently excluded. Economic evaluations eligible for inclusion (three references) were then appraised for their applicability and quality using the methodology checklist for economic evaluations. Finally, two economic studies that fully or partially met the applicability and quality criteria were considered at formulation of the guideline recommendations.

3.7 THE INCORPORATION AND ADAPTATION OF EXISTING NICE GUIDELINE RECOMMENDATIONS

3.7.1 Rationale

The starting point for the current guideline ('Are there grounds for believing that treatment and management of children and young people with psychosis and schizophrenia should be any different from adults?') constituted the main principle underlying the process of incorporation and adaptation in this context. In addition, there are a number of other reasons why it was desirable to reuse recommendations published in NICE guidelines, including to:

1. Increase the efficiency of guideline development and reduce duplication of activity between guidelines.
2. Answer review questions where little evidence exists for the topic under development, but recommendations for a similar topic do exist. For example, recommendations from an adult guideline are reused for children.
3. Facilitate the understanding of, or use of, other recommendations in a guideline where cross-referral to another guideline might impair the use or comprehension of the guideline under development. For example, if a reader is being constantly referred to another guideline it interrupts the flow of recommendations and undermines the usefulness of the guideline.
4. Avoid possible confusion or contradiction that arises where a pre-existing guideline has addressed a similar question and made different recommendations covering the same or very similar areas of activity.

In this context, there are two methods of reusing recommendations, that is, *incorporation* and *adaptation*. Incorporation refers to the placement of one recommendation in a guideline different from that it was originally developed for, where no material changes to wording or structure are made. Recommendations used in this way are referenced appropriately. Adaptation refers to the process by which a recommendation is changed in order to facilitate its placement within a new guideline.

3.7.2 Incorporation

In the current guideline, the following criteria were used to determine when a recommendation could be incorporated:

- the recommendation addresses an issue within the scope of the current guideline
- the review question addressed in the current guideline is judged to be sufficiently similar to that associated with the recommendation in the original guideline
- the recommendation can 'stand alone' and does not need other recommendations from the original guideline to be relevant or understood within the current guideline
- it is possible in the current guideline to link to or clearly integrate the relevant evidence from the original guideline into the current guideline.

3.7.3 Adaptation

When adaptation is used, the meaning and intent of the original recommendation is preserved but the wording and structure of the recommendation may change. Preservation of the original meaning (that is, that the recommendation faithfully represents the assessment and interpretation of the evidence contained in the original guideline evidence reviews) and intent (that is, the intended outcome[s] specified in the original recommendation will be achieved) is an essential element of the process of adaptation.

The precise nature of adaptation may vary but examples include: when terminology in the NHS has changed, the population has changed (for example, from adults to young people) or when two recommendations are combined in order to facilitate integration into a new guideline. This is analogous to the practice when creating NICE Pathways whereby some alterations are made to recommendations to make them 'fit' into a pathway structure.

The following criteria were used to determine when a recommendation could be adapted:

- the original recommendation addresses an issue within the scope of the current guideline
- the review question addressed in the current guideline is judged by the GDG to be sufficiently similar to that associated with the recommendation in the original guideline
- the recommendation can 'stand alone' and does not need other recommendations from the original guideline to be relevant
- it is possible in the current guideline to link to or clearly integrate the relevant evidence from the original guideline into the new guideline
- there is no new evidence relevant to the original recommendation that suggests it should be updated
- any new evidence relevant to the recommendation only provides additional contextual evidence, such as background information about how an intervention is provided in the healthcare setting(s) that are the focus of the guideline. This may

inform the redrafting or restructuring of the recommendation but does not alter its meaning or intent (if meaning or intent were altered, a new recommendation should be developed).

In deciding whether to incorporate or adapt existing guideline recommendations, the GDG first considered whether the direct evidence obtained from the current guideline dataset was of sufficient quality to allow development of recommendations. It was only where such evidence was not available or insufficient to draw robust conclusions, and drawing on the principles of extrapolation (see Section 3.5.7), that the 'incorporation and adaptation' method was used.

3.7.4 Roles and responsibilities

The guideline review team, in consultation with the guideline Facilitator and Chair, were responsible for identifying existing guideline recommendations that may be appropriate for incorporation or adaptation. The GDG were responsible for deciding if the criteria had been met for incorporation or adaptation. For recommendations relating to experience of care, a smaller topic group (see Section 3.3.2) was convened first to discuss the possible inclusion and incorporation or adaptation of recommendations related to that topic. For adapted recommendations, a member of the existing guideline was consulted to ensure the meaning and intent of the original recommendation was preserved.

3.7.5 Drafting of adapted recommendations

The drafting of adapted recommendations conformed to standard NICE procedures for the drafting of guideline recommendations, preserved the original meaning and intent, and aimed to minimise the degree of rewriting and restructuring. In evidence chapters where incorporation and adaptation have been used, tables are provided that set out the original recommendation, the new recommendation and the reasons for adaptation.

3.8 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 GDG and society, the requirements to prevent discrimination and to promote equality[10], and the GDG's awareness of practical issues (Eccles *et al.*, 1998; NICE, 2009b).

[10] 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 (Schünemann *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 12.

3.9 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 stakeholder's national organisations: that represent the healthcare professionals who provide the services described in the guideline
- commercial stakeholders: companies that manufacture drugs or devices used in treatment of the condition covered by the guideline and whose interests may be significantly affected by the guideline
- providers and commissioners of health services in England and Wales
- statutory organisations: including the Department of Health, the Welsh Assembly Government, NHS Quality Improvement Scotland, the Care Quality Commission and the National Patient Safety Agency
- research organisations that have carried out nationally recognised research in the area.

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

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

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

3.10 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 (see Appendix 4) and experts were responded to, and the guideline updated as appropriate. NICE also reviewed the guideline and checked that the stakeholders' comments had been addressed.

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

4 ACCESS TO AND THE DELIVERY OF SERVICES, AND THE EXPERIENCE OF CARE

4.1 INTRODUCTION

It is well established that there are significant social and ethnic inequalities regarding access to and benefit from effective clinical interventions for psychosis and schizophrenia (NCCMH, 2010). Delayed access to mental health services in the early stages of psychosis and schizophrenia – often referred to as the 'duration of untreated psychosis' (DUP) – is associated with slower or less complete recovery, and increased risk of relapse and poorer outcome in subsequent years (Johnstone *et al.,* 1986; Marshall *et al.,* 2005). Attention is now rightly focused on ensuring early access to and delivery of effective services and interventions for psychosis and schizophrenia, reducing periods of untreated psychosis and ensuring prompt and precise diagnosis and quicker recovery to minimise any social deficits.

A good experience of care is underpinned by effective interventions delivered safely by competent professionals in the appropriate service. Nowhere is the experience of care more important than in longer-term conditions, such as schizophrenia, in which repeated use of services is common and contact with professionals frequent and/or prolonged. Children and young people with psychosis and schizophrenia use services in primary and secondary care, in the community and in hospital, and often transfer between services. The need to ensure continuity of care and effective and safe transitions that are experienced positively is, therefore, an important consideration for this guideline. It is also imperative that there is clarity about which service is providing physical healthcare for children and young people with psychosis and schizophrenia.

This chapter aims to review access to and delivery of services available for children and young people with psychosis and schizophrenia and to suggest ways of improving their experience of healthcare, based upon the best evidence available. Where evidence is lacking for children and young people (which is more the rule than the exception), the GDG has reviewed *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a) and the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a).

4.2 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 7. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

Table 7: Summary review protocol for the review of access to and delivery of services and the experience of care

Review question (RQ)	**RQ C2: Access to and delivery of services:** For children and young people with psychosis and schizophrenia (particularly from black and minority ethnic groups), do specialised intensive services (EIP services; specialist CAMHS) improve access and engagement with mental health services? **RQ D1: Experience of care:** For children and young people with psychosis and schizophrenia, what can be done to improve their experience of care?
Objectives	• To provide evidence-based recommendations, via GDG consensus where necessary, regarding ways to improve access to and engagement with mental health services for children and young people with psychosis and schizophrenia, particularly those from black and minority ethnic groups. • To identify the experiences of care (access to services, treatment and management) for children and young people with psychosis and schizophrenia.
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. Consideration should be given to the specific needs of children and young people with a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	• Specialised intensive services (for example CAMHS, EIP)
Comparison	Alternative management strategies: • Non-specialised services • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Symptoms • Psychosocial functioning • Experience of care

Continued

Table 7: (*Continued*)

Secondary outcomes	None
Electronic databases	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases and grey literature databases (see Appendix 8)
Date searched	Systematic reviews: 1995 to May 2012 RCTs: inception of databases to May 2012
Study design	RCTs; systematic reviews Existing NICE guidelines will be reviewed with the aim of incorporating or adapting recommendations pertaining to the experience of care for children and young people with psychosis and schizophrenia using the method described in Chapter 3.

4.3 SOURCES OF INFORMATION CONSIDERED

The GDG advised the NCCMH review team that there was very little high quality research assessing ways to improve access and engagement with mental health services for children and young people with psychosis and schizophrenia. The search for RCTs and systematic reviews confirmed this – no RCT or systematic review investigating intensive services (EIP services or CAMHS) for children and young people with psychosis and schizophrenia was identified. The GDG therefore sought to develop recommendations using a consensus-based approach, as set out in Chapter 3, Section 3.5.8. In brief this process included: a narrative review to answer the review question pertaining to access to and delivery of services; presentation of the narrative review and full group discussion about the findings; and expert opinion regarding current practice. Section 4.4 provides the narrative review of the evidence for access to and delivery of services and current practice.

To address the review question pertaining to experience of care, the GDG made the decision to review the underlying evidence and recommendations in *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) with the aim of incorporating or adapting recommendations pertaining to the experience of care for children and young people with psychosis and schizophrenia using the methodology described in Chapter 3. To aid this process, a topic group of service users and carer representatives was formed in accordance with the methods set out in Chapter 3. The topic group had two aims: (1) identify key issues and areas of concern for children and young people and their experience of care using NHS mental health services, and (2) review and assess the recommendations from the *Service User Experience in Adult Mental Health* and *Schizophrenia* guidelines for their relevance to children and young people with

psychosis and schizophrenia, specifically in relation to the issues and concerns identified. The narrative review, outcome of the topic group discussion and GDG consensus informed the incorporation and adaption of recommendations from other guidelines. Section 4.5 sets out the findings of the topic group and further detail regarding the development of the recommendations for improving the experience of care of children and young people with psychosis and schizophrenia.

4.4 NARRATIVE REVIEW OF THE EVIDENCE FOR ACCESS TO AND DELIVERY OF SERVICES AND CURRENT PRACTICE

4.4.1 Narrative review

Child and adolescent mental health services (CAMHS) Tier 2/3

Child and adolescent mental health services (CAMHS) are specialist mental health teams in secondary care responsible for providing assessment and treatment of mental health disorders up to age 18. In the tiered model of CAMHS (Health Advisory Service, 1995), Tiers 2 and 3 describe outpatient community care and Tier 4 describes inpatient care or highly specialised (tertiary) outpatient services. Tier 2 typically refers to specialist CAMHS staff working alone, often in outreach liaison roles with primary care (for example, primary mental health workers). Meanwhile Tier 3 refers to multidisciplinary specialist CAMHS teams. Most community CAMHS teams describe themselves as providing Tier 2/3 services.

Community CAMHS teams traditionally provide a generic service for the population of a defined geographical area. Tier 2/3 CAMHS can also provide 24-hour emergency services and manage the full range of mental health problems in children and young people. However, the relative rarity of psychosis and schizophrenia in children and young people means that it is difficult for generic teams to develop specialist experience in assessing and managing these conditions. In particular, small generic CAMHS teams may not be able to provide the full range of evidence-based treatments for psychosis and schizophrenia, including outreach and intensive community care (for example, home visiting), and pharmacological and psychosocial interventions.

Over the past decade, various service innovations have occurred including the development of early intervention in psychosis (EIP) teams for people aged 14 to 35 years (see below). EIP teams are typically based and managed within AMHS and although some input from CAMHS trained staff is recommended, implementation of this is variable. In some areas, specialist EIP teams have been established within CAMHS, often serving a wider geographical area than generic Tier 2/3 teams and these teams often have expertise in commonly associated problems such as substance misuse.

Early intervention in psychosis (EIP) services

EIP services are a community service approach with focus on the care and treatment of people in the early phase of psychosis and schizophrenia (usually up to 3 years) including the prodromal phase of the disorders. EIP services include multidisciplinary teams that provide the following: (a) designated responsibility for early identification

and therapeutic engagement of young people aged 14 to 35 with first episode psychosis via youth-friendly low stigma channels and using a modified assertive outreach model; (b) family engagement and support as an integral element (particularly relevant for the adolescent group); (c) provision of specialised pharmacological and psychosocial interventions during, or immediately following, first episode psychosis; (d) emphasis on social, educational and vocational recovery; and (e) education of the wider community to reduce obstacles to early engagement in treatment.

It is over 10 years since EIP services first featured in national policy in the *NHS Plan* (Department of Health, 2000) and they have become a valued part of mainstream service provision in England (Department of Health, 2011b; Department of Health, 2012/13) supported by an evidence base for clinical effectiveness and cost benefit (NICE, 2009b). *No Health without Mental Health* (Department of Health, 2011b) highlights that services caring for young people with psychosis need to take a 'life-course view' and shift their focus towards promoting mental health, preventing mental illness, early identification and intervening as soon as mental illness arises.

It is important to recall that EIP services arose from perceived limitations in how generic services responded to first episode psychosis. There was a recognition that the incidence of psychosis increases through mid-adolescence to reach a peak in early adulthood (Kirkbride *et al.*, 2006) and evidence from prospective studies of first episode psychosis that long-term disability develops rapidly in adolescence and in the 3 to 5 years after the formal onset (Birchwood & Macmillan, 1993; Harrison *et al.*, 2001), which made the case for specialised early intervention. Generic services were linked with more adverse pathways to care for people with first episode psychosis, for example treatment delays of 1 to 2 years (Marshall *et al.*, 2005) and high rates of legal detention of about 40% (50% for young black men) (Morgan *et al.*, 2005). Moreover, following a first episode of psychosis the majority of people had disengaged from generic community mental health services within 6 months (Craig *et al.*, 2004). In contrast, evidence was emerging that EIP teams could achieve high levels of engagement and treatment (Craig *et al.*, 2004; Nordentoft *et al.*, 2002).

In a Scottish study examining a large representative group of people under the age of 18 presenting with first episode psychosis to mainstream mental health services (Boeing *et al.,* 2007), out of 103 patients, 86 required admission (80% to adult wards). This group was characterised by high levels of morbidity: serious to pervasive impairment of functioning and relatively high levels of side effects from drugs, negative symptoms, anxiety, and occupational, friendship and family difficulties. Care provision was better for 'clinical' than for 'social' domains and 20% had five or more unmet needs. The authors commented that community care for many young people with psychotic illnesses falls short of guidelines for standards of provision and concluded that these low-prevalence disorders require an assertive multiagency approach in the context of a national planning framework, as set out in development of EIP services in the *NHS Plan* (Department of Health, 2000) some years previously.

Another ambition of the *NHS Plan* (Department of Health, 2000) was to avoid service transition difficulties that impede care pathways between CAMHS and AMHS. These were investigated in the 'TRACK' study (Singh, S. P., *et al.,* 2010), which concluded: 'For the vast majority of service users, transition from CAMHS to AMHS is poorly planned,

poorly executed and poorly experienced. The transition process accentuates pre-existing barriers between CAMHS and AMHS.' The study also highlighted how services struggled to support the developmental needs of young people in areas beyond healthcare transition such as changes in educational and vocational domains, independent living and social and legal status. This study underlines why EIP services were developed to span the ages of 14 to 35, thereby avoiding the potentially problematic transition from CAMHS to AMHS. It is unclear whether this has been universally achieved.

One of the principles of early intervention is the reduction of treatment delay following the first episode of psychosis. DUP has been well studied since the landmark Northwick Park study (Johnstone *et al.,* 1986) first revealed that longer delays in treatment predicted poorer outcome, which was subsequently confirmed by a systematic review (Marshall *et al.,* 2005). Primary care faces challenges in initiating these pathways for a relatively rare but serious condition, however, it appears that delays within primary care form only a small proportion of overall DUP, considerably less than delays both in initial help seeking and within mental health services (Brunet *et al.,* 2007). A systematic review conducted by the NCCMH (Bird *et al.,* 2010) found that EIP services improved outcomes associated with DUP, including reduced hospital admission, relapse rates and symptom severity, and improved access to and engagement with treatment. The authors concluded: 'For people with early psychosis, early intervention services appear to have clinically important benefits over standard care. Including CBT and family intervention within the service may contribute to improved outcomes in this critical period.'

In summary, a specialist early intervention approach may offer advantages over generic community services such as CAMHS in meeting the complex needs of young people with these potentially disabling disorders. Locally integrated care pathways must avoid unhelpful service transitions if treatment delay is to be reduced in the critical early phase.

CAMHS Tier 4

Inpatient services can form an important part of the care for children and young people with psychosis and schizophrenia and should be part of a comprehensive care package. With the greater emphasis on community treatments and EIP services, fewer patients require admission to hospital. In instances where hospitalisation is required, an age-appropriate bed is sometimes, but not always, available 24 hours a day, 7 days a week for emergency care. This is particularly important for those young people who have severe psychotic experiences, those who are behaviourally disturbed, or those who present a risk to themselves or others. Provision for patients with acute psychosis secondary to drug intoxication is also necessary. The unit should ideally cater for a particular age group (young children or adolescents) and staff need to be trained to work with this age group. It is important that the unit is developmentally appropriate, adopting a proactive family style that involves educating and supporting parents, siblings and other family members. An emphasis upon medical care, initially to include full physical examination, and facilities for examination and assessment (for example, full blood count, drug screen, urine analysis and ECG) is necessary because patients admitted in an acutely disturbed state require considerably high levels of nursing care, a containing environment and, in some instances, access to more secure and intensive

provision. Occasionally it is necessary to use the *Mental Health Act 2007* (HMSO, 2007) to mandate treatment and therefore staff working in hospital settings need to be familiar with its operation and safeguards.

A full range of treatments may include psychopharmacology, CBT and family intervention (including psychoeducation for parents/carers and the child/young person). Admissions need to be kept as short as possible and sometimes, but not always, there is an emphasis upon active engagement of an EIP team and outreach services with a phased discharge. Children and young people with psychosis and schizophrenia may be subject to the CPA (England) or the C&TP (Wales) to ensure continuity of care. The CPA or C&TP documentation should include an up-to-date risk assessment and details on medication and emergency contact numbers.

During the inpatient stay the child or young person needs age appropriate education and, given the metabolic side effects of antipsychotics, nutritional advice and an emphasis upon physical activity. For schizophrenia, in particular, which can be associated with some cognitive impairment, access to psychological input and a full psychometric assessment is helpful. The latter may also be useful in aiding school reintegration or vocational training, particularly if the child or young person cannot perform at levels previously attained. As with all parts of the treatment approach, emphasis should be upon realistic but optimistic collaborative goals with the child or young person and their parents or carers.

The interface between primary and secondary care

The distress of a first episode of psychosis will lead to many children and young people seeking help from their GP, usually with their parents or carers. The nature of their presentation, the symptomatology and changes in psychosocial functioning, are in essence similar to how an adult may present. However, the low frequency of such encounters may make recognition difficult for a GP. Given that about 20% of first episodes of psychosis occur in those aged under 20 and 5% under the age of 16 years (Hollis, 2003), then a GP might expect to see an adolescent presentation about once every 5 years. This rarity of presentation is set against a backdrop of increasing psychological distress through adolescence, with 20% experiencing a diagnosable depressive episode by age 18 (Lewinsohn *et al.,* 1993). It has been estimated that more than a third of GP attendees aged 13 to 16 have a current or recent mental health problem (Kramer & Garralda, 2000). Concerns over acquiring a psychiatric 'label' or receiving treatment may explain why 50% of young people who perceived themselves to have serious psychological difficulties avoided raising these issues in the consultation, thereby potentially impeding recognition (Martinez *et al*., 2006).

Presentations of psychosis in young people should also be seen within the wider context of how young people seek help for health problems. About 75% of young people attend their GP at least once each year (Kari *et al*., 1997) and for those with psychological difficulties the GP is the most consulted healthcare professional (Kramer & Garralda, 1998). Moreover, parents or carers often accompany the young person or present themselves to the GP with a related problem; one study showed that 77.5% of young people who consulted their GP for a psychological difficulty were accompanied by a parent (Martinez *et al*., 2006).

The challenge, therefore, for GPs in promptly detecting psychosis in adolescence is more from its rarity rather than reluctance by young people and their families or carers to seek help for psychological concerns. Moreover, serious disorders like psychosis often start off like milder and far more common mental health problems, and rarely present with clear-cut psychotic symptoms. When asked how to improve detection of emerging first episode psychosis, GPs requested better collaboration with specialist services and low-threshold referral services rather than educational programmes (Simon *et al*., 2005).

An additional issue for this young population is that many will also be embarking on a path towards serious physical illness, including cardiovascular disease (see Chapters 2 and 7). Despite these potential physical consequences, there is evidence that systematic screening and monitoring may often be lacking for children and young people with psychosis (Morrato *et al*., 2010), indicating a need to agree and allocate specific responsibilities for primary care and specialist services. The opportunity lies in altering the current trajectory towards physical ill health by early recognition and intervention to reduce cardiovascular risk rather than waiting until disease endpoints are reached later in life.

Other service settings

While most children and young people with suspected or actual psychosis will be living at home and receiving services from CAMHS or EIP services (dependent upon local provision), there will be a few living in some form of alternative residential setting. This can introduce a variety of complexities.

First, it is important to ascertain who can exercise parental responsibility for the child or young person as it may not be the adult accompanying them. Second, the child or young person may be at some distance from their family and local responsible health, education and social care providers and commissioners; it is important to correctly identify these for future care planning. Third, residential providers vary widely in their knowledge and skills regarding mental health problems in children and young people and it is important that the clinician assesses this and pitches their approach and interventions accordingly.

Children and young people living in custody or in local authority secure care can have particularly elevated rates of mental health problems and risk factors for psychosis. Mental health 'in-reach' into secure care or custodial settings varies markedly and it is sometimes necessary to consider transfer to a hospital for assessment and/or treatment. In England there is a network of specially commissioned secure inpatient mental health beds (NHS Specialised Services, 2012) and arrangements for rapid transfer from custody to one of these beds (Department of Health, 2011c).

Transition to adult services

Young people with psychosis and schizophrenia often face problems when moving from CAMHS to AMHS. The result of a poorly developed transition is that sometimes young people are left with no help when they need it most and have no one to turn to in a crisis. Sometimes the gains made from contact with CAMHS are diminished or lost as a result of inadequate or failed transition to adult services. The negative impact of

an unsuccessful transition can also affect parents, carers and the whole family. Young people and their parents have been clear in saying that they want to be involved in transition planning (Kane, S., 2008), reflecting the Department of Health's guidance on transition support (Department of Health, 2006b).

Young people aged 16 and 17 are making the transition to adulthood and therefore may have a range of needs, including those related to living independently and developing as young adults. Regardless of which service a young person may be moving to, professionals often try and get to know them before the transition, and plans may be in place to ensure that the transition is as smooth and as seamless as possible.

4.4.2 Evidence summary

Over the past decade, various service innovations have occurred including the development of EIP teams for people aged 14 to 35 years. Within these teams some input from trained CAMHS staff is recommended, but not always provided. A specialist early intervention approach may offer advantages over generic community services in meeting the complex needs of children and young people with psychosis and schizophrenia and it is important that they routinely receive care and treatment from a single multidisciplinary team and are not passed from one team to another unnecessarily.

For some children and young people, inpatient services may be required and can form an important part of a comprehensive care package. When a child or young person needs hospital care, it should be provided in a setting appropriate to their age and developmental level. In addition, children and young people should have access to a wide range of meaningful and culturally appropriate occupations and activities, including exercise, and for those of compulsory school age, a full educational programme should be accessible while in hospital.

Children and young people with psychosis and schizophrenia often face problems when moving from CAMHS to AMHS. Withdrawal and ending of treatment or services, and transition from one service to another, may evoke strong emotions and reactions in this population and their parents or carers and therefore transition should be planned and structured carefully, and discussed with the child or young person and their parents or carers.

Finally, children and young people with psychosis and schizophrenia are at serious risk for physical problems such as cardiovascular disease. Promotion of good physical health, including healthy eating, exercise and smoking cessation, as well as physical health monitoring by GPs and other primary healthcare professionals, is crucial.

4.5 EXPERIENCE OF CARE

The *Service User Experience in Adult Mental Health* guidance (NICE, 2011a) sets out the principles for improving the experience of care for people using adult NHS mental health services. The guidance examined the evidence for improving experience of mental health services in seven main areas: (1) access to community care; (2)

assessment (non-acute); (3) community care; (4) assessment and referral in crisis; (5) hospital care; (6) discharge and transfer of care; and (7) detention under the *Mental Health Act 2007* (HMSO, 2007).

While it is expected that health and social care professionals will consult *Service User Experience in Adult Mental Health* to improve all aspects of experience across the care pathway for people using adult NHS mental health services, there may be specific areas of concern for children and young people that are not covered by this guidance and will need to be addressed by the current guideline, such as the role of primary care in treating severe mental illness. The purpose of this chapter is to assess the relevance of particular recommendations from both the *Service User Experience in Adult Mental Health* guidance and also the adult *Schizophrenia* guideline (NICE, 2009a) for children and young people with psychosis and schizophrenia and, if necessary, adapt them for use in the context of the current guideline using the method set out in Chapter 3, Section 3.7.

4.5.1 Method

A topic group of GDG members and NCCMH staff was convened consisting of four representatives from service user and carer organisations and five NCCMH staff members (the facilitator, systematic reviewer, research assistant, senior editor and project manager of the guideline). The principal aims of the topic group were to:

- identify key issues and areas of concern for children and young people with psychosis and schizophrenia using NHS mental health services
- review the underlying evidence and recommendations from *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) for their relevance to children and young people with psychosis and schizophrenia, bearing in mind the identified key issues and areas of concern.

The topic group also considered the narrative review of the evidence for access to and delivery of services for children and young people with psychosis and schizophrenia outlined in Section 4.4.

The topic group discussion was fed back to the GDG in a plenary session. The GDG took into account the key issues and areas of concern and the recommendations from *Service User Experience in Adult Mental Health* and *Schizophrenia* identified by the topic group as being relevant to children and young people with psychosis and schizophrenia, and adapted the recommendations for use in the context of the current guideline using the method set out in Chapter 3, Section 3.7.

4.5.2 Key issues and areas of concern in children and young people's experience of care

The service user and carer representatives discussed what they judged to be some of the key issues and areas of concern for children and young people with psychosis and

schizophrenia using NHS mental health services. They drew on their own experience, considered the reviews in Section 4.4 and collectively identified the following eight key issues and areas of concern:

(1) Stigma:
- the impact of clinical language and the clinical setting
- the need to recognise that stigma can come from medical models.

(2) Communication:
- the link between stigma and clinical explanations of psychosis and schizophrenia (and the need to present information in a way that is normalising rather than pathologising)
- the need for children and young people to be fully informed of the choice of interventions available and their diagnosis
- the need to communicate regularly in more than one format (that is, not just written information)
- the complexity of information sharing and issues of confidentiality
- the need to provide the opportunity for the child or young person to communicate their priorities for their care from the outset
- the need for transparency regarding the uncertainty around causes of psychosis.

(3) Involvement of parents, carers and other family members:
- parents should be involved as a matter of course in the care of younger children except in particular circumstances (for example, there are signs of abuse)
- young people who are of a sufficient developmental level should be asked if they would like their parents or carers involved.

(4) Access to emergency/crisis teams:
- there is a gap in provision of crisis services
- the need to provide access to age appropriate settings that are geographically close to parents, carers and friends
- the need to provide home treatment.

(5) Education:
- assessment of needs
- the need to support children and young people to be in education.

(6) Transition:
- continuity of care
- the need for clear handover.

(7) Hospital care:
- the need to provide a wide range of meaningful activities, education and lifestyle management
- the need to prepare children and young people for what can happen on a ward (including rules, procedures and physical restraint)
- the need to provide a debrief following an incident, such as restraint of another service user.

(8) Physical health needs:
- the need to assess and monitor these from the outset

– the need to provide children and young people with education regarding their physical health.

4.5.3 Review of existing guidelines

Service User Experience in Adult Mental Health

The GDG judged, based on their expert opinion and the reviews conducted in Section 4.4, that although the *Service User Experience in Adult Mental Health* guidance (NCCMH, 2012; NICE, 2011a) was for adult service users, a number of areas from that guideline applied to the experience of care of children and young people with psychosis and schizophrenia. The topic group appraised the existing guidelines and judged that they addressed some of the key issues and concerns they had identified in Section 4.5.2, including: relationships and communication; providing information; avoiding stigma and promoting social inclusion; decisions and capacity; and involving families and carers. Some recommendations required only limited adaptation. Several other recommendations required more extensive adaptation to be relevant to the current context. The topic group discussed ways of adapting the recommendations and the entire GDG then adapted the recommendations based on the methodological principles outlined in Chapter 3 and taking into consideration the narrative review conducted in Section 4.4; in all cases the adaptation retained the original meaning and intent of the recommendations.

Table 8 contains the original recommendations from *Service User Experience in Adult Mental Health* (NICE, 2011a) in column 1 and the adapted recommendations in column 2. Where recommendations required adaptation, the rationale is provided in column 3. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in *Service User Experience in Adult Mental Health* (NICE, 2011a). In column 2 the numbers in brackets following the recommendation refer to Section 4.7 in this guideline.

Schizophrenia

The topic group and GDG also appraised the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) and judged that a number of areas from that guideline, which were not covered by *Service User Experience in Adult Mental Health*, applied to the experience of care of children and young people with psychosis and schizophrenia and addressed some of the key issues and concerns they had identified in Section 4.5.2, including avoiding stigma and promoting social inclusion, and addressing physical health needs. Some recommendations required only limited adaptation. Several other recommendations required more extensive adaptation to be relevant to the current context. The topic group discussed ways of adapting the recommendations and the entire GDG then adapted the recommendations based on the methodological principles outlined in Chapter 3 and considering the narrative review conducted in Section 4.4; in all cases the adaptation retained the original meaning and intent of the recommendations.

Table 8: Adapted and incorporated recommendations from *Service User Experience in Adult Mental Health* (NICE, 2011a) for experience of care

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	Recommendation following adaptation for this guideline	Reasons for adaptation	Key issue(s) identified by topic group
1.1.13 Consider service users for assessment according to local safeguarding procedures for vulnerable adults if there are concerns regarding exploitation or self-care, or if they have been in contact with the criminal justice system.	Consider children and young people with psychosis or schizophrenia for assessment according to local safeguarding procedures if there are concerns regarding exploitation or self-care, or if they have been in contact with the criminal justice system. (4.7.1.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia with no significant adaptation required.	–
1.4.7 Health and social care providers should ensure that service users: • can routinely receive care and treatment from a single multidisciplinary community team • are not passed from one team to another unnecessarily • do not undergo multiple assessments unnecessarily.	Health and social care providers should ensure that children and young people with psychosis or schizophrenia: • can routinely receive care and treatment from a single multidisciplinary community team • are not passed from one team to another unnecessarily • do not undergo multiple assessments unnecessarily. (4.7.1.4)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of transition (in terms of continuity of care), with no significant adaptation required.	• Transition

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
1.1.1 Work in partnership with people using mental health services and their families or carers. Offer help, treatment and care in an atmosphere of hope and optimism. Take time to build trusting, supportive, empathic and non-judgemental relationships as an essential part of care.	Work in partnership with children and young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity and parents or carers. Offer help, treatment and care in an atmosphere of hope and optimism. Take time to build trusting, supportive, empathic and non-judgemental relationships as an essential part of care. (4.7.2.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of communication (in terms of it being the bedrock of a good relationship). This recommendation was adapted because the GDG wished to stress that healthcare professionals need to take account of the child or young person's developmental level, emotional maturity and cognitive capacity when working in partnership with them.	• Communication

1.1.2 When working with people using mental health services: • aim to foster their autonomy, promote active participation in treatment decisions and support self-management • maintain continuity of individual therapeutic relationships wherever possible • offer access to a trained advocate.	When working with children and young people with psychosis or schizophrenia: • aim to foster autonomy, promote active participation in treatment decisions, and support self-management and access to peer support in children and young people of an appropriate developmental level, emotional maturity and cognitive capacity • maintain continuity of individual therapeutic relationships wherever possible • offer access to a trained advocate. (4.7.2.2)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of communication (in terms of it being the bedrock of a good relationship). This recommendation was adapted because the GDG wished to stress that healthcare professionals need to take account of the child or young person's developmental level, emotional maturity and cognitive capacity, particularly when considering their autonomy and ability to make decisions about their treatment. In their expert opinion the GDG judged that children and young people would benefit from access to peer support.	• Communication

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
1.1.4 When working with people using mental health services: • make sure that discussions take place in settings in which confidentiality, privacy and dignity are respected • be clear with service users about limits of confidentiality (that is, which health and social care professionals have access to information about their diagnosis and its treatment and in what circumstances this may be shared with others).	When working with children and young people with psychosis or schizophrenia and their parents or carers: • make sure that discussions take place in settings in which confidentiality, privacy and dignity are respected • be clear with the child or young person and their parents or carers about limits of confidentiality (that is, which health and social care professionals have access to information about their diagnosis and its treatment and in what circumstances this may be shared with others). (4.7.2.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of communication, with no significant adaptation required.	• Communication

1.1.14 Discuss with the person using mental health services if and how they want their family or carers to be involved in their care. Such discussions should take place at intervals to take account of any changes in circumstances, and should not happen only once. As the involvement of families and carers can be quite complex, staff should receive training in the skills needed to negotiate and work with families and carers, and also in managing issues relating to information sharing and confidentiality.	Discuss with young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity how they want their parents or carers to be involved in their care. Such discussions should take place at intervals to take account of any changes in circumstances, including developmental level, and should not happen only once. (4.7.2.4)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of involvement of parents or carers. This recommendation was adapted to take account of young people's developmental level, emotional maturity and cognitive capacity. The last sentence of the original recommendation was removed because it had been covered by another recommendation developed by the GDG (4.7.3.1).	• Involvement of parents or carers
1.1.16 If the person using mental health services wants their family or carers to be involved, give the family or carers verbal and written information about:	Advise parents and carers about their right to a formal carer's assessment of their own physical and mental health needs, and explain how to access this. (4.7.2.5)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of	• Involvement of parents or carers

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
• the mental health problem(s) experienced by the service user and its treatment, including relevant 'Understanding NICE guidance' booklets • 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.		involvement of parents or carers. This recommendation was adapted because, due to the inclusion of other recommendations on working with parents and carers and provision of information from *Service User Experience in Adult Mental Health,* some were restructured. The first two bullet points were included in a separate recommendation (4.7.3.4).	
1.1.5 When working with people using mental health services: • ensure that comprehensive written information about the nature of, and treatments and services for, their mental health problems is available in an appropriate language or format	Provide children and young people with psychosis or schizophrenia and their parents or carers, comprehensive written information about: • the nature of, and interventions for, psychosis and schizophrenia (including biomedical and psychosocial perspectives on causes	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issues of communication and	• Communication • Involvement of parents or carers

including any relevant 'Understanding NICE guidance' booklets • ensure that comprehensive information about other support groups, such as third sector, including voluntary, organisations, is made available.	and treatment) in an appropriate language or format, including any relevant 'Information for the public' booklets • support groups, such as third sector, including voluntary, organisations. (4.7.3.4)	involvement of parents or carers. This recommendation was adapted to account for the specific nature of the information required for children and young people with psychosis or schizophrenia and their parents or carers, which the GDG judged should include biomedical and psychosocial perspectives on causes and treatment. In addition, the title of the NICE booklets was amended to reflect a change in terminology.	
1.1.6 Ensure that you are: • familiar with local and national sources (organisations and websites) of information and/or support for people using mental health services • able to discuss and advise how to access these resources • able to discuss and actively support service users to engage with these resources.	Ensure that you are: • familiar with local and national sources (organisations and websites) of information and/or support for children and young people with psychosis or schizophrenia and their parents or carers • able to discuss and advise how to access these resources • able to discuss and actively support children and young people and their parents or carers to engage with these resources. (4.7.3.5)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of communication (provision of information), with no significant adaptation required.	• Communication

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
1.4.1 When communicating with service users use diverse media, including letters, phone calls, emails or text messages, according to the service user's preference.	When communicating with a child or young person with psychosis or schizophrenia, use diverse media, including letters, phone calls, emails or text messages, according to their preference. (4.7.3.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of communication (the range of media that can be used), with no significant adaptation required.	• Communication
1.3.5 Copy all written communications with other health or social care professionals to the service user at the address of their choice, unless the service user declines this.	Copy all written communications with other health or social care professionals to the child or young person and/or their parents or carers at the address of their choice, unless this is declined. (4.7.3.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of communication, with no significant adaptation required.	• Communication

1.1.7 When working with people using mental health services: • take into account that stigma and discrimination are often associated with using mental health services • be respectful of and sensitive to service users' gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability • be aware of possible variations in the presentation of mental health problems in service users of different genders, ages, cultural, ethnic, religious or other diverse backgrounds.	When working with children and young people with psychosis or schizophrenia and their parents or carers: • take into account that stigma and discrimination are often associated with using mental health services • be respectful of and sensitive to children and young people's gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability • be aware of possible variations in the presentation of mental health problems in children and young people of different genders, ages, cultural, ethnic, religious or other diverse backgrounds. (4.7.4.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of stigma, with no significant adaptation required.	• Stigma
1.2.5 Local mental health services should work with primary care and local third sector, including voluntary, organisations to ensure that:	Local mental health services should work with primary care, other secondary care and local third sector, including voluntary, organisations to ensure that:	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it	• Stigma

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
• all people with mental health problems have equal access to services based on clinical need and irrespective of gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability • services are culturally appropriate.	• all children and young people with psychosis or schizophrenia have equal access to services based on clinical need and irrespective of gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability • services are culturally appropriate. (4.7.4.5)	pertained to the key issue of stigma, with no significant adaptation required.	
1.7.1 Anticipate that withdrawal and ending of treatments or services, and transition from one service to another, may evoke strong emotions and reactions in people using mental health services. Ensure that:	Anticipate that withdrawal and ending of treatments or services, and transition from one service to another, may evoke strong emotions and reactions in children and young people with psychosis or schizophrenia and their parents or carers. Ensure that:	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issues of communication and transition.	• Communication • Transition

• such changes, especially discharge, are discussed and planned carefully beforehand with the service user and are structured and phased • the care plan supports effective collaboration with social care and other care providers during endings and transitions, and includes details of how to access services in times of crisis • when referring a service user for an assessment in other services (including for psychological treatment), they are supported during the referral period and arrangements for support are agreed beforehand with them.	• such changes, especially discharge and transfer from CAMHS to adult services, or to primary care, are discussed and planned carefully beforehand with the child or young person and their parents or carers, and are structured and phased • the care plan supports effective collaboration with social care and other care providers during endings and transitions, and includes details of how to access services in times of crisis • when referring a child or young person for an assessment in other services (including for psychological interventions), they are supported during the referral period and arrangements for support are agreed beforehand with them. (4.7.5.1)	Based on the expert opinion of the GDG, this recommendation was adapted to account for the possible transfer of young people from CAMHS to AMHS or discharge to primary care.	
1.3.3 When carrying out an assessment: • ensure there is enough time for the service user to describe and discuss their problems	When carrying out an assessment: • ensure there is enough time for: – the child or young person and their parents or carers to describe and discuss their problems	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or	• Communication

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	Recommendation following adaptation for this guideline	Reasons for adaptation	Key issue(s) identified by topic group
• allow enough time towards the end of the appointment for summarising the conclusions of the assessment and for discussion, with questions and answers • explain the use and meaning of any clinical terms used • explain and give written material in an accessible format about any diagnosis given • give information about different treatment options, including drug and psychological treatments, and their side effects, to promote discussion and shared understanding • offer support after the assessment, particularly if sensitive issues, such as childhood trauma, have been discussed.	– summarising the conclusions of the assessment and for discussion, with questions and answers • explain and give written material in an accessible format about any diagnosis given • give information about different treatment options, including pharmacological and psychological interventions, and their benefits and side effects, to promote discussion and shared understanding • offer support after the assessment, particularly if sensitive issues, such as childhood trauma, have been discussed. (4.7.7.1)	schizophrenia because it pertained to the key issue of communication (the importance of discussion and provision of information during the assessment process). The bullet point about explaining the use and meaning of any clinical terms used was omitted from the adapted recommendation because it had been covered in another recommendation (4.7.3.3). In the third bullet point, 'benefits' was added because the GDG wished to emphasise that healthcare professionals should discuss in a balanced way the evidence supporting treatment interventions. No other significant adaptation was required.	

1.4.2 Develop care plans jointly with the service user, and: • include activities that promote social inclusion such as education, employment, volunteering and other occupations such as leisure activities and caring for dependants • provide support to help the service user realise the plan • give the service user an up-to-date written copy of the care plan, and agree a suitable time to review it.	Develop a care plan with the parents or carers of younger children, or jointly with the young person and their parents or carers, as soon as possible, and: • include activities that promote physical health and social inclusion, especially education, but also employment, volunteering and other occupations such as leisure activities • provide support to help the child or young person and their parents or carers realise the plan • give an up-to-date written copy of the care plan to the young person and their parents or carers if the young person agrees to this; give a copy of the care plan to the parents or carers of younger children; agree a suitable time to review it • send a copy to the primary healthcare professional who made the referral. [4.7.7.4]	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because part of it pertained to the key issue of communication (dissemination of the care plan) and education. This recommendation was adapted because the GDG wished to emphasise that the activities should include those that promote physical health because physical health problems are a particular issue in people with schizophrenia. The phrase 'caring for dependants' was removed as it was felt that this was unlikely to be an activity that many children and young	• Communication • Education

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
		people with psychosis or schizophrenia would be involved in. The third bullet was adapted to include the parents or carers of younger children and also make it clear that older children may need to give their consent to involve parents and carers. Based on their expert opinion, the GDG also judged that it was important that a copy of the care plan should be sent to the primary care professional who made the referral because they would be responsible for the child or young person's future physical healthcare.	

1.4.3 Support service users to develop strategies, including risk- and self-management plans, to promote and maintain independence and self-efficacy, wherever possible. Incorporate these strategies into the care plan.	Support children and young people to develop strategies, including risk- and self-management plans, to promote and maintain independence and self-efficacy, wherever possible. Incorporate these strategies into the care plan. (4.7.7.5)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia with no significant adaptation required.	-
1.4.5 For people who may be at risk of crisis, a crisis plan should be developed by the service user and their care coordinator, which should be respected and implemented, and incorporated into the care plan. The crisis plan should include: • possible early warning signs of a crisis and coping strategies • support available to help prevent hospitalisation • where the person would like to be admitted in the event of hospitalisation • the practical needs of the service user if they are admitted to hospital (for example, childcare or the care of other dependants, including pets)	If the child or young person is at risk of crisis, develop a crisis plan with the parents or carers of younger children, or jointly with the young person and their parents or carers, and with their care coordinator. The plan should be respected and implemented, incorporated into the care plan and include: • possible early warning signs of a crisis and coping strategies • support available to help prevent hospitalisation • where the child or young person would like to be admitted in the event of hospitalisation • definitions of the roles of primary and secondary care professionals and the degree to which parents or carers are involved	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of access to emergency/crisis teams. Adaptations were made to this recommendation to make it pertinent to children and young people. Based on expert opinion, the GDG judged that children and young people were unlikely to have the practical needs listed in the original recommendation. The bullet point on advance decisions and statements was removed	• Access to emergency/ crisis teams

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
• details of advance statements and advance decisions • whether and the degree to which families or carers are involved • information about 24-hour access to services • named contacts.	• information about 24-hour access to services • the names of key clinical contacts. (4.7.7.6)	because these do not apply to children and young people under the age of 18. The GDG did however wish to make an addition to this recommendation to specify that primary and secondary care professionals should be involved given that the child or young person's care was likely to be shared between them.	
1.3.4 If a service user is unhappy about the assessment and diagnosis, give them time to discuss this and offer them the opportunity for a second opinion.	If the child or young person and/or their parent or carer is unhappy about the assessment, diagnosis or care plan, give them time to discuss this and offer them the opportunity for a second opinion. (4.7.7.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia with no significant adaptation required.	–

1.5.5 When a person is referred in crisis they should be seen by specialist mental health secondary care services within 4 hours of referral.	When a child or young person is referred in crisis they should be seen by specialist mental health secondary care services within 4 hours of referral. (4.7.9.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of access to emergency/crisis teams, with no significant adaptation required.	• Access to emergency/ crisis teams
1.5.8 To avoid admission, aim to: • explore with the service user what support systems they have, including family, carers and friends • support a service user in crisis in their home environment • make early plans to help the service user maintain their day-to-day activities, including work, education, voluntary work, and other occupations such as caring for dependants and leisure activities, wherever possible.	To avoid admission, aim to: • explore with the child or young person and their parents or carers what support systems they have, including other family members and friends • support a child or young person in crisis and parents or carers in their home environment • make early plans to help the child or young person maintain their day-to-day activities, including education, work, voluntary work and other occupations and leisure activities, wherever possible. (4.7.9.2)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of access to emergency/crisis teams, with no significant adaptation required.	• Education • Access to emergency/ crisis teams

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
1.5.9 At the end of a crisis assessment, ensure that the decision to start home treatment depends not on the diagnosis, but on: • the level of distress • the severity of the problems • the vulnerability of the service user • issues of safety and support at home • the person's cooperation with treatment.	At the end of a crisis assessment, ensure that the decision to start home treatment depends not on the diagnosis, but on: • the level of distress • the severity of the problems • the vulnerability of the child or young person and issues of safety and support at home • the child or young person's cooperation with treatment. (4.7.9.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of access to emergency/crisis teams with no significant adaptation required.	• Access to emergency/ crisis teams
1.5.10 Consider the support and care needs of families or carers of service users in crisis. Where needs are identified, ensure they are met when it is safe and practicable to do so.	Consider the support and care needs of parents or carers of children or young people in crisis. Where needs are identified, ensure they are met when it is safe and practicable to do so. (4.7.9.4)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of access to emergency/crisis teams, with no significant adaptation required.	• Involvement of parents or carers • Access to emergency/ crisis teams

1.6.2 Give verbal and written information to service users, and their families or carers where agreed by the service user, about: • the hospital and the ward in which the service user will stay • treatments, activities and services available • expected contact from health and social care professionals • rules of the ward (including substance misuse policy) • service users' rights, responsibilities and freedom to move around the ward and outside • meal times • visiting arrangements. Make sure there is enough time for the service user to ask questions.	Give verbal and written information to children and young people with psychosis or schizophrenia admitted to hospital, and their parents or carers, about: • the hospital and the ward in which the child or young person will stay • treatments, activities and services available • expected contact from health and social care professionals • rules of the ward (including substance misuse policy) • their rights, responsibilities and freedom to move around the ward and outside • meal times • visiting arrangements. Make sure there is enough time for the child or young person and their parents or carers to ask questions. (4.7.10.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issues of hospital care and communication (provision of information) with no significant adaptation required.	• Communication • Hospital care
1.6.3 Undertake shared decision-making routinely with service users in hospital, including, whenever possible, service users who are subject to the Mental Health Act (1983; amended 1995 and 2007).	Undertake shared decision-making routinely with children or young people in hospital who are of an appropriate developmental level, emotional maturity and cognitive capacity, including, whenever	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it	• Hospital care

Continued

Table 8: (*Continued*)

Original recommendation from *Service User Experience in Adult Mental Health* (NICE, 2011a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**	**Key issue(s) identified by topic group**
	possible, those who are subject to the Mental Health Act (1983; amended 1995 and 2007).* Include their parents or carers if appropriate. (4.7.10.4) *(HMSO, 2007)	pertained to the key issue of hospital care. The recommendation was adapted because the GDG wished to stress that the child or young person's developmental level, emotional maturity and cognitive capacity should be taken into account when undertaking shared decision-making and that parents or carers should be included if appropriate.	
1.6.9 Ensure that service users in hospital have access to a wide range of meaningful and culturally appropriate occupations and activities 7 days per week, and not restricted to 9am to 5pm. These should include creative and leisure activities, exercise, self-care and	Ensure that children and young people in hospital continue to have access to a wide range of meaningful and culturally appropriate occupations and activities 7 days per week, and not restricted to 9am to 5pm. These should include creative and leisure activities, exercise, self-care and	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of hospital care, with no significant adaptation required.	Hospital care

community access activities (where appropriate). Activities should be facilitated by appropriately trained health or social care professionals.	community access activities (where appropriate). Activities should be facilitated by appropriately trained educational, health or social care professionals. (4.7.10.6)		
1.6.12 Service users receiving community care before hospital admission should be routinely visited while in hospital by the health and social care professionals responsible for their community care.	Children and young people receiving community care before hospital admission should be routinely visited while in hospital by the health and social care professionals responsible for their community care. (4.7.10.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of transition, with no significant adaptation required.	• Transition

Table 9 contains the original recommendations from *Schizophrenia* (NICE, 2009a) in column 1 and the adapted recommendations in column 2. Where recommendations required adaptation, the rationale is provided in column 3. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in the *Schizophrenia* guideline (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 4.7 in this guideline.

4.5.4 Evidence summary

Service User Experience in Adult Mental Health

Following review of the underlying evidence and recommendations in *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a), 27 recommendations from that guidance were considered relevant and important to the experience of care of children and young people with psychosis and schizophrenia. Twenty required only minor changes to make them relevant to the current context, while seven needed more substantive adaptation.

Based on the expert opinion of the GDG, twelve recommendations were relevant to the key issue of 'communication' because they covered such areas as: provision of information about the disorders and treatments and support for them; the need for health and social care professionals to involve people in discussions about their care and treatment, and ensuring that such discussions take place in an environment where confidentiality, privacy and dignity can be respected; ways of communicating with people (using diverse media); and ensuring that other health and social care professionals are informed about the care plan, where appropriate.

Five recommendations relating to the issue of 'access to emergency/crisis teams' were deemed by the GDG to be appropriate to the care of children and young people with psychosis and schizophrenia, including developing a crisis plan, referral in crisis, strategies to avoid admission to hospital, crisis assessment, and the support needs of parents or carers.

The GDG considered that three recommendations relating to hospital care were also relevant to children and young people with psychosis and schizophrenia, including providing information to people admitted to hospital about the ward, activities that should be available while in hospital, and shared decision-making for people admitted under the *Mental Health Act 2007* (HMSO, 2007). The GDG also considered the narrative review set out in Section 4.4 regarding hospital care.

Four recommendations were identified as being relevant to the experience of parents and carers, particularly their involvement in the child or young person's treatment and care. The topic group advised that involvement of parents or carers should be the norm in the case of younger children, but might need to be negotiated in older children of an appropriate developmental level, emotional maturity and cognitive capacity. Mindful that parents or carers would have their own needs, the GDG identified the relevance of the recommendation on advising parents and carers of their right to a formal carer's assessment.

Table 9: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for experience of care

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation	Key issue(s) identified by topic group
1.1.2.3 Healthcare professionals working with people with schizophrenia should ensure they are competent in: • assessment skills for people from diverse ethnic and cultural backgrounds • using explanatory models of illness for people from diverse ethnic and cultural backgrounds • explaining the causes of schizophrenia and treatment options • addressing cultural and ethnic differences in treatment expectations and adherence • addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the causes of abnormal mental states	Health and social care professionals working with children and young people with psychosis or schizophrenia and their parents or carers should have competence in: • assessment skills for people from diverse ethnic and cultural backgrounds • using explanatory models of illness for people from diverse ethnic and cultural backgrounds • explaining the possible causes of psychosis and schizophrenia and treatment options • addressing cultural and ethnic differences in treatment expectations and adherence • addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the possible causes of mental health problems	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issues of communication and stigma. This recommendation was adapted to remove the penultimate bullet point as this had been covered by another recommendation (4.7.3.1). The GDG preferred the term 'mental health problems' to 'abnormal mental states' because they felt it was less stigmatising.	• Communication • Stigma

Continued

Table 9: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation	Key issue(s) identified by topic group
• negotiating skills for working with families of people with schizophrenia • conflict management and conflict resolution.	• conflict management and conflict resolution. (4.7.4.3)		
1.1.2.2 Healthcare professionals inexperienced in working with people with schizophrenia from diverse ethnic and cultural backgrounds should seek advice and supervision from healthcare professionals who are experienced in working transculturally.	Health and social care professionals inexperienced in working with children and young people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds, and their parents or carers, should seek advice and supervision from healthcare professionals who are experienced in working transculturally. (4.7.4.4)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of stigma, with no significant adaptation required.	• Stigma
1.1.2.4 Mental health services should work with local voluntary BME [black and minority ethnic] groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to people from diverse ethnic and cultural backgrounds.	Mental health services should work with local voluntary black and minority ethnic groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to children and young people from diverse ethnic and cultural backgrounds. (4.7.4.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of stigma, with no significant adaptation required.	• Stigma

1.1.4.2 Routinely monitor for other coexisting conditions, including depression and anxiety, particularly in the early phases of treatment.	Routinely monitor for other coexisting mental health problems, including depression and anxiety, and substance misuse, particularly in the early phases of treatment. (4.7.7.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, and adapted it to include substance misuse, which the GDG, based on their expert opinion, considered to be a particular issue in children and young people with psychosis or schizophrenia.	–
1.3.3.5 Follow the recommendations in 'Self-harm' (NICE clinical guideline 16) when managing acts of self-harm in people with schizophrenia.	Follow the recommendations in 'Self-harm' (NICE clinical guideline 16)* when managing acts of self-harm in children and young people with psychosis or schizophrenia who are 8 years or over. (4.7.9.5) *(NICE, 2004a)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, and adapted it to make it clear that *Self-Harm* (NICE, 2004a) only covered children and young people who were 8 years or over.	–
1.4.1.1 Develop and use practice case registers to monitor the physical and mental health of people with schizophrenia in primary care.	Develop and use practice case registers to monitor the physical and mental health of children and young people with psychosis or schizophrenia in primary care. (4.7.12.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of physical health needs, with no significant adaptation required.	• Physical health needs

Continued

Table 9: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation	Key issue(s) identified by topic group
1.4.1.4 Treat people with schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance*. *See 'Lipid modification' (NICE clnical guideline 67), 'Type 1 diabetes' (NICE clinical guideline 15), 'Type 2 diabetes' (NICE clinical guideline 66). Further guidance about treating cardiovascular disease and diabetes is available from www.nice.org.uk	Treat children and young people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care. Use appropriate NICE guidance for children and young people where available*. (4.7.12.4) *See 'Type 1 diabetes' (NICE clinical guideline 15. [NICE, 2004b].	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of physical health needs. The GDG adapted this recommendation because only NICE guidance for type 1 diabetes is appropriate for children and young people.	• Physical health needs
1.4.1.5 Healthcare professionals in secondary care should ensure, as part of the CPA, that people with schizophrenia receive physical healthcare from primary care as described in recommendations 1.4.1.1–1.4.1.4.	Healthcare professionals in secondary care should ensure, as part of the care programme approach (CPA) in England and care and treatment plans in Wales, that children and young people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 4.7.12.2–4.7.12.4.	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of physical health needs. This recommendation was adapted to clarify the role of secondary care professionals in monitoring and managing side	• Physical health needs

	Healthcare professionals in secondary care should continue to maintain responsibility for monitoring and managing any side effects of antipsychotic medication. (4.7.12.5)	effects of medication. The addition of 'care and treatment plans in Wales', was made by the GDG to ensure that the recommendation would be implementable in Wales.	
1.4.1.6 When a person with an established diagnosis of schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances), primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan.	When a child or young person with a diagnosis of psychosis or schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances) and is still receiving treatment, primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan. (4.7.12.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia because it pertained to the key issue of access to emergency/crisis teams. The GDG adapted the recommendation to clarify the role of primary care professionals in the care of children and young people.	• Access to emergency/crisis teams

Continued

Table 9: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation	Key issue(s) identified by topic group
1.4.1.7 For a person with schizophrenia being cared for in primary care, consider referral to secondary care again if there is: • poor response to treatment • non-adherence to medication • intolerable side effects from medication • comorbid substance misuse • risk to self or others.	For a child or young person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is: • poor response to treatment • non-adherence to medication • intolerable side effects from medication or the child or young person or their parents or carers request a review of side effects • the child or young person or their parents or carers request psychological interventions not available in primary care • comorbid substance misuse • risk to self or others. (4.7.12.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, but made a minor adaptation to account for the fact that it might not be appropriate to deliver some psychological interventions for children and young people with psychosis or schizophrenia in primary care.	

The GDG identified two recommendations that related to the theme of education, one covering plans to ensure that people can continue with their education throughout their illness, including during crises, and one advising that care plans should include activities that promote education.

Bearing in mind that people from black and minority ethnic groups with psychosis and schizophrenia are more likely than people from other groups to be disadvantaged or to have impaired access and/or engagement with mental health services (NCCMH, 2012), the GDG recognised the importance of addressing this and judged that two recommendations pertained to the related issue of stigma.

Three recommendations were deemed appropriate to the key issue of transition because they addressed issues such as continuity of care, withdrawal and ending of treatment and services, or transfer from one service to another (for example, from the community to a hospital setting), all of which were relevant to children and young people with psychosis and schizophrenia. The GDG also considered the narrative review set out in Section 4.4 regarding transition from CAMHS to AMHS.

Finally, one recommendation related to safeguarding procedures, and one advising that people should be supported to develop strategies to promote and maintain independence and self-efficacy wherever possible, were also judged by the GDG to be relevant to the care of children and young people with psychosis and schizophrenia.

Schizophrenia

Following review of the underlying evidence and recommendations in the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a), nine recommendations from that guideline were considered relevant and important to the experience of care of children and young people with psychosis and schizophrenia. Two required only minor changes to make them relevant to the current context, while seven needed more substantive adaptation.

Three recommendations were identified as being relevant to children and young people's physical health needs, including the use of practice case registers to monitor physical health, treating people with diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance, and ensuring people receive general physical healthcare from primary care professionals.

The review of access to services for people from black and minority ethnic groups conducted for *Schizophrenia* (NCCMH, 2010) and three recommendations related to stigma were judged by the GDG to be important and relevant to the experience of care of children and young people.

One recommendation on referral of people with a suspected relapse was considered by the GDG to be relevant to the issue of access to emergency/crisis teams.

Finally, one recommendation on monitoring for coexisting mental health problems and one on indicators for referral to secondary care for people being cared for in primary care, were considered by the GDG to be relevant to the care of children and young people with psychosis and schizophrenia.

4.6 FROM EVIDENCE TO RECOMMENDATIONS

Due to the limited evidence, and the view of the GDG that in order to address important questions identified in the scope they would need to review existing NICE mental health guidelines, the GDG adapted a number of recommendations from *Service User Experience in Adult Mental Health* (NICE, 2011a) and *Schizophrenia* (NICE, 2009a) that were relevant to children and young people with psychosis and schizophrenia. These recommendations were initially selected by the topic group (who were informed by the narrative review), verified by the GDG, and then, based on the advice of the topic group, the GDG as a whole adapted the recommendations so that they were relevant to the current context using the method for incorporation and adaptation set out in Chapter 3 (see Section 3.7). All adapted recommendations are listed in Table 8 and Table 9, with a rationale explaining why the recommendation was considered relevant (linked to the key issues and areas of concern identified by the topic group and the narrative review conducted in Section 4.4), and why and how it was adapted.

In addition to the adapted recommendations, the GDG was of the view that several new recommendations were needed for children and young people with psychosis and schizophrenia to address particular issues that were not covered by either *Service User Experience in Adult Mental Health* or *Schizophrenia*. New recommendations were considered important in five areas of treatment and management of children and young people with psychosis and schizophrenia: general principles of care; referral from primary care; treatment options for first episode psychosis; hospital care; the early post-acute period; and promoting recovery and providing possible future care in primary and secondary care. The GDG adopted an informal consensus approach as outlined in Chapter 3 (see Section 3.5.8) to develop these recommendations.

In considering general principles of care the GDG agreed, based on the narrative review conducted in Section 4.4, expert opinion and via informal consensus methods, that health and social care professionals working in this context should be trained, competent and able to work with different levels of learning ability, cognitive capacity, emotional maturity and developmental levels, and take this into account when communicating with them (see recommendation 4.7.1.1). The GDG was mindful that professionals should use simple, jargon-free language and explain any clinical language, and use communication aids if needed (see recommendation 4.7.3.3). This was an important issue raised by the topic group in their review of the experience care for children and young people with psychosis and schizophrenia (Section 4.5.2). Furthermore, in their discussion of the issues raised by the topic group, the GDG also considered it particularly important that children and young people with psychosis and schizophrenia are treated at a developmentally appropriate level. In addition, the GDG wished to emphasise that health and social care professionals working with children and young people with psychosis and schizophrenia should be skilled in negotiating and working with parents and carers and managing issues relating to information sharing, competence and confidentiality as they pertain to children and young people (see recommendations 4.7.3.1 and 4.7.3.2). They should be able to assess capacity and competence and understand how to apply all relevant legislation including the *Children Act 2004* (HMSO, 2004), the *Mental Health Act 2007* (HMSO, 2007) and the *Mental*

Capacity Act 2005 (HMSO, 2005) (see recommendation 4.7.1.2). Considering the evidence that people from black and minority ethnic groups with psychosis and schizophrenia are more likely than people from other groups to be disadvantaged or to have impaired access and/or engagement with mental health services (NCCMH, 2010), the GDG advised that interpreters should be provided, along with information about where people who have difficulties speaking and understanding English can access English language teaching in their local community (see recommendation 4.7.4.2).

The narrative review of service provision found that specialised intensive services may offer advantages over generic community services in meeting the complex needs of children and young people with psychosis and schizophrenia, which in turn can improve access and engagement to mental health services in this population. As a result the GDG judged that children or young people with a first presentation of sustained (lasting 4 weeks or more) psychotic symptoms should be urgently referred to a specialist mental health service (CAMHS or EIP services) that has a consultant psychiatrist with training in child and adolescent mental health (see recommendation 4.7.6.1), where they should receive a multidisciplinary assessment covering psychiatric, psychosocial, medical, developmental, physical health, social, educational and economic domains (see recommendation 4.7.7.2).

The GDG also considered that in cases where a child or young person showed symptoms and behaviour sufficient for a diagnosis of an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, then relevant NICE guidance, for example for bipolar disorder (NICE, 2006), should be used (see recommendation 4.7.8.1).

The GDG also discussed hospital care for children and young people with psychosis and schizophrenia. It was agreed by the whole GDG, based on the narrative review conducted in Section 4.4, the issues raised by the topic group (see Section 4.5.2) and via informal consensus methods, that if a child or young person needed hospital care then it should be in a unit suitable for their age and developmental level (see recommendation 4.7.10.1). In addition the GDG felt that the distance of inpatient units from the child or young person's family home could have an impact on the child or young person and their parents, carers and other family members and that community-based alternatives should be considered. But where inpatient admission was avoidable, the GDG wished to advise that parents and carers should be provided with support following admission (see recommendation 4.7.10.2). The topic group also raised issues pertaining to care in hospital (see Section 4.5.2) which included lifestyle management and offering a wide range of meaningful activities. It was agreed by the GDG as a whole that shared decision-making should be undertaken routinely with children and young people in hospital care (see recommendation 4.7.10.4). Further, the GDG agreed that hospital care should include access to a full educational programme meeting the National Curriculum (see recommendation 4.7.10.5) and promote physical healthcare such as diet, exercise and smoking cessation (see recommendation 4.7.10.8).

The GDG also discussed the early post-acute period, and thought it was important for the child or young person and the parents or carers to reflect upon the episode of psychosis with their healthcare professional, and make plans for recovery or possible future care (see recommendation 4.7.11.1).

An important issue for the GDG, based on the narrative review conducted in Section 4.4 and agreed via informal consensus, was the responsibility for the physical healthcare of children and young people with psychosis and schizophrenia. They judged that GPs and other primary healthcare professionals should monitor their physical health at least once a year (see recommendation 4.7.12.2). Bearing in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population (NCCMH, 2010), those at increased risk of developing cardiovascular disease and/or diabetes should be identified at the earliest opportunity and monitored for the emergence of these conditions (see recommendation 4.7.12.3).

Finally, and based on the narrative review conducted in Section 4.4, the GDG was of the view that children and young people being treated in an EIP service should remain within the care of that service for 3 years (see recommendation 4.7.13.1).

4.7 RECOMMENDATIONS

4.7.1 Working safely and effectively with children and young people

4.7.1.1 Health and social care professionals working with children and young people with psychosis or schizophrenia should be trained and competent to work with children and young people with mental health problems of all levels of learning ability, cognitive capacity, emotional maturity and development.

4.7.1.2 Health and social care professionals should ensure that they:

- can assess capacity and competence, including 'Gillick competence', in children and young people of all ages, and
- understand how to apply legislation, including the Children Act (1989; amended 2004)[11], the Mental Health Act (1983; amended 1995 and 2007[12])[13] and the Mental Capacity Act (2005)[14], in the care and treatment of children and young people.

4.7.1.3 Consider children and young people with psychosis or schizophrenia for assessment according to local safeguarding procedures if there are concerns regarding exploitation or self-care, or if they have been in contact with the criminal justice system.[15]

4.7.1.4 Health and social care providers should ensure that children and young people with psychosis or schizophrenia:

- can routinely receive care and treatment from a single multidisciplinary community team
- are not passed from one team to another unnecessarily
- do not undergo multiple assessments unnecessarily.[16]

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[11]HMSO, 2004.

[12]Including the Code of Practice: Mental Health Act 1983 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_084597)

[13]HMSO, 2007.

[14] HMSO, 2005.

[15] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

[16] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

4.7.2 Establishing relationships with children and young people and their parents or carers

4.7.2.1 Work in partnership with children and young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity and parents or carers. Offer help, treatment and care in an atmosphere of hope and optimism. Take time to build trusting, supportive, empathic and non-judgemental relationships as an essential part of care.[17]

4.7.2.2 When working with children and young people with psychosis or schizophrenia:

- aim to foster autonomy, promote active participation in treatment decisions, and support self-management, and access to peer support in children and young people of an appropriate developmental level, emotional maturity and cognitive capacity
- maintain continuity of individual therapeutic relationships wherever possible
- offer access to a trained advocate.[18]

4.7.2.3 When working with children and young people with psychosis or schizophrenia and their parents or carers:

- make sure that discussions take place in settings in which confidentiality, privacy and dignity are respected
- be clear with the child or young person and their parents or carers about limits of confidentiality (that is, which health and social care professionals have access to information about their diagnosis and its treatment and in what circumstances this may be shared with others).[19]

4.7.2.4 Discuss with young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity how they want their parents or carers to be involved in their care. Such discussions should take place at intervals to take account of any changes in circumstances, including developmental level, and should not happen only once.[20]

4.7.2.5 Advise parents and carers about their right to a formal carer's assessment of their own physical and mental health needs, and explain how to access this.[21]

4.7.3 Communication and information

4.7.3.1 Health and social care professionals working with children and young people with psychosis or schizophrenia should be trained and skilled in:

- negotiating and working with parents and carers, and
- managing issues relating to information sharing and confidentiality as these apply to children and young people.

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[17] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[18] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[19] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[20] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[21] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

4.7.3.2 If a young person is 'Gillick competent' ask them what information can be shared before discussing their condition and treatment with their parents or carers.

4.7.3.3 When communicating with children and young people with psychosis or schizophrenia and their parents or carers:

- take into account the child or young person's developmental level, emotional maturity and cognitive capacity including any learning disabilities, sight or hearing problems or delays in language development
- use plain language where possible and clearly explain any clinical language
- check that the child or young person and their parents or carers understand what is being said
- use communication aids (such as pictures, symbols, large print, braille, different languages or sign language) if needed.

4.7.3.4 Provide children and young people with psychosis or schizophrenia and their parents or carers, comprehensive written information about:

- the nature of, and interventions for, psychosis and schizophrenia (including biomedical and psychosocial perspectives on causes and treatment) in an appropriate language or format, including any relevant 'Information for the public' booklets
- support groups, such as third sector, including voluntary, organisations.[22]

4.7.3.5 Ensure that you are:

- familiar with local and national sources (organisations and websites) of information and/or support for children and young people with psychosis or schizophrenia and their parents or carers
- able to discuss and advise how to access these resources
- able to discuss and actively support children and young people and their parents or carers to engage with these resources.[23]

4.7.3.6 When communicating with a child or young person with psychosis or schizophrenia, use diverse media, including letters, phone calls, emails or text messages, according to their preference.[24]

4.7.3.7 Copy all written communications with other health or social care professionals to the child or young person and/or their parents or carers at the address of their choice, unless this is declined.[25]

4.7.4 Culture, ethnicity and social inclusion

4.7.4.1 When working with children and young people with psychosis or schizophrenia and their parents or carers:

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[22] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[23] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[24] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[25] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

- take into account that stigma and discrimination are often associated with using mental health services
- be respectful of and sensitive to children and young people's gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability
- be aware of possible variations in the presentation of mental health problems in children and young people of different genders, ages, cultural, ethnic, religious or other diverse backgrounds.[26]

4.7.4.2 When working with children and young people and their parents or carers who have difficulties speaking or reading English:

- provide and work proficiently with interpreters if needed
- offer a list of local education providers who can provide English language teaching.

4.7.4.3 Health and social care professionals working with children and young people with psychosis or schizophrenia and their parents or carers should have competence in:

- assessment skills for people from diverse ethnic and cultural backgrounds
- using explanatory models of illness for people from diverse ethnic and cultural backgrounds
- explaining the possible causes of psychosis and schizophrenia and treatment options
- addressing cultural and ethnic differences in treatment expectations and adherence
- addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the possible causes of mental health problems
- conflict management and conflict resolution.[27]

4.7.4.4 Health and social care professionals inexperienced in working with children and young people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds, and their parents or carers, should seek advice and supervision from healthcare professionals who are experienced in working transculturally.[28]

4.7.4.5 Local mental health services should work with primary care, other secondary care and local third sector, including voluntary, organisations to ensure that:

- all children and young people with psychosis or schizophrenia have equal access to services based on clinical need and irrespective of gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability
- services are culturally appropriate.[29]

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[26] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[27] Adapted from *Schizophrenia* (NICE, 2009a).
[28] Adapted from *Schizophrenia* (NICE, 2009a).
[29] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

4.7.4.6 Mental health services should work with local voluntary black and minority ethnic groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to children and young people from diverse ethnic and cultural backgrounds.[30]

4.7.5 Transfer and discharge[31]

4.7.5.1 Anticipate that withdrawal and ending of treatments or services, and transition from one service to another, may evoke strong emotions and reactions in children and young people with psychosis or schizophrenia and their parents or carers. Ensure that:

- such changes, especially discharge and transfer from CAMHS to adult services, or to primary care, are discussed and planned carefully beforehand with the child or young person and their parents or carers, and are structured and phased
- the care plan supports effective collaboration with social care and other care providers during endings and transitions, and includes details of how to access services in times of crisis
- when referring a child or young person for an assessment in other services (including for psychological interventions), they are supported during the referral period and arrangements for support are agreed beforehand with them.[32]

4.7.6 Referral from primary care

4.7.6.1 Urgently refer all children and young people with a first presentation of sustained psychotic symptoms (lasting 4 weeks or more) to a specialist mental health service, either CAMHS (up to 17 years) or an early intervention in psychosis service (14 years or over), which includes a consultant psychiatrist with training in child and adolescent mental health.

4.7.7 Assessment and care planning in secondary care

4.7.7.1 When carrying out an assessment:

- ensure there is enough time for:
  - the child or young person and their parents or carers to describe and discuss their problems
  - summarising the conclusions of the assessment and for discussion, with questions and answers

[30] Adapted from *Schizophrenia* (NICE, 2009a).
[31] See Department of Health, 2006b.
[32] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

- explain and give written material in an accessible format about any diagnosis given
- give information about different treatment options, including pharmacological and psychological interventions, and their benefits and side effects, to promote discussion and shared understanding
- offer support after the assessment, particularly if sensitive issues, such as childhood trauma, have been discussed.[33]

4.7.7.2 Ensure that children and young people with first episode psychosis receive a comprehensive multidisciplinary assessment. The assessment should address the following domains:

- psychiatric (mental health problems, risk of harm to self or others, alcohol consumption and prescribed and non-prescribed drug history)
- medical, including medical history and full physical examination to identify physical illness (including organic brain disorders) and prescribed drug treatments that may result in psychosis
- psychological and psychosocial, including social networks, relationships and history of trauma
- developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)
- physical health and wellbeing (including weight and height, and information about smoking, diet and exercise, and sexual health)
- social (accommodation, culture and ethnicity, leisure activities and recreation, carer responsibilities [for example, of parents or siblings])
- educational and occupational (attendance at school or college, educational attainment, employment and functional activity)
- economic (family's economic status).

4.7.7.3 Routinely monitor for other coexisting mental health problems, including depression and anxiety, and substance misuse, particularly in the early phases of treatment.[34]

4.7.7.4 Develop a care plan with the parents or carers of younger children, or jointly with the young person and their parents or carers, as soon as possible, and:

- include activities that promote physical health and social inclusion, especially education, but also employment, volunteering and other occupations such as leisure activities
- provide support to help the child or young person and their parents or carers realise the plan
- give an up-to-date written copy of the care plan to the young person and their parents or carers if the young person agrees to this; give a copy of the care plan to the parents or carers of younger children; agree a suitable time to review it
- send a copy to the primary healthcare professional who made the referral.[35]

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[33] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

[34] Adapted from *Schizophrenia* (NICE, 2009a).

[35] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

4.7.7.5 Support children and young people to develop strategies, including risk- and self-management plans, to promote and maintain independence and self-efficacy, wherever possible. Incorporate these strategies into the care plan.[36]

4.7.7.6 If the child or young person is at risk of crisis, develop a crisis plan with the parents or carers of younger children, or jointly with the young person and their parents or carers, and with their care coordinator. The plan should be respected and implemented, incorporated into the care plan and include:

- possible early warning signs of a crisis and coping strategies
- support available to help prevent hospitalisation
- where the child or young person would like to be admitted in the event of hospitalisation
- definitions of the roles of primary and secondary care professionals and the degree to which parents or carers are involved
- information about 24-hour access to services
- the names of key clinical contacts.[36]

4.7.7.7 If the child or young person and/or their parent or carer is unhappy about the assessment, diagnosis or care plan, give them time to discuss this and offer them the opportunity for a second opinion.[37]

4.7.8 Treatment options for first episode psychosis

4.7.8.1 If the child or young person shows symptoms and behaviour sufficient for a diagnosis of an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, follow the recommendations in 'Bipolar disorder' (NICE clinical guideline 38)[38] or 'Depression in children and young people' (NICE clinical guideline 28)[39].

4.7.9 Referral in crisis and challenging behaviour

4.7.9.1 When a child or young person is referred in crisis they should be seen by specialist mental health secondary care services within 4 hours of referral.[40]

4.7.9.2 To avoid admission, aim to:

- explore with the child or young person and their parents or carers what support systems they have, including other family members and friends
- support a child or young person in crisis and their parents or carers in their home environment

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[36] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[37] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[38] NICE, 2006.
[39] NICE, 2005.
[40] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

- make early plans to help the child or young person maintain their day-to-day activities, including education, work, voluntary work, and other occupations and leisure activities, wherever possible.[41]

4.7.9.3 At the end of a crisis assessment, ensure that the decision to start home treatment depends not on the diagnosis, but on:

- the level of distress
- the severity of the problems
- the vulnerability of the child or young person and issues of safety and support at home
- the child or young person's cooperation with treatment.[42]

4.7.9.4 Consider the support and care needs of parents or carers of children or young people in crisis. Where needs are identified, ensure they are met when it is safe and practicable to do so.[43]

4.7.9.5 Follow the recommendations in *Self-Harm* (NICE clinical guideline 16)[44] when managing acts of self-harm in children and young people with psychosis or schizophrenia who are 8 years or over.[45]

4.7.10 Hospital care

4.7.10.1 If a child or young person needs hospital care, this should be in a setting appropriate to their age and developmental level.

4.7.10.2 Before referral for hospital care, think about the impact on the child or young person and their parents, carers and other family members, especially when the inpatient unit is a long way from where they live. Consider alternative care within the community wherever possible. If hospital admission is unavoidable, provide support for parents or carers when the child or young person is admitted.

4.7.10.3 Give verbal and written information to children and young people with psychosis or schizophrenia admitted to hospital, and their parents or carers, about:

- the hospital and the ward in which the child or young person will stay
- treatments, activities and services available
- expected contact from health and social care professionals
- rules of the ward (including substance misuse policy)
- their rights, responsibilities and freedom to move around the ward and outside
- meal times
- visiting arrangements

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[41] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[42] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[43] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[44] NICE, 2004a.
[45] Adapted from *Schizophrenia* (NICE, 2009a).

Make sure there is enough time for the child or young person and their parents or carers to ask questions.[46]

4.7.10.4 Undertake shared decision-making routinely with children or young people in hospital who are of an appropriate developmental level, emotional maturity and cognitive capacity, including, whenever possible, those who are subject to the Mental Health Act (1983; amended 1995 and 2007).[47] Include their parents or carers if appropriate.[48]

4.7.10.5 Ensure that children and young people of compulsory school age have access to a full educational programme while in hospital. The programme should meet the National Curriculum, be matched to the child or young person's developmental level and educational attainment, and should take account of their illness and degree of impairment.

4.7.10.6 Ensure that children and young people in hospital continue to have access to a wide range of meaningful and culturally appropriate occupations and activities 7 days per week, and not restricted to 9am to 5pm. These should include creative and leisure activities, exercise, self-care and community access activities (where appropriate). Activities should be facilitated by appropriately trained educational, health or social care professionals.[49]

4.7.10.7 Children and young people receiving community care before hospital admission should be routinely visited while in hospital by the health and social care professionals responsible for their community care.[50]

4.7.10.8 Promote good physical health, including healthy eating, exercise and smoking cessation.

4.7.11 Early post-acute period

4.7.11.1 In the early period of recovery following an acute episode, reflect upon the episode and its impact with the child or young person and their parents or carers, and make plans for recovery and possible future care.

4.7.12 Promoting recovery and providing possible future care in primary care

4.7.12.1 Develop and use practice case registers to monitor the physical and mental health of children and young people with psychosis or schizophrenia in primary care.[51]

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[46] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[47] HMSO, 2007.
[48] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[49] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[50] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[51] Adapted from *Schizophrenia* (NICE, 2009a).

4.7.12.2 GPs and other primary healthcare professionals should monitor the physical health of children and young people with psychosis or schizophrenia at least once a year. They should bear in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population.

4.7.12.3 Identify children and young people with psychosis or schizophrenia who smoke or who have high blood pressure, raised lipid levels or increased waist measurement at the earliest opportunity and monitor for the emergence of cardiovascular disease and diabetes.

4.7.12.4 Treat children and young people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care. Use the appropriate NICE guidance for children and young people where available.[52,53]

4.7.12.5 Healthcare professionals in secondary care should ensure, as part of the care programme approach (CPA) in England and care and treatment plans in Wales, that children and young people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 4.7.12.2 to 4.7.12.4. Healthcare professionals in secondary care should continue to maintain responsibility for monitoring and managing any side effects of antipsychotic medication.[54]

4.7.12.6 When a child or young person with a diagnosis of psychosis or schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances) and is still receiving treatment, primary healthcare professionals should refer to the crisis section of the care plan. Consider referral to the key clinician or care coordinator identified in the crisis plan.[55]

4.7.12.7 For a child or young person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is:

- poor response to treatment
- non-adherence to medication
- intolerable side effects from medication or the child or young person or their parents or carers request a review of side effects
- the child or young person or their parents or carers request psychological interventions not available in primary care
- comorbid substance misuse
- risk to self or others.[56]

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[52] See *Type 1 Diabetes* (NICE clinical guideline 15) (NICE, 2004b).

[53] Adapted from *Schizophrenia* (NICE, 2009a).

[54] Adapted from *Schizophrenia* (NICE, 2009a).

[55] Adapted from *Schizophrenia* (NICE, 2009a).

[56] Adapted from *Schizophrenia* (NICE, 2009a).

4.7.13 Promoting recovery and providing possible future care in secondary care

4.7.13.1 Children and young people with psychosis or schizophrenia who are being treated in an early intervention in psychosis service should have access to that service for up to 3 years (or until their 18th birthday, whichever is longer) whatever the age of onset of psychosis or schizophrenia.

5 AT RISK MENTAL STATES FOR PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE: RECOGNITION AND MANAGEMENT

5.1 INTRODUCTION

Over the past 2 decades there has been a wealth of research examining the possibility of early recognition of psychosis, with an emphasis on reducing duration of untreated psychosis (DUP), which has been shown to be associated with poor outcomes. As a result, there have also been significant developments in the identification of people who are at high risk of developing a first psychotic episode within a short timeframe.

5.1.1 Reducing duration of untreated psychosis

DUP is defined as the period from the onset of positive psychotic symptoms sufficient to meet criteria for psychosis until the initiation of appropriate treatment. The average DUP has been found to be 1 to 2 years in numerous studies (Norman & Malla, 2001) and research suggests that a longer DUP may predict poor prognosis and outcomes (Birchwood *et al.*, 1998; Norman & Malla, 2001). More specifically, there is evidence that DUP correlates moderately with short-term symptomatic and functional outcomes in first episode psychosis (McGlashan, 1998). This delay in treatment is associated with increased physical, social and legal harm. A delay of more than 6 months has been found to be associated with a significantly reduced chance of early recovery (Loebel *et al.*, 1992). This suggests that there may be a critical period in which interventions can best be delivered to improve outcomes, which has led to the widespread implementation of EIP services (Birchwood *et al.*, 1998). As such, current UK government guidance requires that DUP be reduced to a service median of less than 3 months and an individual maximum of less than 6 months (Department of Health, 2003).

5.1.2 Recognition and identification of at risk mental states

Recent studies have examined the feasibility of detecting and treating people in the 'at risk' stage, prior to the development of psychosis. This approach rests on three assumptions: (1) it is possible to detect such people; (2) these people will be at markedly increased risk of later psychosis; and (3) an effective intervention will reduce this risk. There is evidence to support (1) and (2) in people with a strong

family history of psychosis who are therefore at high genetic risk (Miller *et al.*, 2001) and in those reporting particular perceptual abnormalities (Klosterkötter *et al.*, 2001).

5.1.3 Interventions aimed at prevention, delay or amelioration of psychosis

When those at risk have been identified, there is the question of what can effectively be done to prevent, delay or ameliorate psychosis. To date, there have been nine RCTs, each using similar operational definitions of 'at risk', which have reported findings regarding antipsychotic medication, omega-3 polyunsaturated fatty acids and/or psychological interventions including CBT. These studies have been conducted in Australia (McGorry *et al.*, 2002; Phillips *et al.* 2009a), North America (Addington *et al.,* 2011; McGlashan *et al.*, 2006)and Europe (Amminger *et al.,* 2010; Bechdolf *et al.*, 2012; Morrison *et al.,* 2004a and 2007) and have aimed to achieve one or more of the following outcomes: to prevent, delay or ameliorate rates of transition to psychosis; to reduce severity of psychotic symptoms; to reduce distress and emotional dysfunction; and to improve quality of life.

5.1.4 Therapeutic approaches identified

The following therapeutic approaches have been identified:

- pharmacological interventions:
  - olanzapine
  - risperidone
- dietary interventions:
  - omega-3 fatty acids
- psychological interventions:
  - cognitive behavioural therapy (CBT)
  - integrated psychological therapy
  - supportive counselling.

5.1.5 Combined interventions

Some researchers have combined more than one intervention in order to improve the likelihood of achieving the intended outcomes. For example, antipsychotic medication can be combined with a psychological therapy such as cognitive therapy, or several psychosocial interventions may be combined (such as cognitive therapy, CRT and family intervention). However these combinations do not form a homogenous group and therefore cannot be analysed together in a meta-analysis.

5.2 CLINICAL REVIEW PROTOCOL FOR AT RISK MENTAL STATES FOR PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE

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. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

Table 10: Clinical review protocol for the review of at risk mental states for psychosis and schizophrenia in children and young people

Component	Description
Review questions	**RQ A1:** In children and young people, what are the specific behaviours and symptoms that are associated with an increased risk of developing psychosis[1] and schizophrenia (at risk mental state)? Sub-questions: a) What is the course of these behaviours and symptoms? b) What are the specific behaviours and symptoms that prompt initial recognition of psychosis[1] or prompt diagnosis of schizophrenia? **RQ B1:** For children and young people who are at risk of developing psychosis[1] and schizophrenia (at risk mental state), does the provision of pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes? [2]
Objectives	• To determine the specific behaviours and symptoms that are associated with an increased risk of developing psychosis and schizophrenia. • To evaluate if pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes for children and young people who are at risk of developing psychosis and schizophrenia.
Population	**Inclusion**: Children and young people (aged 18 years and younger) with first episode psychosis. Consideration should be given to the specific needs of children and young people with a mild learning disability and those from black and minority ethnic groups.

Continued

Table 10: (*Continued*)

Component	Description
	Exclusion: Study samples consisting only of individuals with a formal diagnosis of psychosis, schizophrenia or bipolar disorder.
Interventions	**RQ B1:** Licensed antipsychotics drugs.[2] Psychological interventions, including: • CBT • CRT • Counselling and supportive psychotherapy • Family intervention (including family therapy) • Psychodynamic psychotherapy and psychoanalysis • Psychoeducation • Social skills training • Arts therapies Dietary interventions, including: • Any dietary/nutritional supplements
Comparison	Alternative management strategies: • Placebo • Treatment as usual • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Transition to psychosis • Time to transition to psychosis
Secondary outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes and cardiotoxicity)
Electronic databases	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic-specific databases: see Appendix 8 *Note*: any evidence resulting from generic guideline searches also mapped to RQ

Continued

Table 10: (*Continued*)

Component	Description
Date searched	Systematic review: 1995 to May 2012 RCT: inception of databases to May 2012
Study design	RQ A1: Systematic reviews RQ B1: RCTs, systematic reviews
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological, psychological, dietary and combination treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and at or under 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

Note. [1] Children and young people who are at risk of developing psychosis and those who have early psychosis but do not have a formal diagnosis of either schizophrenia or bipolar disorder.
[2] Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia).

5.3 RECOGNITION OF AT RISK MENTAL STATES

5.3.1 Studies considered

No systematic reviews were identified that directly investigated specific behaviours and symptoms associated with an increased risk of developing psychosis and schizophrenia (at risk mental state). However, a recent systematic review (Fusar-Poli *et al*., 2012) was identified that documented transition rates for individuals considered to be at a high risk of developing psychosis and provided information about how operationally defined criteria for at risk mental states was measured in the current literature. The GDG therefore decided to use this systematic review, as well as conduct a narrative review of evidence they had identified. This was used to inform an informal consensus-based approach, as detailed in Chapter 3 (see Section 3.5.8), to develop recommendations. In brief, this process involved full group discussion about the narrative review, the evidence reported by Fusar-Poli and colleagues (2012), and expert opinion regarding what is known about the issues pertaining to specific behaviours and symptoms that are associated with an increased risk of developing psychosis and schizophrenia. Consideration was also given to the ethical implications pertinent to 'labelling' children and young people who are at high risk of developing psychosis and schizophrenia.

5.3.2 Narrative review of the clinical evidence

Behaviours and symptoms

Yung and colleagues (Yung *et al*., 1996; Yung *et al*., 1998) have developed operational criteria to identify three subgroups with at risk mental states for psychosis and schizophrenia. Two subgroups specify state risk factors, defined by the presence of:

- transient psychotic symptoms (or 'brief limited intermittent psychotic symptoms') or
- attenuated (subclinical) psychotic symptoms insufficient for a diagnosis of psychosis or schizophrenia.

The other subgroup comprises trait-plus-state risk factors:

- the presence of diminished functioning plus a pre-existing schizotypal personality disorder or a first-degree relative with a history of psychosis.

All subgroups studied are within a specified age range (usually 14 to 30 years) known to be at greatest risk for onset of psychosis. This approach is a pragmatic one with unknown generalisability to the population of people with diagnosed psychotic disorder. However, at risk individuals are often help-seeking and, therefore, exert demands on clinical services with only a preliminary evidence base to inform practice. Retrospective observations of people with first episode psychosis suggest that over 75% make contact with GPs on matters related to their developing psychosis (Cole *et al*., 1995) and that some 50% of these contacts occur during the prodrome. However, the ambiguous and non-specific nature of prodromal symptoms often leads to poor recognition and response from mental health services (Skeate *et al*., 2002).

Measurement

Reliable and valid criteria incorporating the above strategy are now available to identify help-seeking individuals in diverse settings who are at high risk of imminently developing schizophrenia and related psychoses, using standardised semi-structured interviews (Miller *et al.*, 2003; Yung *et al.*, 2005). A systematic review conducted by Fusar-Poli and colleagues (2012) included 27 studies published between 1996 and 2011 and contained a total of 2,502 help-seeking participants with a high-risk mental state for psychosis. The mean (standard deviation [SD]) age of participants was 19.9 (3.6) years and 58.3% were male. Two forms of diagnostic criteria defining high risk characteristics were used: (1) ultra-high risk and (2) basic symptoms. An ultra-high risk criterion focuses on the subgroups identified by Yung and colleagues (Yung *et al.*, 1996; Yung *et al.*, 1998): brief limited intermittent psychotic symptoms, attenuated (subclinical) psychotic symptoms and trait-plus-state risk factors. Ultra-high risk mental states were assessed using three screening tools:

- Basal Screening Instrument for Psychosis (BSIPS)
- Comprehensive Assessment of At Risk Mental States (CAARMS)
- Structured Interview for Prodromal Syndromes (SIPS).

A basic symptoms criterion is based on self-perceived disturbances and can be assessed using the following two tools:

- BONN Scale for the Assessment of Basic Symptoms (BSAB)
- Schizophrenia Proneness Instrument, Adult version (SPIA).

Twenty-two studies utilised ultra-high risk criteria, two studies used basic symptoms criteria and three studies employed both measures. Transition to psychosis was defined using the two major psychiatric diagnostic guidelines (DSM or ICD - versions not reported) or criteria from the main ultra-high risk clinical schedules (CAARMS or SIPS). The overall mean rate of transition to a DSM or ICD psychotic disorder was 29.2% (95% CI, 27.3 to 31.1), with a mean follow-up of 31 months. Different at risk criteria yielded considerable variability in transition rates: for studies using the ultra-high risk approach (K = 22) the mean transition rate was 27.7% (95% CI, 25.6 to 29.9); for studies using the basic symptoms approach (K = 2) the mean transition rate was 48.5% (95% CI, 41.9 to 55.9); and for studies combining both approaches (K = 3) the mean transition rate was 22.5% (95% CI, 18.4 to 27.3). Transition risks were similar when psychosis was defined using criteria from the main ultra-high risk clinical schedules: 27.3% (95% CI, 25.0 to 29.7) and 27.5% (95% CI, 24.3 to 30.9) respectively. However when transition was defined according to DSM-III, DSM-IV or ICD-10, significant variance in risk was observed across studies and the risk was higher than that using the main ultra-high risk clinical schedules (range 43.4% to 58.7%, $I^2 = 97.23$). Although there was variation in transition rates between studies, these instruments correctly identified people who later developed psychosis.

5.3.3 Ethical considerations

There has been considerable debate within the scientific and clinical communities regarding the desirability of 'labelling' people as being at high risk of developing

psychosis and schizophrenia. This is partly because the rates of transition suggest that the majority of such samples (between 80 and 90%) do not convert to first episode psychosis within a 12-month period (that is, there are many 'false positives'), and there is some evidence that these rates are declining (Yung *et al.,* 2007). This may mean exposing people to risks associated with the label, such as unnecessary stigma (Bentall & Morrison, 2002; Yang *et al.*, 2010), restrictions that people may impose upon themselves (such as avoidance of stress) (Warner, 2001) and unwanted consequences for employment, obtaining insurance and so on (Corcoran *et al.,* 2005). There are also concerns about the risks of exposure to unnecessary treatments with potential adverse effects within this population, and hence the risks and benefits of any intervention must be balanced carefully (Bentall & Morrison, 2002; Warner, 2001). The proposal to include a psychosis risk syndrome, so-called 'attenuated psychotic disorder' in DSM-V, has led to many concerns for such reasons (Carpenter, 2009; Corcoran *et al.,* 2010; Morrison *et al.,* 2010).

5.3.4 Clinical evidence summary

Operationally defined criteria have been developed to recognise individuals 'at risk' for developing psychosis. Such criteria describe specific behaviours and symptoms associated with this increased risk, including brief limited intermittent psychotic symptoms and attenuated (subclinical) psychotic symptoms, as well as highlighting the role of trait-plus-state factors. Several measures exist to measure at risk mental states and aid diagnosis. Despite variation in transition rates between studies employing these different measures, these instruments correctly identify people who later developed psychosis. However, the variability in transition rates suggests that the criteria for at risk mental states need further refinement in order to better predict the course of at risk behaviours and symptoms, as well as recognise those who will and will not go on to develop psychosis and schizophrenia. Moreover, study participants are most often treatment-seeking individuals, necessarily omitting people who may need help but do not seek it, and therefore further work is needed to investigate the influence of sampling strategies on rates of transition to psychosis.

5.4 PHARMACOLOGICAL INTERVENTIONS

5.4.1 Studies considered[57]

Three RCTs (N = 234) providing relevant clinical evidence met the eligibility criteria for this review: MCGLASHAN2003 (McGlashan *et al.*, 2003), MCGORRY2002 (McGorry *et al.*, 2002) and PHILLIPS2009 (Phillips *et al.*, 2009a). Of these, one

[57]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).

contained unpublished data (PHILLIPS2009). The mean age was 25 years or younger, but all studies contained a sample in which some participants were under 18. Further information about the included studies can be found in Appendix 13a.

Of the three included trials, there was one comparing olanzapine with placebo, two comparing risperidone plus CBT with supportive counselling and one comparing risperidone plus CBT with placebo plus CBT (see Table 11 for a summary of the study characteristics).

5.4.2 Clinical evidence for olanzapine versus placebo

Efficacy

One study (N = 60) compared olanzapine with placebo (MCGLASHAN2003). At 1 year post-treatment 16 participants had transitioned to psychosis and there was no statistically significant difference between groups (RR = 0.43; 95% CI, 0.17 to 1.08). Effects on symptoms of psychosis, depression and mania were also not significant. Evidence from each reported outcome and overall quality of evidence are presented in Table 12 and Table 13.

Side effects

There were more olanzapine dropouts at 1 year (17 out of 31 versus 10 out of 29; see Appendix 14a [2.1]), but the difference was not statistically significant (RR = 1.59; 95% CI, 0.88 to 2.88). Participants taking olanzapine gained significantly more weight (SMD = 1.18; 95% CI, 0.62 to 1.73) at 1 year post-treatment. Furthermore, compared with the placebo group the sitting pulse of participants in the olanzapine group increased significantly more from baseline to post-treatment (SMD = 0.61; 95% CI, 0.08 to 1.13). Effects on standing pulse were not significant. At 104 weeks' follow-up, transition to psychosis and side effects were measured, however, the data were considered unusable because there were fewer than 10 people remaining in each group. Evidence from each reported outcome and overall quality of evidence are presented in Table 13.

The full evidence profiles can be found in Appendix 17a.

5.4.3 Clinical evidence for risperidone plus CBT versus supportive counselling

Efficacy

Two studies (N = 130) compared risperidone plus CBT with supportive counselling (MCGORRY2002; PHILLIPS2009). Within the first 26 weeks of treatment fewer people receiving risperidone plus CBT transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder) (RR = 0.35; 95% CI, 0.13 to 0.95), but these trials included 17 events. By 52 weeks' follow-up the effect was no longer significant (RR = 0.63; 95% CI, 0.33 to 1.21) and this remained non-significant at 156 to 208 weeks' follow-up (RR = 0.59; 95% CI, 0.34 to 1.04).

Table 11: Study information table for trials of antipsychotic medication

	Olanzapine versus placebo	Risperidone + CBT versus supportive counselling	Risperidone + CBT versus placebo + CBT
Total no. of studies (N)	1 (N = 60)	2 (N = 130)	1 (N = 87)
Study ID	MCGLASHAN2003	(1) MCGORRY2002 (2) PHILLIPS2009	PHILLIPS2009
Screening tool	SIPS	(1) Not reported (2) CAARMS	CAARMS
Diagnosis	At risk mental state	Ultra-high risk mental state	Ultra-high risk mental state
Mean age (range)	17.8 (range 12 to 36)	(1) 20 (range 14 to 28) (2) 17.9 (not reported)[1]	17.9 (not reported)[1]
Sex (% male)	65	(1) 58 (2) 39[1]	39[1]
Ethnicity (% white)	67	(1)–(2) Not reported	Not reported
Mean (range) medication dose (mg/day)	8 (range 5 to 15)	(1) 1.3 (range 1 to 2) (2) 2 (not reported)	2 (not reported)

Sessions of therapy	N/A	(1) Mean (SD) sessions attended: CBT: 11.3 (8.4); supportive counselling: 5.9 (4.3). (2) Up to of 35 hours of CBT or supportive counselling	Up to 35 hours
Treatment follow-up (weeks)	104	(1) 156 to 208 (2) 104	104
Setting	Specialist clinic/ward	(1)–(2) Specialist clinic/ward	Specialist clinic/ward
Country	US	(1)–(2) Australia	Australia
Funding	Eli Lilly	(1) Commonwealth Government of Australia Research and Development Grants Advisory Committee and Janssen-Cilag Pharmaceuticals (2) Janssen-Cilag Pharmaceuticals	Janssen-Cilag Pharmaceuticals

Note. [1] In the whole study (N = 115; PHILLIPS2009 is a three way comparison evaluating risperidone, CBT and supportive counselling).

Table 12: Summary of findings table for outcomes reported for olanzapine versus placebo at 52 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCGLASHAN2003	K = 1, N = 59	–0.12 [–0.63, 0.39]	N/A	Very low[1,2,3]	Appendix 14a (1.1)
Positive symptoms (SMD)	MCGLASHAN2003	K = 1, N = 59	–0.40 [–0.91, 0.12]	N/A	Very low[1,2,3]	Appendix 14a (1.2)
Negative symptoms (SMD)	MCGLASHAN2003	K = 1, N = 59	0.05 [–0.46, 0.56]	N/A	Very low[1,2,3]	Appendix 14a (1.3)
Global state (severity) (SMD)	MCGLASHAN2003	K = 1, N = 59	–0.17 [–0.68, 0.34]	N/A	Very low[1,2,3]	Appendix 14a (1.4)
Depression (SMD)	MCGLASHAN2003	K = 1, N = 59	0.32 [–0.19, 0.83]	N/A	Very low[1,2,3]	Appendix 14a (1.5)
Mania (SMD)	MCGLASHAN2003	K = 1, N = 59	–0.15 [–0.66, 0.36]	N/A	Very low[1,2,3]	Appendix 14a (1.6)
Psychosocial functioning (SMD)	MCGLASHAN2003	K = 1, N = 59	–0.16 [–0.67, 0.35]	N/A	Very low[1,2,3]	Appendix 14a (1.7)
Transition to psychosis (RR)	MCGLASHAN2003	K = 1, N = 60	0.43 [0.17, 1.08]	N/A	Very low[1,2,3]	Appendix 14a (1.8)
Leaving the study early for any reason (RR)	MCGLASHAN2003	K = 1, N = 60	1.59 [0.88, 2.88]	N/A	Very low[1,2,3]	Appendix 14a (2.1)
Weight gain (kg; SMD)	MCGLASHAN2003	K = 1, N = 59	1.18 [0.62, 1.73]*	N/A	Very low[1,2,3]	Appendix 14a (3.1)
Sitting pulse (beats per minute [BPM]; SMD)	MCGLASHAN2003	K = 1, N = 60	0.61 [0.08, 1.13]*	N/A	Very low[1,2,3]	Appendix 14a (3.2)
Standing pulse (BPM; SMD)	MCGLASHAN2003	K = 1, N = 59	0.37 [–0.15, 0.88]	N/A	Very low[1,2,3]	Appendix 14a (3.3)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours placebo.
[1] Serious risk of bias (including unclear sequence generation and allocation concealment and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Serious risk of reporting bias.

Table 13: Summary of findings table for outcomes reported for olanzapine versus placebo at 104 weeks' follow-up (change scores from post-treatment until follow-up when no treatment was received)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Leaving the study early for any reason (RR)	MCGLASHAN2003	K = 1, N = 60	0.98 [0.71, 1.35]	N/A	Very low[1,2,3]	Appendix 14a (4.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

At follow-up, only data for completers were reported and therefore a sensitivity analysis for transition to psychosis was conducted, assuming dropouts had made transition. In sensitivity analysis the effect remained non-significant (RR = 0.67; 95% CI, 0.46 to 0.96). Both studies reported mean endpoint scores for symptoms of psychosis, quality of life, depression, anxiety, mania and psychosocial functioning. No significant differences between treatment groups were found on these outcomes at post-treatment or follow-up. At post-treatment, there was no dropout in one study (MCGORRY2002) and dropout in the other (PHILLIPS2009) was similar between groups (RR = 0.76; 95% CI, 0.28 to 2.03). Evidence from each reported outcome and overall quality of evidence are presented in Table 14, Table 15 and Table 16.

Side effects
Six out of the 21 participants for whom side effect data were reported experienced EPS (as measured by the Udvalg for Kliniske Undersøgelser (UKU) Neurologic Subscale, see Appendix 14a [6.2]). However, observing only six events, there was no significant difference between groups at post-treatment (RR = 0.55; 95% CI, 0.13 to 2.38) (see Table 14).

The full evidence profiles can be found in Appendix 17a.

5.4.4 Clinical evidence for risperidone plus CBT versus placebo plus CBT

Efficacy
One study (N = 87) compared risperidone plus CBT with placebo plus CBT (PHILLIPS2009). By 52 weeks post-treatment, seven participants in each group had transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder) and there was no significant difference between groups [RR = 1.02; 95% CI, 0.39 to 2.67]). Differences in symptoms of psychosis, depression, psychosocial functioning and quality of life were not significant, and dropout was similar between groups (RR = 1.09; 95% CI, 0.62 to 1.92). Evidence from each reported outcome and overall quality of evidence are presented in Table 17.

Side effects
Five out of the 23 participants for whom side effect data were reported experienced EPS (as measured by the UKU Neurologic Subscale, see Appendix 14a [12.1]). However, there was no significant difference between groups (RR = 0.87; 95% CI, 0.18 to 4.24). Evidence from each reported outcome and overall quality of evidence are presented in Table 17.

The full evidence profiles can be found in Appendix 17a.

5.4.5 Clinical evidence summary for pharmacological interventions

Three RCTs (N = 234) conducted in children and young people aged 25 years or younger with an at risk mental state for psychosis and schizophrenia were reviewed.

Table 14: Summary of findings table for outcomes reported for risperidone + CBT versus supportive counselling at post-treatment

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 102	0.15 [–0.39, 0.70]	(P = 0.12); I^2 = 59%	Very low[1,2,3]	Appendix 14a (5.1)
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.02 [–0.33, 0.37]	(P = 0.39); I^2 = 0%	Very low[1,2,3]	Appendix 14a (5.2)
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.13 [–0.68, 0.94]	(P = 0.02); I^2 = 81%	Very low[1,2,3]	Appendix 14a (5.3)
Depression (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.24 [–0.12, 0.59]	(P = 0.003) I^2 = 88%	Very low[1,2,3]	Appendix 14a (5.4)
Mania (SMD)	MCGORRY2002	K = 1, N = 59	–0.20 [–0.71, 0.32]	N/A	Very low[1,2,3]	Appendix 14a (5.5)
Anxiety (SMD)	MCGORRY2002	K = 1, N = 59	–0.15 [–0.66, 0.36]	N/A	Very low[1,2,3]	Appendix 14a (5.6)
Psychosocial functioning (SMD)	PHILLIPS2009	K = 1, N = 43	–0.12 [–0.73, 0.49]	N/A	Very low[1,2,3]	Appendix 14a (5.7)
Quality of life (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	–0.13 [–0.49, 0.22]	(P = 0.31); I^2 = 2%	Very low[1,2,3]	Appendix 14a (5.8)
Transition to psychosis (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.35 [0.13, 0.95]	(P = 0.44); I^2 = 0%	Very low[1,2,3]	Appendix 14a (5.9)
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.76 [0.28, 2.03]	N/A [no events observed by MCGORRY2002]	Very low[1,2,3]	Appendix 14a (6.1)
EPS (RR)	PHILLIPS2009	K = 1, N = 21	0.55 [0.13, 2.38]	N/A	Very low[1,2,3]	Appendix 14a (6.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Table 15: Summary of findings table for outcomes reported for risperidone + CBT versus supportive counselling at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 101	0.07 [–0.32, 0.46]	(P = 0.39); I^2 = 0%	Very low[1,2,3]	Appendix 14a (7.1)
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 101	0.05 [–0.35, 0.44]	(P = 0.90); I^2 = 0%	Very low[1,2,3]	Appendix 14a (7.2)
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 101	0.08 [–0.31, 0.47]	(P = 0.41); I^2 = 0%	Very low[1,2,3]	Appendix 14a (7.3)
Depression (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 68	0.15 [–0.33, 0.62]	(P = 0.93); I^2 = 0%	Very low[1,2,3]	Appendix 14a (7.4)
Mania (SMD)	MCGORRY2002	K = 1, N = 59	0.00 [–0.51, 0.51]	N/A	Very low[1,2,3]	Appendix 14a (7.5)
Anxiety (SMD)	MCGORRY2002	K = 1, N = 59	0.06 [–0.45, 0.57]	N/A	Very low[1,2,3]	Appendix 14a (7.6)
Psychosocial functioning (SMD)	MCGORRY2002	K = 1, N = 59	0.00 [–0.51, 0.51]	N/A	Very low[1,2,3]	Appendix 14a (7.7)
Quality of life (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 102	–0.07 [–0.46, 0.32]	(P = 0.84); I^2 = 0%	Very low[1,2,3]	Appendix 14a (7.8)
Transition to psychosis (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.63 [0.33, 1.21]	(P = 0.61); I^2 = 0%	Very low[1,2,3]	Appendix 14a (7.9)
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.85 [0.43, 1.67]	(P = 0.19); I^2 = 43%	Very low[1,2,3]	Appendix 14a (8.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Table 16: Summary of findings table for outcomes reported for risperidone + CBT versus supportive counselling at 156 to 208 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCGORRY2002	K = 1, N = 41	–0.33 [–0.96, 0.29]	N/A	Very low[1,2,3]	Appendix 14a (9.1)
Positive symptoms (SMD)	MCGORRY2002	K = 1, N = 41	–0.04 [–0.66, 0.58]	N/A	Very low[1,2,3]	Appendix 14a (9.2)
Negative symptoms (SMD)	MCGORRY2002	K = 1, N = 41	–0.24 [–0.87, 0.38]	N/A	Very low[1,2,3]	Appendix 14a (9.3)
Depression (SMD)	MCGORRY2002	K = 1, N = 41	0.23 [–0.39, 0.86]	N/A	Very low[1,2,3]	Appendix 14a (9.4)
Mania (SMD)	MCGORRY2002	K = 1, N = 41	–0.36 [–0.98, 0.27]	N/A	Very low[1,2,3]	Appendix 14a (9.5)
Anxiety (SMD)	MCGORRY2002	K = 1, N = 41	0.14 [–0.49, 0.76]	N/A	Very low[1,2,3]	Appendix 14a (9.6)
Psychosocial functioning (SMD)	MCGORRY2002	K = 1, N = 41	–0.15 [–0.77, 0.47]	N/A	Very low[1,2,3]	Appendix 14a (9.7)
Quality of life (SMD)	MCGORRY2002	K = 1, N = 41	0.08 [–0.54, 0.71]	N/A	Very low[1,2,3]	Appendix 14a (9.8)
Completer analysis: transition to psychosis (RR)	MCGORRY2002	K = 1, N = 41	0.59 [0.34, 1.04]	N/A	Very low[1,2,3]	Appendix 14a (9.9)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	MCGORRY2002	K = 1, N = 59	0.67 [0.46, 0.96]	N/A	–	Appendix 14a (9.10)
Number of participants requiring hospitalisation (RR)	MCGORRY2002	K = 1, N = 41	0.51 [0.19, 1.33]	N/A	Very low[1,2,3]	Appendix 14a (9.11)
Leaving the study early for any reason (RR)	MCGORRY2002	K = 1, N = 59	0.57 [0.26, 1.28]	N/A	Very low[1,2,3]	Appendix 14a (10.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, raters unblind to psychological intervention, trial registration could not be found and missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Table 17: Summary of findings table for outcomes reported for risperidone plus CBT versus placebo plus CBT at 52 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	PHILLIPS2009	K = 1, N = 51	–0.24 [–0.79, 0.31]	N/A	Very low[1,2,3]	Appendix 14a (11.1)
Positive symptoms (SMD)	PHILLIPS2009	K = 1, N = 51	–0.07 [–0.62, 0.48]	N/A	Very low[1,2,3]	Appendix 14a (11.2)
Negative symptoms (SMD)	PHILLIPS2009	K = 1, N = 51	0.12 [–0.43, 0.67]	N/A	Very low[1,2,3]	Appendix 14a (11.3)
Psychosocial functioning (SMD)	PHILLIPS2009	K = 1, N = 52	0.24 [–0.31, 0.78]	N/A	Very low[1,2,3]	Appendix 14a (11.4)
Quality of life (SMD)	PHILLIPS2009	K = 1, N = 51	–0.23 [–0.78, 0.33]	N/A	Very low[1,2,3]	Appendix 14a (11.5)
Transition to psychosis (RR)	PHILLIPS2009	K = 1, N = 56	1.02 [0.39, 2.67]	N/A	Very low[1,2,3]	Appendix 14a (11.6)
Leaving the study early for any reason (RR)	PHILLIPS2009	K = 1, N = 87	1.09 [0.62, 1.92]	N/A	Very low[1,2,3]	Appendix 14a (12.2)
EPS (RR)	PHILLIPS2009	K = 1, N = 23	0.87 [0.18, 4.24]	N/A	Very low[1,2,3]	Appendix 14a (12.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, trial registration not found, uneven sample sizes).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

One study investigated the effect of an antipsychotic medication alone against placebo (MCGLASHAN2003) and two studies investigated the effect of an antipsychotic medication in combination with CBT against a psychological therapy (MCGORRY2002, PHILLIPS2009). The findings suggest that antipsychotic medication is no more effective than a psychological intervention or placebo in preventing transition to psychosis or in reducing psychotic symptoms. What is more, olanzapine treatment can result in significant weight gain.

5.5 DIETARY INTERVENTIONS

5.5.1 Studies considered[58]

One RCT (N = 81) providing relevant clinical evidence met the eligibility criteria for this review (AMMINGER2010 [Amminger *et al*., 2010]). Post-treatment data were identified in a systematic review (Marshall & Rathbone, 2011), while follow-up data were published in 2010 (Amminger *et al*., 2010; see Table 18 for a summary of the study characteristics). Further information about the included study can be found in Appendix 14a.

Table 18: Study information table for trials of dietary interventions

Omega-3 fatty acids versus placebo	
Total no. of studies (N)	1 (N = 81)
Study ID	AMMINGER2010
Screening tool	Positive and Negative Syndrome Scale (PANSS)
Diagnosis	Ultra-high risk mental state
Mean age (range)	16.4 (not reported)
Sex (% male)	33
Ethnicity (% white)	Not reported
Mean (range) medication dose (mg/day)	1200
Treatment length (weeks)	12
Treatment follow-up (weeks)	52
Setting	Specialist clinic/ward
Country	Austria
Funding	Stanley Medical Research Institute

[58]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).

5.5.2 Clinical evidence for omega-3 fatty acids versus placebo

One study compared omega-3 polyunsaturated fatty acids (ω-3 PUFAs) with placebo. At 12 weeks post-treatment significantly more participants in the placebo group had transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder) (RR = 0.13; 95% CI, 0.02 to 0.95). However, there were only nine events in total. As only data for completers were reported a sensitivity analysis for transition to psychosis was conducted, assuming dropouts had made transition, and the effect became non-significant (RR = 0.27; 95% CI, 0.08 to 0.88). No other outcomes were reported at this timepoint. At 52 weeks' follow-up including all participants randomised the effect was significant (RR = 0.18; 95% CI, 0.04 to 0.75), with two out of 41 participants in the omega-3 fatty acids group and 11 out of 40 participants in the placebo group having transitioned. Large effects on total symptoms of psychosis, (SMD = –1.26; 95% CI, –1.74, –0.78), positive (SMD = –2.08; 95% CI, –2.63 to –1.54) and negative symptoms of psychosis (SMD = –2.22; 95% CI, –2.77 to –1.66), depression (SMD = –0.56; 95% CI, –1.01 to –0.12) and psychosocial functioning (SMD = –1.28; 95% CI, –1.76 to –0.80) also favoured omega-3 fatty acids at 52 weeks' follow-up. Dropout after 52 weeks was low (only five events; see Appendix 14a [13.1]) and similar between groups (RR = 1.46; 95% CI, 0.26 to 8.30). Evidence from each reported outcome and overall quality of evidence are presented in Table 19 and Table 20.

The full evidence profiles can be found in Appendix 17a.

5.5.3 Clinical evidence summary for dietary interventions

One RCT (N = 81) comparing omega-3 fatty acids with placebo was reviewed. Although the study was well conducted, sample sizes were small. The findings suggest that omega-3 fatty acids may be effective at preventing transition to psychosis and improving symptoms of psychosis, depression and psychosocial functioning in young people. However, owing to the paucity of evidence (lack of independent replication) no robust conclusions can be made.

5.6 PSYCHOSOCIAL INTERVENTIONS

5.6.1 Studies considered[59]

Six RCTs (N = 800) providing relevant clinical evidence met the eligibility criteria for this review (ADDINGTON2011 [Addington *et al.*, 2011], BECHDOLF2012 [Bechdolf *et al.*, 2012], MORRISON2004 [Morrison *et al.*, 2004a], MORRISON2011 [Morrison *et al.*, 2011], PHILLIPS2009, VANDERGAAG2012 [Van der Gaag *et al.*, 2012]). Of these, two (MORRISON2004, PHILLIPS2009) contained some unpublished data.

[59]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 19: Summary of findings table for outcomes reported for omega-3 fatty acids versus placebo at 12 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Completer analysis: transition to psychosis (RR)	AMMINGER2010	K = 1, N = 76	0.13 [0.02, 0.95]*	N/A	Low[1,2]	Appendix 14a (13.1)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	AMMINGER2010	K = 1, N = 81	0.39 [0.13, 1.14]*	N/A	–	Appendix 14a (13.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours omega-3 fatty acids.
[1]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[2]Serious risk of reporting bias.

Table 20: Summary of findings table for outcomes reported for omega-3 fatty acids versus placebo at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	AMMINGER2010	K = 1, N = 81	–1.26 [–1.74, –0.78]*	N/A	Low[1,2]	Appendix 14a (14.1)
Positive symptoms (SMD)	AMMINGER2010	K = 1, N = 81	–2.08 [–2.63, –1.54]*	N/A	Low[1,2]	Appendix 14a (14.2)
Negative symptoms (SMD)	AMMINGER2010	K = 1, N = 81	–2.22 [–2.77, –1.66]*	N/A	Low[1,2]	Appendix 14a (14.3)
Depression (SMD)	AMMINGER2010	K = 1, N = 81	–0.56 [–1.01, –0.12]*	N/A	Low[1,2]	Appendix 14a (14.4)
Psychosocial functioning (SMD)	AMMINGER2010	K = 1, N = 81	–1.28 [–1.76, –0.80]*	N/A	Low[1,2]	Appendix 14a (14.5)
Transition to psychosis (RR)	AMMINGER2010	K = 1, N = 81	0.18 [0.04, 0.75]*	N/A	Low[1,2]	Appendix 14a (14.6)
Leaving the study early for any reason (RR)	AMMINGER2010	K = 1, N = 81	1.46 [0.26 to 8.30]	N/A	Low[1,2]	Appendix 14a (15.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours omega-3 fatty acids.
[1]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[2]Serious risk of reporting bias.

All studies contained a sample in which some participants were under 18 and the mean age was 25 years or younger. Further information about the included studies can be found in Appendix 13a.

Of the six included trials, five compared individual CBT with supportive counselling and one compared a multimodal intervention (integrated psychological therapy) with supportive counselling (see Table 21 for a summary of the study characteristics).

5.6.2 Clinical evidence for CBT versus supportive counselling

Five RCTs (ADDINGTON2011; MORRISON2004, MORRISON2011, PHILLIPS2009, VANDERGAAG2012; N = 672) compared CBT with supportive counselling. Within the first 26 weeks of treatment CBT did not significantly reduce transition to psychosis (defined as the development of a DSM-IV psychotic disorder) compared with supportive counselling (RR = 0.62; 95% CI, 0.29 to 1.31), observing 40 events in total (N = 591). However, at 52 weeks' follow-up, CBT significantly reduced transition to psychosis (RR = 0.54; 95% CI, 0.34 to 0.86). As one study in the meta-analysis only reported data for completers a sensitivity analysis for transition to psychosis (assuming dropouts had made transition) was conducted. In sensitivity analysis this effect remained significant (RR = 0.64; 95% CI, 0.44 to 0.93). Furthermore, at 78 weeks' (or more) follow-up CBT was significantly associated with fewer transitions to psychosis (RR = 0.63; 95% CI, 0.40 to 0.99); however, this did not remain significant in sensitivity analysis (RR = 0.55; 95% CI, 0.25 to 1.19).

Combined effects for total symptoms of psychosis, positive and negative symptoms of psychosis, depression, anxiety, psychosocial functioning and quality of life were not significant at any timepoint. However, one study (VANDERGAAG2012) reported secondary outcomes only for participants who had not transitioned; participants with the most severe symptoms were omitted from these analyses. In sensitivity analyses excluding this study, there was a significant effect for positive symptoms (SMD = −0.27; 95% CI, −0.47 to −0.06) at 52 weeks' follow-up, but effects for other outcomes remained non-significant. Dropout was similar between groups within the first 6 months (RR = 1.09; 95% CI, 0.88 to 1.35). Evidence from each reported outcome and overall quality of evidence are presented in Table 22, Table 23 and Table 24. The full evidence profiles can be found in Appendix 17a.

5.6.3 Clinical evidence for integrated psychological therapy versus supportive counselling

One study (BECHDOLF2012; N = 128) compared integrated psychological therapy with supportive counselling in participants in the early initial prodromal state. Integrated psychological therapy included individual CBT, group skills training, CRT and family treatments, in the absence of antipsychotic medication. Transition to psychosis was defined as either the development of attenuated (subclinical) or

Table 21: Study information table for trials of psychosocial interventions

	CBT versus supportive counselling	Integrated psychological therapy versus supportive counselling
Total no. of studies (N)	5 (N = 672)	1 (N = 128)
Study ID	(1) ADDINGTON2011 (2) MORRISON2004 (3) MORRISON2011 (4) PHILLIPS2009 (5) VANDERGAAG2012	BECHDOLF2012
Screening tool	(1) SIPS (2) PANSS (3)–(5) CAARMS	Early Recognition Inventory and Interview for the Retrospective Assessment of the Onset of Schizophrenia
Diagnosis	'At risk/ultra-high risk mental state'	Early initial prodromal state
Mean age (range)	(1) 20.9 (not reported) (2) 22 (range 16 to 36) (3) 20.7 (range 14 to 34) (4) 17.9 (not reported)[1] (5) 22.7	25.8 (not reported)
Sex (% male)	(1) 71 (2) 67 (3) 63 (4) 39[1] (5) 49	66
Ethnicity (% white)	(1) 57 (2) Not reported (3) 88 (4)–(5) Not reported	Not reported
Sessions of therapy	(1) CBT and supportive counselling: up to 20 (2) CBT: 26; supportive counselling: 13 (3) CBT: 26; supportive counselling: not reported	25 individual therapy sessions; 15 group sessions; 12 CRT sessions; three information and counselling of relatives sessions

Continued

Table 21: (*Continued*)

	CBT versus supportive counselling	**Integrated psychological therapy versus supportive counselling**
	(4) Up to of 35 hours (5) CBT: up to 26; supportive counselling: not reported	
Treatment length (weeks)	(1) 26 (2) 52 (3) 26 (4) 52 (5) 26	52
Treatment follow-up (weeks)	(1) 78 (2) 156 (3) 104 (4) 52 (5) 78	104
Setting	(1) Specialist clinic/ward (2)–(3) Not reported (4) Specialist clinic/ward (5) Mental health centres (multisite)	Specialist clinic/ward
Country	(1) Canada (2)–(3) UK (4) Australia (5) Netherlands	Germany

Note. [1]In the whole study (a three-way comparison evaluating risperidone, CBT and supportive counselling, N = 115).

transient symptoms (subthreshold psychosis) or a DSM-IV psychotic disorder. At 1 year post-treatment fewer people receiving integrated psychological therapy transitioned (RR = 0.19; 95% CI, 0.04 to 0.81), but there were only 13 events. The effect was maintained at 2 years' follow-up (RR = 0.32; 95% CI, 0.11 to 0.92). Dropout was similar between groups at 1 year (RR = 1.55; 95% CI, 0.68 to 3.53) and 2 years (RR = 0.95; 95% CI, 0.61 to 1.49) post-treatment. Other symptoms were not reported as outcomes, although the PANSS and Global Assessment of Functioning (GAF) were recorded at baseline. Evidence from each reported outcome and overall quality of evidence are presented in Table 25 and Table 26. The full evidence profiles can be found in Appendix 17a.

Table 22: Summary of findings table for outcomes reported for CBT versus supportive counselling at post-treatment (within or at 26 weeks)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ADDINGTON2011 PHILLIPS2009	K = 2, N = 123	0.004 [–0.32, 0.40]	(P = 0.77); I^2 = 0%	Low[1,2]	Appendix 14a (16.1)
Completer analysis: positive symptoms (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 489	–0.12 [–0.30, 0.06]	(P = 0.90); I^2 = 0%	Moderate[1]	Appendix 14a (16.2)
Sensitivity analysis: positive symptoms (SMD)[b]	ADDINGTON2011 MORRISON2011 PHILLIPS2009	K = 3, N = 319	–0.11 [–0.33 to 0.11]	(P = 0.75); I^2 = 0%	–	Appendix 14a (16.3)
Negative symptoms (SMD)	ADDINGTON2011 PHILLIPS2009	K = 2, N = 123	0.17 [–0.19, 0.53]	(P = 0.54); I^2 = 0%	Low[1,2]	Appendix 14a (16.4)
Depression (completer analysis) (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 478	0.13 [–0.20, 0.47]	(P = 0.03); I^2 = 67%	Low[1,2]	Appendix 14a (16.5)
Sensitivity analysis: depression (SMD)[b]	ADDINGTON2011 MORRISON2011 PHILLIPS2009	K = 3, N = 308	0.27 [0.15, 0.69]	(P = 0.06); I^2 = 64%	–	Appendix 14a (16.6)
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 172	0.01 [–0.28, 0.31]	N/A	Low[1,2]	Appendix 14a (16.7)

Psychosocial functioning (SMD)	ADDINGTON2011 MORRISON2011 PHILLIPS2009	K = 3, N = 291	0.02 [–0.22, 0.26]	(P = 0.96); I^2 = 0%	Low[1,2]	Appendix 14a (16.8)
Quality of life (completer analysis) (SMD)	MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 3, N = 383	0.01 [–0.19, 0.21]	(P = 0.78); I^2 = 0%	Low[1,2]	Appendix 14a (16.9)
Sensitivity analysis: quality of life (SMD)[b]	MORRISON2011 PHILLIPS2009	K = 2, N = 213	0.01 [–0.26, 0.28]	(P = 0.78); I^2 = 0%	-	Appendix 14a (16.10)
Transition to psychosis (completer analysis) (RR)	ADDINGTON2011* MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 591	0.62 [0.29, 1.31]	(P = 0.31); I^2 = 17%	Low[1,2]	Appendix 14a (16.11)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 4, N = 612	0.66 [0.40 to 1.08]	(P = 0.50); I^2 = 0%	-	Appendix 14a (16.12)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2011 PHILLIPS2009	K = 3, N = 411	1.01 [0.75, 1.36]	(P = 0.93); I^2 = 0%	Low[1,3]	Appendix 14a (17.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[b]The sensitivity analysis excluded VANDERGAAG2012.
*15 weeks during treatment.
[1]Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]$I^2 \geq 50\%$, $p < .05$.

Table 23: Summary of findings table for outcomes reported for CBT versus supportive counselling at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ADDINGTON2011 MORRISON2004 PHILLIPS2009	K = 3, N = 154	0.05 [–0.27, –0.37]	(P = 0.08); I^2 = 0%	Low[1,2]	Appendix 14a (18.1)
Positive symptoms (completer analysis) (SMD)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 493	–0.17 [–0.35, 0.01]	(P = 0.47); I^2 = 0%	Moderate[1]	Appendix 14a (18.2)
Sensitivity analysis: positive symptoms (SMD)[b]	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009	K = 4, N = 342	–0.27 [–0.49, –0.06]*	(P = 0.82); I^2 = 0%	–	Appendix 14a (18.3)
Negative symptoms (SMD)	ADDINGTON2011 MORRISON2004 PHILLIPS2009	K = 3, N = 154	0.11 [–0.21, 0.43]	(P = 0.95); I^2 = 0%	Low[1,2]	Appendix 14a (18.4)
Completer analysis: depression (SMD)	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	K = 3, N = 385	–0.05 [–0.25, 0.15]	(P = 0.63); I^2 = 0%	Low[1,2]	Appendix 14a (18.5)
Sensitivity analysis: depression (SMD)[b]	ADDINGTON2011 MORRISON2011	K = 2, N = 234	–0.01 [–0.26, 0.25]	(P = 0.61); I^2 = 0%	–	Appendix 14a (18.6)
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 188	0.15 [–0.15, 0.44]	N/A	Low[1,2]	Appendix 14a (18.7)

Psychosocial functioning (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 240	–0.10 [–0.36, 0.15]	(P = 0.70); I^2 = 0%	Low[1,2]	Appendix 14a (18.8)
Completer analysis: quality of life (SMD)	MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 3, N = 329	–0.01[–0.23, 0.21]	(P = 0.75); I^2 = 0%	Low[1,2]	Appendix 14a (18.9)
Sensitivity analysis: quality of life (SMD)[b]	MORRISON2011 PHILLIPS2009	K = 2, N = 178	–0.05 [–0.35, –0.25]	(P = 0.40); I^2 = 0%	–	Appendix 14a (18.10)
Completer analysis: transition to psychosis (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 645	0.54 [0.34, 0.86]*	(P = 0.64); I^2 = 0%	Moderate[2]	Appendix 14a (18.11)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 672	0.64 [0.44, 0.93]*	(P = 0.59); I^2 = 0%	–	Appendix 14a (18.12)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009 VANDERGAAG2012	K = 5, N = 665	1.03 [0.82, 1.30]	(P = 0.83); I^2 = 0%	Low[1,2]	Appendix 14a (19.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[b]The sensitivity analysis excluded VANDERGAAG2012.
*Favours CBT.
[1]Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 24: Summary of findings table for outcomes reported for CBT versus supportive counselling ≥78 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ADDINGTON2011	K = 1, N = 51	–0.04 [–0.59, 0.51]	N/A	Low[1,2]	Appendix 14a (20.1)
Completer analysis: positive symptoms (SMD)	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	K = 3, N = 256	–0.17 [–0.42, 0.07]	(P = 0.72); I^2 = 0%	Low[1,2]	Appendix 14a (20.2)
Sensitivity analysis: positive symptoms (SMD)[b]	ADDINGTON2011 MORRISON2011	K = 2, N = 116	–0.14 [–0.50, 0.23]	(P = 0.45); I^2 = 0%	–	Appendix 14a (20.3)
Negative symptoms (SMD)	ADDINGTON2011	K = 1, N = 51	–0.10 [–0.65, 0.45]	N/A	Low[1,2]	Appendix 14a (20.4)
Completer analysis: depression (SMD)	ADDINGTON2011 MORRISON2011 VANDERGAAG2012	K = 3, N = 352	–0.11 [–0.36, 0.13]	(P = 0.49); I^2 = %	Low[1,2]	Appendix 14a (20.5)
Sensitivity analysis: depression (SMD)[b]	ADDINGTON2011 MORRISON2011	K = 2, N = 112	–0.05[–0.46, 0.37]	(P = 0.27); I^2 = 19%	–	Appendix 14a (20.6)
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 58	–0.46 [–0.99, 0.06]	N/A	Low[1,2]	Appendix 14a (20.7)
Psychosocial functioning (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 116	–0.03 [–0.45, 0.40]	(P = 0.25); I^2 = 25%	Low[1,2]	Appendix 14a (20.8)

Completer analysis: quality of life (SMD)	MORRISON2011 VANDERGAAG2012	K = 2, N = 188	0.18 [–0.10, 0.47]	(P = 0.39); I^2 = 0%	Low[1,2]	Appendix 14a (20.9)
Sensitivity analysis: quality of life (SMD)[b]	MORRISON2011	K = 1, N = 48	0.40 [–0.17, 0.98]	N/A	–	Appendix 14a (20.10)
Completer analysis: transition to psychosis (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 VANDERGAAG2012	K = 4, N = 570	0.63 [0.40, 0.99]	(P = 0.48); I^2 = 0%	Low[1,2]	Appendix 14a (20.11)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 VANDERGAAG2012	K = 4, N = 595	0.55 [0.25, 1.19]	(P = 0.002); I^2 = 79%	Low[1,2]	Appendix 14a (20.12)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 VANDERGAAG2012	K = 4, N = 593	1.09 [0.88, 1.35]	(P = 0.58); I^2 = 0%	Low[1,2]	Appendix 14a (21.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[b]The sensitivity analysis excluded VANDERGAAG2012.
[1]Serious risk of bias (including unclear sequence generation, trial registration could not be found, missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 25: Summary of findings table for outcomes reported for integrated psychological therapy versus supportive counselling at 52 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Transition to psychosis (RR)	BECHDOLF2012	K = 1, N = 125	0.19 [0.04, 0.81]*	N/A	Very low[1,2,3]	Appendix 14a (22.1)
Leaving the study early for any reason (RR)	BECHDOLF2012	K = 1, N = 128	1.55 [0.68, 3.53]	N/A	Very low[1,2,]	Appendix 14a (23.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours integrated psychological therapy.
[1] Serious risk of bias (missing data).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state and transition is defined as the development of either attenuated/transient symptoms or a DSM-IV psychotic disorder).

Table 26: Summary of findings table for outcomes reported for integrated psychological therapy versus supportive counselling at 104 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Transition to psychosis (RR)	BECHDOLF2012	K = 1, N = 125	0.32 [0.11, 0.92]*	N/A	Very low[1,2,3]	Appendix 14a (24.1)
Leaving the study early for any reason (RR)	BECHDOLF2012	K = 1, N = 128	0.95 [0.61, 1.49]	N/A	Very low[1,2,3]	Appendix 14a (25.1)

Note. *Favours integrated psychological therapy.
[a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (participants classified as in the early initial prodromal state as opposed to a high risk mental state and transition is defined as the development of either attenuated/transient symptoms or a DSM-IV psychotic disorder).

5.6.4 Clinical evidence summary for psychosocial interventions

Six RCTs (N = 800) investigated the efficacy of psychological interventions in young people at risk of developing psychosis and schizophrenia. Five trials (N = 672) compared CBT with supportive counselling and the findings suggest that CBT may have a beneficial effect on rate of transition to psychosis. However, CBT was found to be no more effective than supportive counselling on psychotic symptoms, depression, psychosocial functioning and quality at life. One RCT (N = 128) compared integrated psychological therapy with supportive counselling and found small effects that integrated psychological therapy decreases transition to psychosis. However, significant effects were lost when dropouts in both groups were assumed to have transitioned and the authors did not report how many participants transitioned to a DSM-IV psychotic disorder, as opposed to an ultra-high/high risk mental state (attenuated/transient symptoms). Overall, heterogeneity between samples in terms of their degree of risk for developing psychosis, alongside the paucity and low quality of evidence, means that no robust conclusions can be drawn.

5.7 HEALTH ECONOMIC EVIDENCE

Systematic literature review

The systematic search of the economic literature undertaken for this guideline identified two eligible studies on people at risk of psychosis (Valmaggia *et al*., 2009; Phillips *et al*., 2009b). One study was conducted in the UK (Valmaggia *et al.,* 2009) and one in Australia (Phillips *et al*., 2009b). Details on the methods used for the systematic review of the economic literature are described in Chapter 3; evidence tables for all economic evaluations included in the systematic literature review are provided in Appendix 16. Completed methodology checklists of the studies are provided in Appendix 15. Economic evidence profiles of studies considered during guideline development (that is, studies that fully or partly met the applicability and quality criteria) are presented in Appendix 17a, accompanying the respective clinical evidence profiles.

Valmaggia and colleagues (2009) conducted a cost-effectiveness analysis of an EIP service for people at high risk of psychosis. The study assessed Outreach and Support in South London (OASIS), a service for people with an at risk mental state for psychosis and schizophrenia. The service comprised information about symptoms, practical and social support, and the offer of CBT and medication. The early intervention was compared with care as usual, which did not include any provision of specialised mental health interventions. The data on care as usual was obtained from the same geographical area of south London. The decision analytic model was developed for a period of 1 and 2 years from two perspectives (the health sector and society).

The decision analytic model took into account the cost of the intervention and usual care, initial GP visit, outpatient care (including contact with the community mental health team), informal inpatient stay and formal inpatient stay. The societal perspective also included lost productivity costs incurred during DUP. The resource use and cost data are acquired from national published sources and the studies reviewed.

The clinical evidence showed that the EIP service for people at high risk of psychosis reduced the risk of developing psychosis, and it also reduced the DUP. These outcomes were used as key parameters in the economic analysis. The long and short DUP were defined as more than or less than 8 weeks of untreated psychosis.

Valmaggia and colleagues (2009) showed that probability of transition to psychosis with an EIP service is 0.20 compared with 0.35 in the case of usual care. The probability of long DUP in the intervention group (OASIS) is 0.05. This is lower than the usual care probability of 0.80, which consequently leads to a higher proportion of formal and informal inpatients in the usual care group.

According to the cost results, at 1 year the expected total service cost per person was £2,596 for the EIP service and £724 for usual care in 2004 prices. The 1-year duration did not capture the transition to psychosis because it was assumed to occur at 12 months after referral. The model estimated the expected cost of intervention at £4,313 per person and £3,285 for usual care. Including cost of lost productivity, the 2-year model showed cost savings with expected intervention costs of £4,396 per person and usual care of £5,357. Therefore, the perspective taken in the analysis, health sector or societal, is important as it changes the findings of the model. Using the reported data, the estimated incremental cost-effectiveness ratio (ICER) is £6,853 per person of avoiding risk of psychosis in 2004 prices.

The one-way sensitivity analysis showed that the 2-year model from a societal perspective is robust to changes in parameter values. There was no sensitivity analysis conducted using the NHS perspective. The economic model only covered the 2 years' duration of the study, however psychotic disorders can be lifelong. A longer study is required to analyse whether a lower rate of transition to psychosis in the intervention group is temporary or permanent. The lower rate of transition to psychosis and long DUP in the intervention group could also have substantial economic benefits accruing beyond 2 years. Another limitation of the model is that it used data from observational studies and not from RCTs, which could affect the robustness of the results. The settings of the service and the local cost estimates might not be applicable to other areas. However, sensitivity analysis mitigates this limitation and the tree model structure can be tailored to other settings and estimates of costs and transition probabilities. The model only took into account indirect cost of lost employment. The cost to parents and carers for unpaid care, to social care, and to the criminal justice system might also contribute to indirect costs that are not accounted for.

Phillips and colleagues (2009b) conducted a cost-minimisation study of specific and non-specific treatment for young people at ultra-high risk of developing first episode of psychosis in Australia. The analysis compared the costs of a specific preventive intervention with a needs-based intervention. The specific preventive intervention comprised a combination of risperidone and cognitively-oriented psychotherapy in addition to 'needs-based treatment' (supportive counselling, regular case management and medication) for 6 months.

The mean age of participants in both groups was 20 years. The analysis took the perspective of the Australian healthcare sector. The costs of inpatient and outpatient services and pharmacological interventions were calculated at the end of treatment (at 6 months) and at 12 and 36 months' follow-up for young people attending the Personal

Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, Australia. The costs were measured in Australian dollars in 1997 prices and the 36 months' follow-up costs were discounted at 3%.

As the cost analysis was conducted after the completion of the trial, several assumptions were made regarding resource use during the treatment. Resource use was calculated via a patient questionnaire during follow-up, which could have introduced errors. The unit costs were acquired from the budget and financial information of the service and national published sources on mental health costs in Australia.

The results were presented as mean costs for both groups for inpatient and outpatient services and pharmacological interventions and total costs of the treatment phase (6 months) and 12 and 36 month's follow-up. The specific preventive intervention had significantly higher cost for outpatient services of AU$2,585 during the treatment phase compared with the needs-based intervention of AU$1,084. However, the outpatient cost of specific preventive intervention at 36 months is AU$4,102, which is significantly lower than the needs-based intervention cost of AU$10,423. The differences between total costs and other components of the two intervention groups during the treatment phase and 12 and 36 months' follow-up were not statistically significant.

The findings of the study were not definitive; however, the analysis indicated substantial cost savings associated with the specific preventive intervention in the longer term. Most importantly, the study highlights that despite high outpatient costs of the specific preventive intervention during the treatment phase and at 12 months' follow-up, it incurred significantly lower outpatient costs than the needs-based intervention at 36 months' follow-up. The lower cost of the specific preventive intervention at 36 months was not associated with the treatment outcome as there were no differences in functioning or quality of life. The side effects of the intervention captured in the clinical trial are not accounted for in the health economic analysis, which could alter the findings substantially. The analysis is valuable because it used patient-level data and compared two services of different levels of intensity. However, the sample size of the study is small and not representative beyond the ultra-high risk subgroup, which is a limitation. In addition, the resource-use data were based on assumptions because the cost analysis was conducted after the completion of the trial and the patient questionnaire at follow-up could have led to patients erroneously recalling resource use. On reflection, the GDG concluded that the health economic analysis was unsupportable within the context of this guideline.

5.8 FROM EVIDENCE TO RECOMMENDATIONS

Recent studies have examined the feasibility of detecting and treating individuals with at risk mental states, prior to the development of psychosis and schizophrenia. Criteria are now available to identify and recognise help-seeking individuals who are at high risk of imminently developing schizophrenia and related psychoses, using standardised semi-structured interviews. These criteria require further refinement in order to better predict the course of these 'at risk' behaviours and symptoms, as well as recognition of those who will and those who will not go on to develop psychosis. In

addition, in order to obtain precise estimates of rates of transition to psychosis in this population, further work is needed that looks at the influence of sampling strategies in this population.

Transition to psychosis is the primary outcome for interventions conducted in populations at risk of developing psychosis and schizophrenia. However, this is often a highly comorbid, help-seeking group that requires support and treatment and as a result, outcomes pertaining to psychotic symptoms, anxiety and depression are also important. When meta-analysed, there was no clear evidence to suggest that antipsychotic medication can prevent transition. Moreover, adverse effects, specifically weight gain, were clearly evident and indicate that the harms associated with antipsychotic medication significantly outweigh the benefits.

Overall, the results for psychological, psychosocial and dietary interventions suggest that transition to psychosis from a high-risk mental state may be preventable. These findings also provide a baseline for developing future research strategies, and they highlight treatments that have the most potential for reducing transition to psychosis. Moderate quality evidence was identified in five trials of CBT (N = 672), which showed a moderately sized effect on transition to psychosis at 12 months, and low quality evidence for a moderately sized effect at 18 months. In sensitivity analyses (assuming dropouts had transitioned) the effect observed for CBT on transition at 12 months remained significant. In addition, in one small trial of integrated psychological therapy a between-group difference in transition (defined as either the development of attenuated/transient symptoms or a DSM-IV psychotic disorder) was found, but in sensitivity analysis (assuming dropouts transitioned) the effect was lost. The assumption made in the sensitivity analyses may not be the most appropriate approach in this context because those that do transition and ultimately must remain in services will be easier to find. On the other hand, participants who drop out because they do not wish to continue treatment (that is, because they do not like the treatment or have got better) will not remain in contact with services and therefore will be harder to locate. An important additional consideration is that there is good evidence from data in adults that family intervention is effective in reducing relapse rates in both first episode psychosis and in established schizophrenia. Importantly, family intervention was a key component of integrated psychological therapy.

Finally, one small RCT indicated that omega-3 fatty acids may also be effective in preventing transition from at risk mental states to the development of psychosis (even when sensitivity analysis is applied and dropouts are assumed to have transitioned) and improving symptoms of psychosis, depression and psychosocial functioning in young people. Given the very small sample from which these results were obtained, there is not sufficient evidence with which to recommend the use of omega-3 fatty acids.

Ultimately, the majority of individuals in these at risk samples do not convert to psychosis and as a result there are serious concerns regarding the risk of exposure to unnecessary interventions. The harms associated with intervening include stigma, a fear of becoming psychotic (because that is why they have been included in the trial or offered the treatment), the side effects of antipsychotic medication, in particular weight gain, the potential for type 2 diabetes, long-term cardiovascular disease and the risk of irreversible brain changes resulting in effectively untreatable

and permanent movement disorders when antipsychotic drugs are used at higher dose in the long term. Given the seriousness of these effects, and that only a small proportion of individuals will go on to develop psychosis, it seems that for the majority of children and young people treatment will result in unacceptable harm. Consequently, there is a strong basis for not prescribing antipsychotic medication or researching its use further in this population.

The GDG, however, noted that because these children and young people are treatment seeking, often distressed and have comorbidities, they should have access to help for their distress (CBT) and treatments recommended in NICE guidance for any comorbid conditions such as anxiety, depression, emerging personality disorder or substance misuse, or whatever other problem presents.

It is important to note that many of the trials included in this review had a range of different limitations, which led to a high risk of bias for almost all of the studies that were considered to be of low or very low quality and difficult to interpret. Such limitations included small sample sizes, lack of outcome assessor blinding and likely publication bias. Furthermore, there is some suggestion that among this high risk group, the number of transitions increases over 3 years and then settles. Therefore, trials require longer periods of follow-up.

The GDG was of the view that several research recommendations, as well as clinical recommendations, were needed for children and young people at risk of developing psychosis and schizophrenia. No systematic reviews were identified that specifically investigated specific behaviours and symptoms associated with an increased risk of developing psychosis and schizophrenia (at risk mental state). However one recent systematic review (Fusar-Poli *et al.,* 2012) was identified providing information about how operationally defined criteria for at risk mental states were measured in the current literature and demonstrated that these criteria require further refinement in order to better predict the course of associated behaviours and symptoms, as well as those people who will go on to develop psychosis. Therefore the GDG agreed that further research was needed examining the long-term outcomes in this population, refining the current criteria and investigating the influence of sampling strategies on rates of transition (see Section 5.10).

The GDG considered it important that children and young people experiencing transient psychotic symptoms or other experiences suggestive of possible psychosis were referred urgently to a specialist mental health service where a multidisciplinary assessment should be carried out (see recommendations 5.9.1.1 and 5.9.2.1). In addition, the GDG decided to recommend individual CBT with or without family intervention for child and young people at risk of developing psychosis delivered with the aim of lowering the risk of transition to psychosis and reducing current distress (see recommendation 5.9.3.1). It was also deemed important to monitor individuals for up to 3 years (see recommendation 5.9.2.2), offering follow-up appointments to those who requested discharge from the service (see recommendation 5.9.2.3). Further research into the use of family intervention to prevent a first occurrence of psychosis in those at high risk was considered necessary. Based on the evidence from adult populations for the first episode that family intervention can prevent relapse (see Chapter 6), and the promise shown in the trials conducted

in children and young people on integrated psychological therapy (which included a family treatment) and CBT, the GDG was of the opinion that a large multicentre RCT of family intervention and CBT with a cost-effectiveness analysis should be undertaken (see Section 5.10).

As no evidence was found to support the early promise that some antipsychotics may delay or prevent transition, and because antipsychotics are associated with significant side effects, the GDG decided there was no reason to pursue this line of enquiry, particularly since many children and young people at ultra-high risk will not progress to psychosis and schizophrenia (see recommendation 5.9.3.2).

Finally, given that the results of the omega-3 fatty acids trial suggest this intervention may have a beneficial effect on transition rates, and that it appears to be a relatively safe treatment with few health risks and has a number of other potential benefits for cardiovascular status, the GDG deemed that this relatively inexpensive treatment should be examined further in a large, multicentre, placebo-controlled trial (see Section 5.10).

5.9 RECOMMENDATIONS

5.9.1 Referral from primary care

5.9.1.1 When a child or young person experiences transient or attenuated psychotic symptoms or other experiences suggestive of possible psychosis, refer for assessment without delay to a specialist mental health service such as CAMHS or an early intervention in psychosis service (14 years or over).

5.9.2 Assessment in specialist mental health services

5.9.2.1 Carry out an assessment of the child or young person with possible psychosis, ensuring that:

- assessments in CAMHS include a consultant psychiatrist
- assessments in early intervention in psychosis services are multidisciplinary
- where there is considerable uncertainty about the diagnosis, or concern about underlying neurological illness, there is an assessment by a consultant psychiatrist with training in child and adolescent mental health.

5.9.2.2 If a clear diagnosis of psychosis cannot be made, monitor regularly for further changes in symptoms and functioning for up to 3 years. Determine the frequency and duration of monitoring by:

- the severity and frequency of symptoms
- the level of impairment and/or distress in the child or young person, and
- the degree of family disruption or concern.

5.9.2.3 If discharge from the service is requested, offer follow-up appointments and the option to self-refer at a later date. Ask the GP to continue monitoring changes in mental state.

5.9.3 Treatment options for symptoms not sufficient for a diagnosis of psychosis or schizophrenia

5.9.3.1 When transient or attenuated psychotic symptoms or other mental state changes associated with distress, impairment or help-seeking behaviour are not sufficient for a diagnosis of psychosis or schizophrenia:

- consider individual cognitive behavioural therapy (CBT) (delivered as set out in recommendation 6.5.13.3) with or without family intervention (delivered as set out in recommendation 6.6.9.3), and
- offer treatments recommended in NICE guidance for children and young people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse.

5.9.3.2 Do not offer antipsychotic medication:

- for psychotic symptoms or mental state changes that are not sufficient for a diagnosis of psychosis or schizophrenia, or
- with the aim of decreasing the risk of psychosis.

5.10 RESEARCH RECOMMENDATIONS

- What are the long-term outcomes, both psychotic and non-psychotic, for children and young people with attenuated or transient psychotic symptoms suggestive of a developing psychosis, and can the criteria for 'at risk states' be refined to better predict those who will and those who will not go on to develop psychosis? (See Appendix 12 for further details.)
- What is the clinical and cost effectiveness of omega-3 fatty acids in the treatment of children and young people considered to be at high risk of developing psychosis? (See Appendix 12 for further details.)
- What is the clinical and cost effectiveness for family intervention combined with individual CBT in the treatment of children and young people considered to be at high risk of developing psychosis and their parents or carers? (See Appendix 12 for further details.)
- An adequately powered RCT should be conducted to investigate the influence of sampling strategies on rates of transition to psychosis.

6 PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS

6.1 INTRODUCTION

Interest in psychological and broader psychosocial interventions for the treatment of psychosis and schizophrenia re-emerged in the 1980s due to increasing recognition of the limitations, side effects and health risks associated with antipsychotic medication and low rates of adherence (Perkins *et al.*, 2008). In children and young people with psychosis and schizophrenia, there is particular caution given the greater cumulative lifetime exposure to antipsychotic medication and concerns regarding physical health risks. Over the last decade, there has been a revolution in our understanding of the role that ecological and psychological processes have on the risk for psychosis and on resilience (Van Os & Kapur, 2009). This includes, for example, the impact of an urban upbringing and living in unstable and fragmented areas (Kirkbride *et al.*, 2010) and the impact that low self-esteem can have on the way in which individuals interpret and give meaning to their psychotic symptoms

Demand for psychological therapies in general has also grown, culminating in the Department of Health's Improving Access to Psychological Therapies (IAPT)[60] initiative. Indeed, in the coalition government's mental health strategy, funding has been made available to extend IAPT to children and young people and to those with major mental health problems, particularly schizophrenia.

6.1.1 Developmental processes and the emergence of psychosis

The term 'first episode psychosis' is a misnomer because rather than marking the onset of psychosis, it is, in reality, the 'end of the beginning'. With few exceptions, the formal onset of psychosis is preceded by many months of untreated psychosis and before that, many years of changes stretching back into late childhood. Important prospective studies, particularly the 'Dunedin Study' (Poulton *et al.*, 2000), have shown that the subtle psychotic-like experiences at age 11 strongly predict the later emergence of psychosis; however, many individuals manage to escape this outcome. Population studies such as the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Kuepper *et al.*, 2011) and the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AeSOP) study in the UK (Kirkbride *et al.*, 2010) have shown that a number of 'environmental' factors predict those who are more likely to show persistence and worsening of symptoms, including cannabis exposure in adolescence, social deprivation, absence of a parent and childhood abuse or neglect. Affective dysregulation has been shown to be highly comorbid with psychosis (and is now argued

[60] At time of publication, IAPT services are only available in England.

to be a dimension of psychosis) and a strong feature in its early development; the presence of affective dysfunction in adolescence, particularly depression and social anxiety, has been shown to be a predictor of transition from psychotic experience to psychotic disorder (Van Os & Kapur, 2009).

Social disability is one of the hallmarks of psychosis and schizophrenia and those with onset in adolescence tend to fare worse in this regard. Prospective studies of social disability and recovery have shown that early functional and vocational recovery, rather than the remitting of psychotic symptoms, play a pivotal role in preventing the development of chronic negative symptoms and disability, underlining the need for interventions that specifically address early psychosocial recovery (Álvarez-Jiménez *et al.*, 2011). These developmental processes can inform the focus of interventions for children and young people with psychosis and schizophrenia, embracing the family, developmental trauma (and their sequelae), affective dysfunction, substance misuse and peer social engagement.

6.1.2 Aims of psychological and psychosocial interventions

The aims of psychological and psychosocial intervention in children and young people with psychosis and schizophrenia are numerous. Interventions should include those that improve symptoms but also those that address vulnerability and are embedded in adolescent developmental processes. The aims will include: reduction of distress associated with psychosis symptoms; promoting social and educational recovery; reducing depression and social anxiety; and relapse prevention. Reducing vulnerability and promoting resilience will require reducing cannabis misuse, promoting social stability and family support, and dealing with the sequelae of abuse and neglect including attachment formation.

Further consideration needs to be given to younger children (13 years or younger). Because of developmental immaturity, cognitive treatments are more difficult to implement in young children and treatment more likely to rely on behavioural interventions, which may involve rewarding the child's gradual involvement in appropriate everyday age activities. Family work to reduce high levels of criticism, emotional negativity or over-involvement, and to manage parental expectations of the child's level of functioning in line with the severity of the symptoms (especially during the acute phase of the illness), will be especially important in this age group. Following an acute episode, rehabilitation back into school will require careful assessment of the educational environment that will best meet the child's general needs, associated developmental deficits and psychiatric comorbidity and sequelae.

6.1.3 Competence to deliver psychological and psychosocial interventions

In order to implement this guideline, it is important to have an understanding of the level of competence needed to deliver the psychological and psychosocial interventions reviewed and recommended in this guideline particularly those for younger

children. Therefore the included trials were reviewed for details of training or level of competence of the therapists delivering the intervention.

6.2 CLINICAL REVIEW PROTOCOL FOR THE REVIEW OF PSYCHOLOGICAL AND PSYCHOSOCIAL INTERVENTIONS FOR CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS AND SCHIZOPHRENIA

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 27. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

Table 27: Clinical review protocol for the review of psychological and psychosocial interventions for children and young people with psychosis and schizophrenia

Component	Description
Review question	**RQ B11**: Do the advantages and disadvantages of psychological or psychosocial interventions, compared with alternative management, differ between children/young people and adults with psychosis and schizophrenia? **RQ B12**: Are the advantages and disadvantages of combining particular psychological/psychosocial interventions with an antipsychotic, either concurrently or sequentially, different for children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? **RQ B13:** Should the duration (and, where relevant, frequency) of an initial psychological/psychosocial intervention be different in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? **RQ B14**: Is the most effective format for particular psychological/psychosocial interventions (for example, group or individual) the same for children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?
Objectives	To provide evidence-based recommendations regarding the psychological and psychosocial treatment and management of children and young people with psychosis and schizophrenia, including a review of the adult *Schizophrenia* guideline (NICE, 2009a; NCCMH, 2010) for its relevance to children and young people.

Continued

Table 27: (*Continued*)

Component	Description
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	• Cognitive behavioural therapy (CBT) • Counselling and supportive psychotherapy • Family intervention (including family therapy) • Psychodynamic psychotherapy and psychoanalysis • Psychoeducation • Social skills training • Arts therapies
Comparison	Alternative management strategies: • Treatment as usual • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Remission
Secondary outcomes	None
Electronic databases	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases and grey literature (see Appendix 8)
Date searched	Systematic reviews: 1995 to May 2012 RCT: inception of databases to May 2012
Study design	RCTs; systematic reviews
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of psychological and psychosocial

Continued

Table 27: (*Continued*)

Component	Description
	• interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and 18. The review will seek to identify whether modifications in treatment and management of children aged at or under 13 years and younger need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

6.3 STUDIES CONSIDERED FOR REVIEW[61]

For children and young people with psychosis and schizophrenia, only one RCT (N = 30) was identified that provided relevant clinical evidence meeting the eligibility criteria for this review and conducted in individuals under 18 years (APTER1978 [Apter *et al*., 1978]). A further eight RCTs (N = 618) were identified in samples that included individuals under 18 years, but with a mean age of under 25 years, which provided relevant clinical evidence and met the eligibility criteria for this review (EDWARDS2011 [Edwards *et al*., 2011]; GLEESON2009 [Gleeson *et al*., 2009]; HADDOCK2006 [Haddock *et al*., 2006]; JACKSON2008 [Jackson *et al*., 2008]; JACKSON2009 [Jackson *et al*., 2009]); LINSZEN1996 [Linszen *et al*., 1996]; MAK2007 [Mak *et al*., 2007]; POWER2003 [Power *et al*., 2003]). Data from these studies were included and extrapolated. The interventions included CBT, family intervention and a specialised treatment as usual provided by the Early Psychosis Prevention and Intervention Centre (EPPIC) in Australia. Given the limited evidence in children and young people, this evidence was considered alongside the evidence reported and the recommendations made in the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) and recommendations for this guideline were developed accordingly.

[61] 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).

Schizophrenia included a broad range of different types of psychosocial and psychological interventions including CBT, counselling and supportive therapy, CRT, family intervention, psychodynamic and psychoanalytic therapy, psychoeducation, social skills training, adherence therapy and arts therapies.

All RCTs reviewed in this chapter were published between 1978 and 2012. An additional 213 studies were reviewed by full text and excluded from the analysis. Further information about both included and excluded studies can be found in Appendix 13b.

The following psychological therapies and psychosocial interventions were reviewed:

- arts therapies (Section 6.4)
- cognitive behavioural therapy (CBT) (Section 6.5)
- family intervention (Section 6.6)
- specialised treatment as usual (Section 6.7).

6.4 ARTS THERAPIES

6.4.1 Introduction

Definition

Arts therapies are complex interventions that combine psychotherapeutic techniques with activities aimed at promoting creative expression. In all arts therapies:

- the creative process is used to facilitate self-expression within a specific therapeutic framework
- the aesthetic form is used to 'contain' and give meaning to the person's experience
- the artistic medium is used as a bridge to verbal dialogue and insight-based psychological development if appropriate
- the aim is to enable the individual to experience him/herself differently and develop new ways of relating to others.

Arts therapies currently provided in the UK comprise art therapy or art psychotherapy, dance movement therapy, body psychotherapy, dramatherapy and music therapy.

6.4.2 Studies considered

One RCT (APTER1978; N = 30) compared individual body movement therapy with group body movement therapy and a non-specific dance therapy control (see Table 28 for a summary of the study characteristics). It was conducted in a sample of children and young people aged 13 to 18 years with acute psychosis. No data could be extracted and analysed and so results are reported narratively in this review.

6.4.3 Clinical evidence for body movement therapy (individual or group)

The only efficacy outcome of interest reported by APTER1978 was global improvement (as measured by the Clinical Global Impression [CGI] scale), however these data were not reported in a sufficient way to enable extraction. The authors stated that

Table 28: Study information table for trials comparing arts therapies

	Individual body movement therapy versus group body movement versus group non-specific dance therapy
Total no. of studies (N)	1 (N = 30)
Study ID	APTER1978
Diagnosis	Acute psychosis (bipolar disorder not specified)
Age (range)	Range: 13 to 18 years
Sex (% male)	50%
Ethnicity (% white)	Not reported
Treatment length (weeks)	12
Length of follow-up (weeks)	12
Setting	Inpatient
Country	Unclear

global improvement tended to favour the two treatment groups (individual and group body movement therapy) over the control group, but that this effect failed to reach statistical significance.

6.4.4 Clinical evidence summary – evidence for children and young people

Only one RCT (N = 30) of body movement therapy in children and young people aged 18 years and younger was reviewed. Data were not reported in a sufficient way to enable extraction and analysis. As a result, no robust conclusions about the efficacy of arts therapies in this population can be made. Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?') as well as the paucity and low quality of the evidence identified in children and young people the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 6.4.5)

6.4.5 Clinical evidence summary – evidence for adults

The review in the adult *Schizophrenia* guideline (NCCMH, 2010) contained six RCTs (N = 382) comparing arts therapies with any control (see Section 8.3 of *Schizophrenia*). The review found consistent evidence that arts therapies are effective in reducing negative symptoms when compared with any other control. There was some evidence indicating that the medium to large effects found at the end of treatment were sustained

at up to 6 months' follow-up. Additionally, there is consistent evidence to indicate a medium effect size regardless of the modality used within the intervention (that is, music, body-orientated or art), and that arts therapies were equally as effective in reducing negative symptoms in both inpatient and outpatient populations.

6.4.6 Economic considerations

A simple threshold analysis undertaken for the adult *Schizophrenia* guideline (NCCMH, 2010) estimated the minimum annual improvement in HRQoL in adults with schizophrenia that would be required in order for arts therapies, provided by a Health Professions Council (HPC) registered arts therapist, to be cost effective. Using the lower NICE cost-effectiveness threshold of £20,000 per quality-adjusted life year (QALY), the analysis indicated that arts therapies are cost effective if they improve the HRQoL of people with schizophrenia by 0.005 to 0.007 annually, on a scale of 0 (death) to 1 (perfect health). Using the upper cost-effectiveness threshold of £30,000 per QALY, the improvement in HRQoL of people with schizophrenia required for arts therapies to be cost effective fell by 0.003 to 0.004 annually. The use of this upper cost-effectiveness threshold can be justified because arts therapies are the only interventions to have large effects on negative symptoms. *Schizophrenia* (NCCMH, 2010) estimated that the magnitude of the improvement in negative symptoms associated with arts therapies could be translated into an improvement in HRQoL probably above 0.0035, and possibly even above 0.006 annually, given that the therapeutic effect of arts therapies was shown to last (and was even enhanced) at least up to 6 months following treatment. Therefore, it was concluded that arts therapies were likely to be a cost-effective option for adults with schizophrenia.

6.4.7 From evidence to recommendations

This review identified extremely limited data investigating the efficacy of arts therapies in children and young people with psychosis and schizophrenia. However, the adult evidence suggests that arts therapies are effective in reducing negative symptoms across a range of treatment modalities, and for both inpatient and outpatient populations. The data for the effectiveness of arts therapies on other outcomes such as social functioning and quality of life are more limited and less frequently reported. Nevertheless, the GDG recognises that arts therapies are currently the only interventions (both psychological and pharmacological) known to have medium to large effects on reducing negative symptoms in adult populations. As a result, large-scale investigations of arts therapies in children and young people should be undertaken.

The health economic model produced for the adult *Schizophrenia* guideline (NCCMH, 2010) considered arts therapies, provided by HPC registered arts therapists, to be cost effective at both the lower (£20,000 per QALY) and upper (£30,000 per QALY) NICE cost-effectiveness thresholds. This was based on annual improvements in HRQoL of adults with schizophrenia of approximately 0.006 and 0.0035 respectively. Ultimately,

the use of this upper cost-effectiveness threshold can be justified because arts therapies are the only interventions to have large effects on negative symptoms.

In summary, based on the absence of evidence in children and young people and the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), the GDG decided to adapt recommendations from *Schizophrenia* (NCCMH, 2010; NICE, 2009a) based on the methodological principles outlined in Chapter 3 and recommend the use of arts therapies for the acute episode in children and young people with psychosis and schizophrenia. Provision of such treatments by HPC registered arts therapists with previous experience of working with children and young people with schizophrenia was emphasised. Where recommendations required adaptation, the rationale is provided in Table 29 in the third column. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in the *Schizophrenia* guideline (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 6.4.8 in this guideline.

Finally, a large multicentre RCT is required to investigate the efficacy of arts therapies on all critical outcomes in this population.

6.4.8 Recommendations

6.4.8.1 Consider arts therapies (for example, dance movement, music or art therapy or drama-therapy) for all children and young people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings.[62]

6.4.8.2 If arts therapies are considered, they should be provided by Health Professions Council (HPC) registered arts therapists, with experience of working with children and young people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured and led by the child or young person. Aims of arts therapies should include:

- enabling children and young people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others
- helping children and young people to express themselves and to organise their experience into a satisfying aesthetic form
- helping children and young people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to them.[63]

[62] Adapted from *Schizophrenia* (NICE, 2009a).
[63] Adapted from *Schizophrenia* (NICE, 2009a).

Table 29: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for the use of arts therapies

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.3.4.3 Consider offering arts therapies to all people with schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings.	Consider arts therapies (for example, dance movement, music or art therapy or dramatherapy) for all children and young people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings. (6.4.8.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, and adapted it because they wished to make it clear that the term 'arts therapies' covers a range of interventions. No other significant adaptation was required.
1.3.4.14 Arts therapies should be provided by a Health Professions Council (HPC) registered arts therapist, with previous experience of working with people with schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured	If arts therapies are considered, they should be provided by Health Professions Council (HPC) registered arts therapists, with experience of working with children and young people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, and adapted it to provide clarity. The GDG felt that the strength of the original recommendation may be misinterpreted ('Arts therapies should be provided') and wished to make it clear in the use of the word 'considered' that the evidence for arts therapies is not as strong as for other psychological therapies. No other significant adaptation was required.

and led by the service user. Aims of arts therapies should include: • enabling people with schizophrenia to experience themselves differently and to develop new ways of relating to others • helping people to express themselves and to organise their experience into a satisfying aesthetic form • helping people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to the person.	and led by the child or young person. Aims of arts therapies should include: • enabling children and young people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others • helping children and young people to express themselves and to organise their experience into a satisfying aesthetic form • helping children and young people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to them. (6.4.8.2)	
1.4.3.4 Consider offering arts therapies to assist in promoting recovery, particularly in people with negative symptoms.	Consider arts therapies (see recommendation 6.4.8.2) to assist in promoting recovery, particularly in children and young people with negative symptoms. (6.4.8.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, and adapted it to conform with changes to NICE style for recommendations ('consider' rather than 'consider offering'). No other significant adaptation was required.

6.4.8.3 Consider arts therapies (see recommendation 6.4.8.2) to assist in promoting recovery, particularly in children and young people with negative symptoms.[64]

6.5 COGNITIVE BEHAVIOURAL THERAPY

6.5.1 Introduction

Definition of cognitive behavioural therapy (CBT)

CBT was defined as a discrete psychological intervention where service users:

- establish links between their thoughts, feelings or actions with respect to the current or past symptoms, and/or functioning, and
- re-evaluate their perceptions, beliefs or reasoning in relation to the target symptoms.

A further component of the intervention should involve the following:

- service users monitoring their own thoughts, feelings or behaviours with respect to the symptom or recurrence of symptoms, and/or
- promotion of alternative ways of coping with the target symptom, and/or
- reduction of distress, and/or
- improvement of functioning.

6.5.2 Studies considered

Six RCTs (N = 460) compared individual CBT with a control (see Table 30). All studies were conducted in children and young people aged 25 years and younger and were published between 2003 and 2012. One (MAK2007) compared CBT with waitlist, two (HADDOCK2006, JACKSON2009) compared CBT with treatment as usual, and one compared CBT with supportive counselling (HADDOCK2006). The remaining three studies (EDWARDS2011, JACKSON2008, POWER2003) were conducted in a specialist centre, EPPIC, in Australia (for further information about EPPIC, see Section 6.7). All participants in these studies received treatment as usual by the EPPIC staff, which was considered by the GDG to be highly specialised. One study compared CBT with befriending (JACKSON2008), one compared CBT for acutely suicidal participants with EPPIC treatment as usual (POWER2003) and one compared CBT plus clozapine with clozapine alone in participants who had not adequately responded to treatment with at least one atypical antipsychotic (EDWARDS2011). Two studies (HADDOCK2006, MAK2007) reported outcomes in insufficient detail to allow for extraction and analysis, one of which (HADDOCK2006) was a sub-analysis of an RCT (Lewis *et al*., 2002) designed to evaluate the effectiveness of CBT, supportive counselling and treatment as usual in the UK in participants of different ages. It compared the efficacy of treatments in participants aged 21 years and younger (N = 71) with those aged over 21 years (N = 238).

[64] Adapted from *Schizophrenia* (NICE, 2009a).

Table 30: Study information table for trials comparing CBT

	CBT (individual) versus waitlist	CBT (individual) versus treatment as usual	CBT (individual) versus supportive counselling	CBT (individual) + EPPIC treatment as usual versus befriending + EPPIC treatment as usual	CBT (individual) + EPPIC treatment as usual versus EPPIC treatment as usual in acutely suicidal participants	CBT (individual) + clozapine + EPPIC treatment as usual versus clozapine + EPPIC treatment as usual
Total no. of studies (N)	1 (N = 48)	2 (N = 269)	1 (N = 207)	1 (N = 62)	1 (N = 56)	1 (N = 25)[l]
Study ID	MAK2007	(1) JACKSON2009* (2) HADDOCK2006	HADDOCK 2006	JACKSON2008*	POWER2003*	EDWARDS2011*
Diagnosis	Schizophrenia	(1) First episode psychosis (bipolar disorder not specified) (2) Schizophrenic disorders	Schizophrenic disorders	First episode psychosis (including bipolar disorder)	First episode psychosis mixed (bipolar disorder not specified)	First episode psychosis (excluding bipolar disorder) not adequately responding to treatment
Mean age/range	24	(1) 23.3 (2) Not reported	Not reported	22.3	Range: 15 to 29	21.4
Sex (% male)	56	(1) 74 (2) Not reported	Not reported	73	Not reported	71
Ethnicity (% white)	Not reported	(1) 71 (2) Not reported	Not reported	Not reported	Not reported	Not reported
Mean medication dose (mg/day)	N/A	N/A	N/A	N/A	N/A	Clozapine: 326.12 Clozapine + CBT: 281.28

Continued

Table 30: (*Continued*)

	CBT (individual) versus waitlist	**CBT (individual) versus treatment as usual**	**CBT (individual) versus supportive counselling**	**CBT (individual) + EPPIC treatment as usual versus befriending + EPPIC treatment as usual**	**CBT (individual) + EPPIC treatment as usual versus EPPIC treatment as usual in acutely suicidal participants**	**CBT (individual) + clozapine + EPPIC treatment as usual versus clozapine + EPPIC treatment as usual**
Sessions of therapy	Minimum 20	(1) Maximum of 26 (2) 15–20, plus 'booster' sessions at 2 weeks and 1, 2 and 3 months	Not reported	Maximum of 20	Range: 8 to 10	CBT: mean (SD): 15.25 (6.5)
Treatment length (weeks)	CBT: 39 Waitlist: 26	(1) 26 (2) 18	18	14	10	12
Length of follow- up (weeks)	65	(1) 52 (2) 78	78	52	26	24
Setting	Non-specified psychiatric	(1) Non-specified psychiatric (2) Inpatient and outpatient	Inpatient and outpatient	Specialist clinic/ ward	Specialist clinic/ward	Specialist clinic/ward
Country	China	(1) Australia (2) UK	UK	Australia	Australia	Australia

Note. *Extractable outcomes.
[1]EDWARDS2011 had four treatment arms: clozapine, clozapine + CBT, thioridazine, and thioridazine + CBT (N = 48), but thioridazine was not included in the review protocol.

6.5.3 Clinical evidence for CBT versus waitlist

One study (N = 48) compared individual CBT with a waitlist control in China (MAK2007). Efficacy data could not be extracted for this study and the methods of analysis were unclearly reported. Outcome measures were taken at 9 months post-treatment and 15 months' follow-up and included positive symptoms (measured using the Present State Examination - 9th edition), negative symptoms (using the Family Interview Schedule), depression (using the Beck Depression Inventory) and psychosocial functioning (measured using the GAF). A quarter of the whole sample did not continue with the study, but dropout according to group was not reported. Although the authors reported greater improving trends in the clinical and functional status of the CBT group compared with waitlist control, the results did not reach statistical significance.

6.5.4 Clinical evidence for CBT versus treatment as usual

Two studies (HADDOCK2006, JACKSON2009; N = 269) compared individual CBT with treatment as usual from local mental health services. However, only one study (JACKSON2009) reported outcomes in sufficient detail to allow extraction and analysis. The CBT-based intervention in this study (JACKSON2009) was primarily aimed at reducing problems related to adjustment and adaptation following a first episode of psychosis. As a result, the primary outcomes reported in the paper were depression, self-esteem and post-traumatic phenomena and not psychotic symptoms. However, at 6 months post-treatment and 1-year follow-up, effects on depression were not significant (SMD = −0.29; 95% CI, −0.87 to 0.30 and SMD = −0.05; 95% CI, −0.65 to 0.54, respectively). Seventeen out of 36 participants had dropped out of the CBT group by 52 weeks compared with eight out of 30 in the treatment as usual group, but the difference was not statistically significant (see forest plot in Appendix 14b [1.2]). Evidence from each reported outcome and overall quality of evidence are presented in Table 31 and Table 32. The full evidence profiles can be found in Appendix 17b.

In a sub-analysis HADDOCK2006 evaluated outcomes by age, comparing participants aged 21 years and younger with those aged over 21 years receiving either CBT or treatment as usual. The authors reported that there were no significant interactions between therapy and age group on psychotic symptoms (as measured by the PANSS) or social functioning (as measured by the Social Functioning Scale [SFS]), at 3 months post-treatment or 18 months' follow-up.

6.5.5 Clinical evidence for CBT versus supportive counselling

One study (HADDOCK2006) compared CBT with supportive counselling. Outcomes were reported in insufficient detail to allow extraction and analysis and so results are reported narratively in this review. HADDOCK2006 is a sub-analysis of an RCT (Lewis *et al.,* 2002) evaluating the effectiveness of CBT, supportive counselling

Table 31: Summary of findings table for outcomes reported for CBT versus treatment as usual at 26 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Depression (SMD)	JACKSON2009	K = 1, N = 46	−0.29 [−0.87, 0.30]	N/A	Low[1,2]	Appendix14b (1.1)
Leaving the study early for any reason (RR)	JACKSON2009	K = 1, N = 66	1.94 [0.85, 4.43]	N/A	Low[1,2]	Appendix14b (1.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, trial registration not found and missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 32: Summary of findings table for outcomes reported for CBT versus treatment as usual at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Depression (SMD)	JACKSON2009	K = 1, N = 46	–0.05 [–0.65, 0.54]	N/A	Low[1, 2]	Appendix14b (2.1)
Leaving the study early for any reason (RR)	JACKSON2009	K = 1, N = 66	1.77 [0.89, 3.52]	N/A	Low[1, 2]	Appendix14b (2.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, trial registration not found and missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

and treatment as usual, in participants of different ages. Participants aged 21 years and younger (N = 71) are compared with those over 21 (N = 238). Authors reported that there were significant interactions between therapy and age group on PANSS General Subscale scores (F [1,147] = 6.44, P = 0.012), and a trend towards a significant interaction on Psychotic Symptoms Rating Scale (PSYRATS) Delusions Subscale scores (F [1,138] = 3.81, P = 0.053) at 3 months post-treatment and for PANSS Positive Subscale scores at 18 months' follow-up (F [1,147] = 4.422, P = 0.037). No significant interactions between therapy and age group were found for social functioning (as measured by the SFS). The authors suggest that supportive counselling is more effective than both CBT and treatment as usual at reducing positive symptoms in younger participants. Furthermore, they suggest the opposite pattern for older participants. At 18 months' follow-up they purport that CBT appears to have a greater effect than supportive counselling on positive symptoms in older compared with younger participants.

This is a subgroup analysis with small sample sizes particularly of participants aged 21 years and younger in which no effect sizes are reported. As a result, no robust conclusions can be drawn.

6.5.6 Clinical evidence for CBT versus EPPIC treatment as usual

One study (JACKSON2008) (N = 62) compared CBT plus treatment as usual in a specialised centre (EPPIC) with befriending plus EPPIC treatment as usual. EPPIC is described by the authors as a comprehensive treatment service for 15 to 25 year-old people experiencing a first episode of psychosis. It includes a 16-bed inpatient unit, an outpatient case management system, family work, accommodation, prolonged recovery programmes and tailored group programmes. Medication is also administered, in line with a low-dose protocol. At 14 weeks post-treatment and 1-year follow-up effects on symptoms of psychosis and social functioning were not significant, and dropout was similar between groups (RR = 0.57; 95% CI, 0.19 to 1.76). During the 1-year follow-up period two participants died by suicide and 12 were hospitalised in the CBT group, whereas in the befriending group there were no deaths by suicide and eight participants were hospitalised (see forest plots in Appendix 14b [4.4 and 4.5]). However, this difference is not statistically significant. Evidence from each reported outcome and overall quality of evidence are presented in Table 33 and Table 34. The full evidence profiles can be found in Appendix 17b.

6.5.7 Clinical evidence for CBT (individual) versus EPPIC treatment as usual in acutely suicidal participants

One study (POWER2003; N = 56) compared individual CBT plus EPPIC treatment as usual with EPPIC treatment as usual in acutely suicidal children and young people experiencing first episode psychosis. The CBT-based intervention was called 'LifeSpan therapy' and specifically aimed to reduce participants' suicidality. Similarly

Table 33: Summary of findings table for outcomes reported for CBT versus EPPIC treatment as usual at 14 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Positive symptoms (SMD)	JACKSON2008	K = 1, N = 62	–0.05 [–0.55, 0.45]	N/A	Very low[1,2,3]	Appendix14b (3.1)
Negative symptoms (SMD)	JACKSON2008	K = 1, N = 62	–0.46 [–0.96, 0.05]	N/A	Very low[1,2,3]	Appendix14b (3.2)
Social functioning (SMD)	JACKSON2008	K = 1, N = 62	–0.40 [–0.90, 0.11]	N/A	Very low[1,2,3]	Appendix14b (3.3)
Leaving the study early for any reason (RR)	JACKSON2008	K = 1, N = 62	0.57 [0.19, 1.76]	N/A	Very low[1,2,3]	Appendix14b (3.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, trial registration not found).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness as 21% of participants had bipolar disorder and 8.1% of participants were receiving electroconvulsive therapy (ECT).

Table 34: Summary of findings table for outcomes reported for CBT versus EPPIC treatment as usual at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Positive symptoms (SMD)	JACKSON2008	K = 1, N = 62	−0.08 [−0.58, 0.42]	N/A	Very low[1,2,3]	Appendix14b (4.1)
Negative symptoms (SMD)	JACKSON2008	K = 1, N = 62	−0.37 [−0.87, 0.13]	N/A	Very low[1,2,3]	Appendix14b (4.2)
Social functioning (SMD)	JACKSON2008	K = 1, N = 62	−0.08 [−0.58, 0.41]	N/A	Very low[1,2,3]	Appendix14b (4.3)
Relapse (RR; number of participants requiring hospitalisation)	JACKSON2008	K = 1, N = 57	1.35 [0.65, 2.80]	N/A	Very low[1,2,3]	Appendix14b (4.4)
Suicide (number of participants; assuming dropouts did not die by suicide) (RR)	JACKSON2008	K = 1, N = 62	5.00 [0.25, 100.08]	N/A	Very low[1,2,3]	Appendix14b (4.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, trial registration not found).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness as 21% of participants had bipolar disorder and 8.1% of participants were receiving ECT.

to previous studies (JACKSON2008), the EPPIC service was described as containing an early detection and crisis assessment team, an acute inpatient unit, an outpatient group programme, assertive follow-up teams and an intensive outreach mobile support team. At 10 weeks post-treatment and 36 weeks' follow-up there were no significant differences between groups in quality of life (SMD = −0.04; 95% CI, −0.54 to 0.47 and SMD = 0.03; 95% CI, −0.66 to 0.71 respectively). There were no deaths by suicide at 10 weeks post-treatment; however during the follow-up period the authors reported that one participant from each group died by suicide (RR = 0.81; 95% CI, 0.05 to 12.26). Dropout at 10 weeks was higher in the CBT group (10 participants versus four but the difference was not statistically significant (RR = 2.02; 95% CI, 0.72 to 5.66; see Appendix 14b [5.2]). Dropout was not reported by group at 36 weeks' follow-up. Evidence from each reported outcome and overall quality of evidence are presented in Table 35 and Table 36. The full evidence profiles can be found in Appendix 17b.

6.5.8 Clinical evidence for CBT (individual) plus clozapine versus clozapine in first episode psychosis that has not adequately responded to treatment

One RCT (N = 25) compared individual CBT plus clozapine versus clozapine alone, in children and young people experiencing first episode psychosis that had not adequately responded to at least one atypical antipsychotic (defined as persisting positive symptoms). Both groups also received EPPIC treatment as usual. At 12 weeks post-treatment and 24 weeks' follow-up no significant between-group differences were found on symptoms of psychosis, global state, depression, psychosocial functioning, quality of life, and number of participants' achieving remission (defined as a score of 'mild' or less on each of the three items of the Brief Psychiatric Rating Scale – Psychotic Subscale [BPRS-P] and a CGI severity item rating of 'mild' or less). The number of participants leaving the study early for any reason was not reported. See Table 37 and Table 38 for evidence from each reported outcome and overall quality of evidence for individual CBT plus clozapine versus clozapine alone at 12 and 24 weeks respectively. The full evidence profiles can be found in Appendix 17b.

6.5.9 Clinical evidence summary – evidence for children and young people

There were no RCTs of CBT in children and young people aged 18 years and younger with psychosis and schizophrenia. Six RCTs (N = 460) conducted in children and young people 25 years and younger were reviewed, including one targeting trauma, one targeting suicide and one targeting persistent positive symptoms. The findings suggest that in this age group CBT is no more effective at improving psychotic symptoms, depression, quality of life, social functioning or suicide, than a control. EPPIC is a very intensive and comprehensive treatment centre and may account for the lack of differential effects between intervention and control. However, no differential effects were found between CBT and treatment as usual provided by services in the UK (JACKSON2009).

Table 35: Summary of findings table for outcomes reported for CBT versus EPPIC treatment as usual in acutely suicidal participants at 10 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Quality of life (SMD)	POWER2003	K = 1, N = 42	–0.04 [–0.54, 0.47]	N/A	Very low[1,2,3]	Appendix14b (5.1)
Mortality (number of deaths by suicide; assuming dropouts did not die by suicide) (RR)	POWER2003	K = 1, N = 56	Not estimable (no events)	N/A	Very low[1,2,3]	Appendix14b (5.3)
Leaving the study early for any reason (RR)	POWER2003	K = 1, N = 56	–2.02 [0.72, 5.66]	N/A	Very low[1,2,3]	Appendix14b (5.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, trial registration not found and missing data analysis not reported).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness because participants were acutely suicidal.

Table 36: Summary of findings table for outcomes reported for CBT versus EPPIC treatment as usual in acutely suicidal participants at 36 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Quality of life (SMD)	POWER2003	K = 1, N = 33	0.03 [−0.66, 0.71]	N/A	Very low[1,2,3]	Appendix14b (6.1)
Mortality (number of deaths by suicide; assuming dropouts did not die by suicide) (RR)	POWER2003	K = 1, N = 56	0.81 [0.05, 12.26]	N/A	Very low[1,2,3]	Appendix14b (6.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, trial registration not found and missing data analysis not reported).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness as participants were acutely suicidal.

Table 37: Summary of findings table for outcomes reported for CBT + clozapine versus clozapine alone in participants whose symptoms have not adequately responded to treatment at 12 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Positive symptoms (SMD)	EDWARDS2011	K = 1, N = 25	0.19 [–0.60, 0.98]	N/A	Low[1, 2]	Appendix14b (7.1)
Negative symptoms (SMD)	EDWARDS2011	K = 1, N = 25	–0.30 [–1.09, 0.50]	N/A	Low[1, 2]	Appendix14b (7.2)
Global state (severity) (SMD)	EDWARDS2011	K = 1, N = 25	0.00 [–0.79, 0.79]	N/A	Low[1, 2]	Appendix14b (7.3)
Depression (SMD)	EDWARDS2011	K = 1, N = 25	0.56 [–0.25, 1.37]	N/A	Low[1, 2]	Appendix14b (7.4)
Social functioning (SMD)	EDWARDS2011	K = 1, N = 25	0.18 [–0.61, 0.97]	N/A	Low[1, 2]	Appendix14b (7.5)
Quality of life (SMD)	EDWARDS2011	K = 1, N = 25	–0.04 [–0.83, 0.75]	N/A	Low[1, 2]	Appendix14b (7.6)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, single blind trial but unclear if it is providers, participants or raters who were blind, trial registration not found and missing data not reported, average daily dose of clozapine was 44.8 mg/day higher in the clozapine only group than the clozapine + CBT group).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 38: Summary of findings table for outcomes reported for CBT + clozapine versus clozapine in participants whose symptoms have not adequately responded to treatment at 24 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Positive symptoms (SMD)	EDWARDS2011	K = 1, N = 25	−0.24 [−1.03, 0.55]	N/A	Low[1, 2]	Appendix14b (8.1)
Negative symptoms (SMD)	EDWARDS2011	K = 1, N = 25	−0.28 [−1.07, 0.51]	N/A	Low[1, 2]	Appendix14b (8.2)
Global state (severity) (SMD)	EDWARDS2011	K = 1, N = 25	0.12 [−0.67, 0.91]	N/A	Low[1, 2]	Appendix14b (8.3)
Depression (SMD)	EDWARDS2011	K = 1, N = 25	0.62 [−0.19, 1.43]	N/A	Low[1, 2]	Appendix14b (8.4)
Social functioning (SMD)	EDWARDS2011	K = 1, N = 25	−0.15 [−0.94, 0.64]	N/A	Low[1, 2]	Appendix14b (8.5)
Quality of life (SMD)	EDWARDS2011	K = 1, N = 25	−0.56 [−1.36, 0.25]	N/A	Low[1, 2]	Appendix14b (8.6)
Sensitivity analysis: remission (number of participants: assuming dropouts did not achieve remission) (RR)	EDWARDS2011	K = 1, N = 25	1.09 [0.51, 2.31]	N/A	Low[1, 2]	Appendix14b (8.7)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, single-blind trial but unclear if it is providers, participants or raters who were blind, trial registration not found and missing data not reported, the average daily dose of clozapine was 44.8 mg/day higher in the clozapine only group than the clozapine + CBT group).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Overall, the paucity and low to very low quality of evidence means no robust conclusions can be drawn. Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?') as well as the paucity and low quality of the evidence identified in children and young people the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 6.5.10).

6.5.10 Clinical evidence summary – evidence for adults

The review in the adult *Schizophrenia* guideline (NCCMH, 2010) contained 31 RCTs (N = 3,052) comparing CBT with any control (see Section 8.4 of *Schizophrenia*). The review found consistent evidence that, when compared with standard care, CBT was effective in reducing rehospitalisation rates up to 18 months following the end of treatment. Additionally, there was robust evidence indicating that the duration of hospitalisation was also reduced (8.26 days on average). CBT was shown to be effective in reducing symptom severity as measured by total scores on scales such as the PANSS and BPRS, both at end of treatment and at up to 12 months' follow-up. Robust small to medium effects (SMD ~0.30) were also demonstrated for reductions in depression when comparing CBT with both standard care and other active treatments. Furthermore, when compared with any control, there was some evidence for improvements in social functioning up to 12 months.

Although the evidence for positive symptoms was more limited, analysis of PSYRATS data demonstrated some effect for total hallucination measures at the end of treatment. Further to this, there was some limited but consistent evidence for symptom-specific measures including voice compliance, frequency of voices and believability, all of which demonstrated large effect sizes at both end of treatment and follow-up. However, despite these positive effects for hallucination-specific measures, the evidence for there being any effect on delusions was inconsistent. Although no RCTs directly compared group-based with individual CBT, indirect comparisons indicated that only the latter had robust effects on rehospitalisation, symptom severity and depression. Subgroup analyses also demonstrated additional effects for people with schizophrenia in the promoting recovery phase both with and without persistent symptoms. In particular, when compared with any other control, studies recruiting people in the promoting recovery phase demonstrated consistent evidence for a reduction in negative symptoms up to 24 months following the end of treatment.

6.5.11 Health economic evidence

The systematic search of the economic literature undertaken for the guideline did not identify any eligible studies on CBT. The adult *Schizophrenia* guideline (NCCMH, 2010) presented a simple economic analysis of CBT in addition to standard care. The analysis showed cost savings associated with the intervention when compared with

standard care alone. The meta-analysis of clinical data in the guideline demonstrated reduction in the rates of future hospitalisation, which contributed to the cost saving to the NHS.

A simple economic model estimated the net total cost of individually-delivered CBT in addition to standard care. The model took into account two categories of costs: the intervention cost of CBT and the hospitalisation cost over the duration of 18 months post-treatment. The meta-analysis estimated the rate of hospitalisation of the control arm at 29.98% and of the treatment arm at 21.47% using an RR of 0.74. It was assumed that CBT consisted of 16 individually-delivered sessions of 60 minutes each. The average duration of hospitalisation for people with schizophrenia was taken from the Hospital Episode Statistics, which was reported as being 110.6 days in England in 2006/07. The unit costs were taken from national published sources.

The base-case analysis results showed that the savings in hospital costs offset the CBT intervention cost. The net cost saving from the lower rate of hospitalisation was estimated at £989 per person. One-way sensitivity analyses were also conducted, such as substituting values of 95% CI of the RR of hospitalisation and varying the number of sessions of CBT (12 and 20), the hospitalisation rate of standard care (40 to 20%) and the mean length of hospitalisation to 69 days (average duration of hospitalisation of 110.6 days was considered too long by the GDG). The sensitivity analysis was undertaken using 95% CIs of the RR. Under all these scenarios the total net cost of providing CBT was estimated between –£2,277 (that is, net saving) to £751 per person in 2006/07 prices.

The economic analysis did not take into account reduction in other types of health and social care cost saving to the NHS and broader benefits to society such as an increase in productivity. The clinical benefits of CBT on symptoms and HRQoL following reduction in hospitalisation can also be considered in cost-effectiveness analysis, which can even outweigh the conservative cost of CBT of £751 per person.

The economic considerations from *Schizophrenia* (NCCMH, 2010) should be interpreted with caution for children and young people with psychosis and schizophrenia. The pathways of treatment for the younger population can differ in terms of resource use and cost; for instance the duration of stay in hospital might be longer for children and young people due to the relative lack of alternative intensive or assertive community provision, compared with that for adults. Nevertheless, the economic considerations from *Schizophrenia* (NCCMH, 2010) provide useful insights for children and young people with psychosis and schizophrenia.

6.5.12 From evidence to recommendations

Symptom reduction, relapse prevention and reduced hospital admissions are critical outcomes for psychological interventions conducted in children and young people with psychosis and schizophrenia. However, this is often a highly complex and comorbid group and, thus, outcomes pertaining to anxiety, depression, psychosocial functioning and quality of life are also important. The systematic review identified studies investigating arts therapies, CBT and family intervention in children and young people. Of the trials investigating CBT, heterogeneity across studies meant that it was

not possible to meta-analyse these trials. Evidence from individual trials indicates that CBT is no more effective than an active control at improving outcomes in young people with psychosis and schizophrenia. Conversely, evidence from the significantly larger adult dataset suggests that CBT is effective at reducing rehospitalisation rates and duration of admissions. Furthermore, the effectiveness of CBT was corroborated by the evidence for symptom severity, including total symptoms and depression.

No eligible economic studies of CBT were identified for this guideline. However, the economic analysis in the adult *Schizophrenia* guideline (NCCMH, 2010) concluded that CBT is likely to be an overall cost-saving intervention for people with schizophrenia. Ultimately, intervention costs are offset by savings resulting from a reduction in the number of future hospitalisations.

A paucity of evidence in children and young people aged 18 years and younger with psychosis and schizophrenia, and design problems in individual trials (for example, unclear methods of randomisation and allocation concealment, lack of blinding and small sample sizes), meant that it was difficult to make robust conclusions regarding the efficacy of CBT or the commonly used comparators (such as supportive counselling) in this population. Given this, and considering the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), the GDG decided to adapt recommendations from the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) based on the methodological principles outlined in Chapter 3. While, there is no strong evidence to signify that children and young people with psychosis and schizophrenia should be treated any differently from adults, there is also lack of evidence from the trials reviewed for the efficacy of CBT for psychosis and schizophrenia in young people and younger age adults (that is, data extrapolated from studies with a mean age of under 25). Therefore, particular care must be taken when drawing on the evidence reported in *Schizophrenia* (NCCMH, 2010) and the GDG deemed that it was especially important to take the child or young person's cognitive development into consideration when determining how to adjust CBT appropriately.

In summary, the GDG decided to recommend CBT as an adjunct to antipsychotic medication for children and young people with psychosis and schizophrenia, for both symptom reduction and relapse prevention. However, the evidence base for this has been predominantly drawn from RCTs conducted in adult populations. The much larger dataset in adults includes high-quality evidence supporting the use of antipsychotics to improve symptoms and improve relapse rates (see Chapter 7), family intervention to reduce relapse rates (see Section 6.6), and CBT to decrease rehospitalisation and duration of rehospitalisation as well as symptoms. Although the evidence presented in this guideline for children and young people is equivocal in some of these areas, the adult evidence is strong enough to maintain the use of a combination of oral antipsychotics, family intervention and CBT as the central treatments in most settings for the first episode and subsequent acute episodes (see recommendations 6.5.13.1 and 6.5.13.4).

In discussing recommending psychological interventions in children and young people the GDG considered the following issues: (a) the fact that evidence for pharmacological interventions in children and young people, although similar to adults, is of low quality, and the strong suggestion that side effects may be worse in children and young people; (b) some new evidence in adults that treatment with psychological interventions

without antipsychotics may produce some benefits; and (c) some limited evidence from young adults that psychological interventions may be effective in the absence of antipsychotic medication. On this basis, the GDG took the view that if the child or young person and their parents or carers wished to try a psychological intervention without antipsychotic medication in the first instance, this could be trialled over the course of a month. The GDG wished to emphasise that it was important that children and young people and parents and carers were advised that there is little evidence that psychological interventions are effective without medication (see recommendation 6.5.13.2).

The evidence reviewed in children and young people suggests that the benefits of CBT for psychosis and schizophrenia may well be fewer in younger patients who are generally seen in the first episode and early phase of illness compared with older adults who are predominantly in remission or experiencing chronic positive symptoms. Future research will necessitate the development of treatment manuals for children and young people under the age of 18 with psychosis and schizophrenia. Following this, a large multicentre RCT will be critical to determining the efficacy of CBT and any other psychological therapies in this population.

In the development of recommendations for psychological interventions in children and young people with psychosis and schizophrenia, the GDG considered recommendations for CBT, counselling and supportive psychotherapy, adherence therapy and social skills training for adults in *Schizophrenia* (NICE, 2009a) and made the decision to adapt them (see Table 39) based on the methodological principles outlined in Chapter 3. Where recommendations required adaptation, the rationale is provided in the third column. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in the *Schizophrenia* guideline (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 6.5.13 in this guideline.

6.5.13 Recommendations

Treatment options for first episode psychosis

6.5.13.1 For children and young people with first episode psychosis offer:

- oral antipsychotic medication[65] (see recommendations 7.8.2.1–7.8.3.11) in conjunction with
- psychological interventions (family intervention with individual CBT delivered as set out in recommendations 6.6.9.3, 6.5.13.3 and 6.8.3.1–6.8.3.5).[66]

[65] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[66] This recommendation also appears in Section 6.6.9 where family intervention is reviewed and in Chapter 7 where the pharmacological evidence is presented.

Table 39: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for the use of CBT

Original recommendation from *Schizophrenia* (NICE, 2009a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**
1.3.4.12 CBT should be delivered on a one-to-one basis over at least 16 planned sessions and: • follow a treatment manual* so that: – people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning – the re-evaluation of people's perceptions, beliefs or reasoning relates to the target symptoms • also include at least one of the following components: – people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms – promoting alternative ways of coping with the target symptom – reducing distress – improving functioning. *Treatment manuals that have evidence for their efficacy from clinical trials are preferred.	CBT should be delivered on a one-to-one basis over at least 16 planned sessions (although longer may be required) and: • follow a treatment manual* so that: – children and young people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning – the re-evaluation of the child or young person's perceptions, beliefs or reasoning relates to the target symptoms • also include at least one of the following components: – normalising, leading to understanding and acceptability of their experience – children and young people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms – promoting alternative ways of coping with the target symptom – reducing distress – improving functioning. (6.5.13.3) * Treatment manuals that have evidence for their efficacy from clinical trials are preferred. If developed for adults, the approach should be adapted to suit the age and developmental level of the child or young person.	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it to add normalising as a component of CBT for the treatment of children and young people. Normalising was defined as the provision of normalising information regarding the high prevalence of psychotic experiences in non-clinical populations, personal stories emphasising recovery, positive and functional aspects of psychosis, famous and successful people who have experienced psychosis, and common psychosocial causes of psychosis, in order to promote understanding and acceptance of their experiences. Based on expert opinion, the GDG also wished to emphasise that treatment manuals should be adapted for children and young people.

1.3.4.1 Offer cognitive behavioural therapy (CBT) to all people with schizophrenia. This can be started either during the acute phase* or later, including in inpatient settings. *CBT should be delivered as described in recommendation 1.3.4.12.	**Subsequent acute episodes of psychosis or schizophrenia** Offer CBT (delivered as set out in recommendation 6.5.13.3) to all children and young people with psychosis or schizophrenia, particularly for symptom reduction. This can be started either during the acute phase or later, including in inpatient settings. (6.5.13.4)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it to clarify the purpose and focus of CBT based on the expert opinion of the GDG.
1.3.4.4 Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to people with schizophrenia. However, take service user preferences into account, especially if other more efficacious psychological treatments, such as CBT, family intervention and arts therapies, are not available locally.	Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to children and young people with psychosis or schizophrenia. However, take the child or young person's and their parents' or carers' preferences into account, especially if other more efficacious psychological interventions, such as CBT, family intervention and arts therapies, are not available locally. (6.5.13.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.4.5 Do not offer adherence therapy (as a specific intervention) to people with schizophrenia.	Do not offer adherence therapy (as a specific intervention) to children and young people with psychosis or schizophrenia. (6.5.13.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.4.6 Do not routinely offer social skills training (as a specific intervention) to people with schizophrenia.	Do not routinely offer social skills training (as a specific intervention) to children and young people with psychosis or schizophrenia. (6.5.13.8)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Continued

Table 39: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**
1.4.3.1 Offer CBT to assist in promoting recovery in people with persisting positive and negative symptoms and for people in remission. Deliver CBT as described in recommendation 1.3.4.12.	Offer CBT to assist in promoting recovery in children and young people with persisting positive and negative symptoms and for those in remission. Deliver CBT as described in recommendation 6.5.13.3. (6.5.13.9)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.4.6.1 For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment: • review the diagnosis • establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration • review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families • consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.	For children and young people with psychosis or schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions: • review the diagnosis • establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration • review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families • consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. (6.5.13.10)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

6.5.13.2 If the child or young person and their parents or carers wish to try psychological interventions (family intervention or individual CBT) alone without antipsychotic medication, advise that psychological interventions are more effective when delivered in conjunction with antipsychotic medication. If the child or young person and their parents or carers still wish to try psychological interventions alone, then offer family intervention with individual CBT. Agree a time limit (1 month or less) for reviewing treatment options, including introducing antipsychotic medication. Continue to monitor symptoms, level of distress, impairment and level of functioning, including educational engagement and achievement, regularly.[67]

How to deliver psychological interventions

6.5.13.3 CBT should be delivered on a one-to-one basis over at least 16 planned sessions (although longer may be needed) and:

- follow a treatment manual[68] so that:
  - children and young people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning
  - the re-evaluation of the child or young person's perceptions, beliefs or reasoning relates to the target symptoms
- also include at least one of the following components:
  - normalising, leading to understanding and acceptability of their experience
  - children and young people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms
  - promoting alternative ways of coping with the target symptom
  - reducing distress
  - improving functioning.[69]

Subsequent acute episodes

6.5.13.4 For children and young people with an acute exacerbation or recurrence of psychosis or schizophrenia offer:

- oral antipsychotic medication[70] in conjunction with
- psychological interventions (family intervention with individual CBT).[71]

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[67] This recommendation also appears in Section 6.6.9 where family intervention is reviewed.

[68] Treatment manuals that have evidence for their efficacy from clinical trials are preferred. If developed for adults, the approach should be adapted to suit the age and developmental level of the child or young person.

[69] Adapted from *Schizophrenia* (NICE, 2009a).

[70] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[71] This recommendation also appears in Section 6.6.9 where family intervention is reviewed and in Chapter 7 where the pharmacological evidence is presented.

Psychological and psychosocial interventions

6.5.13.5 Offer CBT (delivered as set out in recommendation 6.5.13.3) to all children and young people with psychosis or schizophrenia, particularly for symptom reduction. This can be started either during the acute phase or later, including in inpatient settings.

6.5.13.6 Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to children and young people with psychosis or schizophrenia. However, take the child or young person's and their parents' or carers' preferences into account, especially if other more efficacious psychological interventions, such as CBT, family intervention and arts therapies, are not available locally.[72]

6.5.13.7 Do not offer adherence therapy (as a specific intervention) to children and young people with psychosis or schizophrenia.[73]

6.5.13.8 Do not routinely offer social skills training (as a specific intervention) to children and young people with psychosis or schizophrenia.[74]

Promoting recovery and providing possible future care in secondary care

6.5.13.9 Offer CBT to assist in promoting recovery in children and young people with persisting positive and negative symptoms and for those in remission. Deliver CBT as described in recommendation 6.5.13.3.[75]

Interventions for children and young people whose illness has not responded adequately to treatment

6.5.13.10 For children and young people with psychosis or schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions:

- review the diagnosis
- establish that there has been adherence to antipsychotic medication[76], prescribed at an adequate dose and for the correct duration
- review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families

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[72] Adapted from Schizophrenia (NICE, 2009a).

[73] Adapted from Schizophrenia (NICE, 2009a).

[74] Adapted from Schizophrenia (NICE, 2009a).

[75] Adapted from Schizophrenia (NICE, 2009a).

[76] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

- consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.[77,78]

6.6 FAMILY INTERVENTION

6.6.1 Introduction

Definition of family intervention
Family intervention was defined as discrete psychological interventions where:

- family sessions have a specific supportive, educational or treatment function and contain at least one of the following components:
  - problem solving/crisis management work
  - intervention with the identified service user.

6.6.2 Studies considered

Two RCTs (N = 158) compared family intervention with an active control. Both studies were conducted in children and young people aged 25 years and younger in remission and published between 1996 and 2009. In one study (LINSZEN1996), comparing individual CBT with family CBT, all participants completed an inpatient phase (mean [SD] duration 13.8 [5.1] weeks) aimed at remission or stabilisation of psychotic symptoms, before randomisation with their family to an outpatient phase targeting relapse prevention. The second study (GLEESON2009) compared individual and family CBT plus EPPIC treatment as usual with EPPIC treatment as usual. Key differences between the interventions included: an individualised formulation regarding relapse risk; a systematic and phased approach to relapse prevention via a range of cognitive behavioural interventions; parallel individual and family sessions focused on relapse prevention; and supervision specifically focused on relapse prevention. See Table 40 for a summary of the study characteristics.

6.6.3 Clinical evidence for CBT (individual) versus CBT (family)

One study (LINSZEN1996) reported efficacy outcomes at treatment endpoint associated with individual CBT versus family CBT in the treatment of children and young people with psychosis and schizophrenia that is in remission. At 1 year post-treatment a total of 12 participants had relapsed (measured using the BPRS; see Appendix 14b [9.1]); and there was no significant difference between groups (RR = 0.95, 0.34 to 2.68). Evidence from each reported outcome and overall quality of evidence is presented in Table 41. The full evidence profiles can be found in Appendix 17b.

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[77] Adapted from *Schizophrenia* (NICE, 2009a).
[78] This recommendation also appears in Section 6.6.9 where family intervention is reviewed.

Table 40: Study information table for trials comparing family intervention

	CBT (individual) versus CBT (family)	**CBT (individual + family) versus EPPIC treatment as usual**
Total no. of studies (N)	1 (N = 76)	1 (N = 82)
Study ID	LINSZEN1996*	GLEESON2009*
Diagnosis	Schizophrenic disorders in remission	First episode psychosis in remission (including bipolar disorder)
Mean age	20.6	20.1
Sex (% male)	70	63
Ethnicity (% white)	Not reported	Not reported
Treatment length (weeks)	52	30.33
Length of follow-up (weeks)	260	30.33
Setting	Inpatient and outpatient	Specialist clinic/ward
Country	Netherlands	Australia
Note. *Extractable outcomes.		

6.6.4 Clinical evidence for CBT (individual and family) versus EPPIC treatment as usual

One study (GLEESON2009) reported outcomes for CBT (individual and family) versus EPPIC treatment as usual. At 7 months there were no significant differences between groups on symptoms of psychosis, depression, quality of life, social functioning and study discontinuation. Eight of the 41 participants in the treatment as usual group relapsed, compared with two of the 41 participants in the family group (see Appendix14b [10.8]), but this difference did not reach statistical significance (RR = 0.24, 0.06 to 1.08). However, time to relapse in the family group was significantly extended by 32.25 days (SMD = –3.26; 95% CI, –3.94 to –2.59). Evidence from each reported outcome and overall quality of evidence are presented in Table 42. The full evidence profiles can be found in Appendix 17b.

Table 41: Summary of findings table for outcomes reported for individual CBT versus family CBT at 52 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Sensitivity analysis: relapse (number of participants: assuming dropouts relapsed) (RR)	LINSZEN1996	K = 1, N = 76	0.95 [0.34, 2.68]	N/A	Low[1,2]	Appendix14b (9.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, only raters were blind, trial registration not found, and missing data analysis was not reported).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

6.6.5 Clinical evidence summary – evidence for children and young people

There were no RCTs of family intervention in children and young people aged 18 years and younger with psychosis and schizophrenia. Two studies (N = 158) in children and young people aged 25 years and younger in remission found family intervention to be no more effective than an active control in reducing the number of participants who relapsed. EPPIC is a very intensive, comprehensive treatment centre and may account for the lack of differential effects between intervention and control. However, one study found that combined individual and family CBT in addition to EPPIC treatment as usual could extend time to relapse by approximately 1 month. Overall, the evidence base is drawn from small, non-UK studies with methodological limitations.

Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence identified in children and young people, the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 6.6.6).

6.6.6 Clinical evidence summary – evidence for adults

The review of family intervention in the adult *Schizophrenia* guideline (NCCMH, 2010) contained 32 RCTs (N = 2,429) and found robust and consistent evidence for the efficacy of family intervention (see Section 8.7 of *Schizophrenia*). When compared with standard care (K = 19, N = 2,118) or any other control, there was a reduction

Table 42: Summary of findings table for outcomes reported for individual and family CBT versus EPPIC treatment as usual at 30.33 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	GLEESON2009	K = 1, N = 81	−0.08 [−0.51, 0.36]	N/A	Low [1,2]	Appendix14b (10.1)
Positive symptoms (SMD)	GLEESON2009	K = 1, N = 81	−0.28 [−0.72, 0.15]	N/A	Low [1,2]	Appendix14b (10.2)
Negative symptoms (SMD)	GLEESON2009	K = 1, N = 81	−0.03 [−0.46, 0.41]	N/A	Low [1,2]	Appendix14b (10.3)
Depression (SMD)	GLEESON2009	K = 1, N = 81	−0.24 [−0.68, 0.20]	N/A	Low [1,2]	Appendix14b (10.4)
Quality of life (SMD)	GLEESON2009	K = 1, N = 81	0.00 [−0.44, 0.44]	N/A	Low [1,2]	Appendix14b (10.5)
Social functioning (SMD)	GLEESON2009	K = 1, N = 81	0.06 [−0.37, 0.50]	N/A	Low [1,2]	Appendix14b (10.6)
Relapse (time in days) (SMD)	GLEESON2009	K = 1, N = 81	−3.26 [−3.94, −2.59]*	N/A	Low [1,2]	Appendix14b (10.7)
Relapse (number of participants assuming dropouts relapsed) (RR)	GLEESON2009	K = 1, N = 81	0.24 [0.06, 1.08]	N/A	Low [1,2]	Appendix14b (10.8)
Leaving the study early for any reason (RR)	GLEESON2009	K = 1, N = 82	1.40 [0.48, 4.05]	N/A	Low [1,2]	Appendix14b (10.9)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours CBT (individual and family).
[1]Serious risk of bias (unclear allocation concealment, missing data).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

in the risk of relapse with numbers needed to treat of 4 (95% CI, 3.23 to 5.88) at the end of treatment and 6 (95% CI, 3.85 to 9.09) up to 12 months following treatment. In addition, family intervention also reduced hospital admission during treatment and the severity of symptoms both during and up to 24 months following the intervention. Family intervention may also be effective in improving additional critical outcomes, such as social functioning and the service user's knowledge of the disorder. However, it should be noted that evidence for the latter is more limited and comes from individual studies reporting multiple outcomes across a range of scale-based measures. The subgroup analyses conducted to explore the variation in intervention delivery consistently indicated that where practicable the service user should be included in the intervention. Although direct format comparisons did not indicate any robust evidence for single over multiple family intervention in terms of total symptoms, single family intervention was seen as more acceptable to service users and carers as demonstrated by the numbers leaving the study early. Additionally, subgroup comparisons that indirectly compared single with multiple family intervention demonstrated some limited evidence to suggest that only the former may be efficacious in reducing hospital admission.

6.6.7 Health economic evidence

The systematic search of the economic literature undertaken for the guideline did not identify any eligible studies on family intervention. The adult *Schizophrenia* guideline (NCCMH, 2010) presented the cost analysis of family intervention for people with schizophrenia showing a cost saving to the NHS. The meta-analysis of the clinical studies estimated significantly lower rates of relapse in people receiving family intervention in addition to standard care when compared with standard care alone. The lower rate of relapse resulted in lower rate of hospitalisation, which contributed in the cost saving to the NHS.

The meta-analysis of clinical studies estimated the RR of relapse (at 12 months into treatment) of family intervention in addition to standard care versus standard care alone at 0.52. The beneficial effect remained significant up to at least 24 months after the end of the intervention. The baseline rate of relapse (that is, standard care alone) of 50% was used and the analysis assumed that 77.3% of the people experiencing a relapse were admitted to hospital.

The economic analysis took into account two categories of costs: the cost of family intervention and the cost of hospitalisation (cost savings from reduction in hospitalisation rates) over 12 months into treatment. The single family intervention in the analysis consisted of 20 hour-long sessions by two therapists. The average duration of hospitalisation for people with schizophrenia was taken from the Hospital Episode Statistics, which was reported at 110.6 days in England in 2006/07. The unit costs were taken from national published sources.

The base-case analysis showed that the cost savings due to a lower rate of hospitalisation offset the family intervention cost. The net total saving per person was estimated at £2,634 in 2006/07 prices.

The economic analysis also conducted one-way and two-way sensitivity analyses on the base-case by: using the 95% CI of the RR of relapse; changing the number of hours of family intervention in the range of 15 to 25 hours, the baseline rate of relapse to 30%, and the rate of hospitalisation to 61.6%; simultaneously changing the relapse rate to 30% and the hospitalisation rate to 61.6%; and using the lower duration of hospitalisation of 69 days. The results of the base-case were robust to all scenarios except when the relapse rate and rate of hospitalisation were changed simultaneously, which incurred a net cost of £139 per person.

The cost analysis only considered cost savings related to hospitalisation caused by a lower relapse rate. The lower relapse rate of family intervention also affects the use of crisis resolution and home treatment teams—taking into account cost savings associated with reduced use of such teams would further increase the savings to the NHS. The meta-analysis of the follow-up data demonstrated that the clinical benefits of family intervention remained significant for up to at least 24 months after the end of intervention. Therefore, the savings of family intervention are expected to be even higher if the longer time period is accounted for in the cost analysis. The reduction in relapse rate also leads to improvement in HRQoL of people with schizophrenia and their families or carers, which strengthens the case for family intervention to be cost effective for people with schizophrenia in the UK.

The economic considerations from *Schizophrenia* (NCCMH, 2010) should be interpreted with caution for children and young people with psychosis and schizophrenia. The pathways of treatment for children and young people can differ in terms of resource use and cost, for instance the duration of stay in hospital might be longer for children and young people due to the relative lack of alternative intensive or assertive community provision, compared with that for adults. Nevertheless, the economic considerations from *Schizophrenia* provide useful insights for children and young people with psychosis and schizophrenia.

6.6.8 From evidence to recommendations

The primary outcome of interest for family intervention is relapse and following this, symptoms of psychosis, depression, anxiety, psychosocial functioning and quality of life. Owing to the paucity of studies and heterogeneity of interventions no meta-analysis was performed for family intervention in children and young people with psychosis and schizophrenia. Data from two trials conducted in samples containing some individuals aged under and some over 18 years, with a mean age of 25 years, were extrapolated and it was found that family intervention did not significantly reduce the number of individuals who relapsed. However, one trial of combined individual and family CBT suggests that it can extend time to relapse, even when compared with a highly specialised treatment as usual. Evidence drawn from a significantly larger number of RCTs in the adult *Schizophrenia* guideline (NCCMH, 2010) demonstrates that family intervention effectively reduces the number of participants relapsing up to 12 months following treatment, hospital admission during treatment and symptom severity up to 24 months following treatment.

No eligible economic studies of family intervention were identified for this guideline. However, the robust evidence presented in the adult *Schizophrenia* guideline (NCCMH, 2010) supports the incorporation and adaptation of conclusions and recommendations in this guideline.

Ultimately, no studies of family intervention in children and young people aged 18 years and younger were identified and the evidence extrapolated from two non-UK studies conducted in children and young people aged 25 years and younger was graded low quality (that is, owing to small sample sizes, lack of blinding, methodological limitations and unclear statistical analysis). Based on this extremely limited evidence and the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?') the GDG decided to incorporate and adapt recommendations from the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) based on the methodological principles outlined in Chapter 3. There is no clear evidence to indicate that we should treat children and young people with psychosis and schizophrenia any differently to adults, however the GDG did emphasise the particular importance of family involvement and interventions in this young age group, owing to their great dependency and continuing development.

In conclusion, the GDG decided to recommend family intervention in conjunction with antipsychotic medication for children and young people with psychosis and schizophrenia, for both symptom reduction and relapse prevention. However, the evidence base for this has been predominantly drawn from RCTs conducted in older adult populations. The much larger dataset in adults includes high-quality evidence supporting the use of oral antipsychotics to improve symptoms and improve relapse rates (see Chapter 7); family intervention to reduce relapse rates; and CBT to decrease rehospitalisation and duration of rehospitalisation as well as symptoms (see Section 6.5). Although the evidence presented in this guideline for children and young people is in some of these areas equivocal, the adult evidence is strong enough to maintain the use of a combination of oral antipsychotics, family intervention and CBT as the central treatments in most settings for the first episode and subsequent acute episodes (see recommendations 6.6.9.1 and 6.6.9.4).

In discussing recommending psychological interventions in children and young people the GDG considered the following issues: (a) the fact that evidence for pharmacological interventions in children and young people, although similar to adults, is of low quality, and the strong suggestion that side effects may be worse in children and young people; (b) some new evidence in adults that treatment with psychological interventions without antipsychotics may produce some benefits; and (c) some limited evidence from young adults that psychological interventions may be effective in the absence of antipsychotic medication. On this basis, the GDG took the view that if the child or young person and their parents or carers wished to try a psychological intervention without antipsychotic medication in the first instance, this could be trialled over the course of a month. The GDG wished to emphasise that it was important that children and young people and parents and carers were advised that there is little evidence that psychological interventions are effective without medication (see recommendation 6.6.9.2).

In the development of recommendations for the use of family intervention in children and young people with psychosis and schizophrenia, the GDG considered recommendations for family intervention for adults in *Schizophrenia* (NICE, 2009a) and adapted them (see Table 43) based on the methodological principles outlined in Chapter 3. Where recommendations required adaptation, the rationale is provided in the third column. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in *Schizophrenia* (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 6.6.9 in this guideline.

6.6.9 Recommendations

Treatment options for first episode psychosis

6.6.9.1 For children and young people with first episode psychosis offer:

- oral antipsychotic medication[79] (see recommendations 7.8.2.1–7.8.3.11) in conjunction with
- psychological interventions (family intervention with individual CBT, delivered as set out in recommendations 6.6.9.3, 6.5.13.3 and 6.8.3.1–6.8.3.5).[80]

6.6.9.2 If the child or young person and their parents or carers wish to try psychological interventions (family intervention or individual CBT) alone without antipsychotic medication, advise that psychological interventions are more effective when delivered in conjunction with antipsychotic medication. If the child or young person and their parents or carers still wish to try psychological interventions alone, then offer family intervention with individual CBT. Agree a time limit (1 month or less) for reviewing treatment options, including introducing antipsychotic medication. Continue to monitor symptoms, level of distress, impairment and level of functioning, including educational engagement and achievement, regularly.[81]

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[79] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[80] This recommendation also appears in Section 6.5.13 where CBT is reviewed and in Chapter 7 where the pharmacological evidence is presented.

[81] This recommendation also appears in 6.5.13 where CBT is reviewed.

Table 43: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for the use of family intervention

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.3.4.13 Family intervention should: • include the person with schizophrenia if practical • be carried out for between 3 months and 1 year • include at least 10 planned sessions • take account of the whole family's preference for either single-family intervention or multi-family group intervention • take account of the relationship between the main carer and the person with schizophrenia • have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work.	Family intervention should: • include the child or young person with psychosis or schizophrenia if practical • be carried out for between 3 months and 1 year • include at least 10 planned sessions • take account of the whole family's preference for either single-family intervention or multi-family group intervention • take account of the relationship between the parent or carer and the child or young person with psychosis or schizophrenia • have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work. (6.6.9.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Continued

Table 43: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.3.4.2 Offer family intervention to all families of people with schizophrenia who live with or are in close contact with the service user. This can be started either during the acute phase* or later, including in inpatient settings. * Family intervention should be delivered as described in recommendation 1.3.4.13.	**Subsequent acute episodes of psychosis or schizophrenia** Offer family intervention (delivered as set out in recommendation 6.6.9.3) to all families of children and young people with psychosis or schizophrenia, particularly for preventing and reducing relapse. This can be started either during the acute phase or later, including in inpatient settings. (6.6.9.4)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.4.3.2 Offer family intervention to families of people with schizophrenia who live with or are in close contact with the service user. Deliver family intervention as described in recommendation 1.3.4.13.	Offer family intervention to families of children and young people with psychosis or schizophrenia to promote recovery. Deliver family intervention as described in recommendation 6.6.9.3. (6.6.9.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it to make it clear that the context was for promoting recovery.
1.4.3.3 Family intervention may be particularly useful for families of people with schizophrenia who have: • recently relapsed or are at risk of relapse • persisting symptoms.	Consider family intervention particularly for families of children and young people with psychosis or schizophrenia who have: • recently relapsed or are at risk of relapse • persisting symptoms. (6.6.9.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia and adapted it to conform with changes to NICE style for recommendations (making the recommendation more active).

1.4.6.1 For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment: • review the diagnosis • establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration • review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families • consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.	For children and young people with psychosis or schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions: • review the diagnosis • establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration • review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families • consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. (6.6.9.8)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Psychological and psychosocial interventions

6.6.9.3 Family intervention should:

- include the child or young person with psychosis or schizophrenia if practical
- be carried out for between 3 months and 1 year
- include at least 10 planned sessions
- take account of the whole family's preference for either single-family intervention or multi-family group intervention
- take account of the relationship between the parent or carer and the child or young person with psychosis or schizophrenia
- have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work.[82]

Subsequent acute episodes

6.6.9.4 For children and young people with an acute exacerbation or recurrence of psychosis or schizophrenia offer:

- oral antipsychotic medication[83] in conjunction with
- psychological interventions (family intervention with individual CBT).[84]

6.6.9.5 Offer family intervention (delivered as set out in recommendation 6.6.9.3.) to all families of children and young people with psychosis or schizophrenia, particularly for preventing and reducing relapse. This can be started either during the acute phase or later, including in inpatient settings.[85]

Promoting recovery and providing possible future care in secondary care

6.6.9.6 Offer family intervention to families of children and young people with psychosis or schizophrenia to promote recovery. Deliver family intervention as described in recommendation 6.6.9.3.[86]

6.6.9.7 Consider family intervention particularly for families of children and young people with psychosis or schizophrenia who have:

- recently relapsed or are at risk of relapse
- persisting symptoms.[87]

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[82] Adapted from *Schizophrenia* (NICE, 2009a).

[83] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[84] This recommendation also appears in Section 6.5.13 where CBT is reviewed and in Chapter 7 where the pharmacological evidence is presented.

[85] Adapted from *Schizophrenia* (NICE, 2009a).

[86] Adapted from *Schizophrenia* (NICE, 2009a).

[87] Adapted from *Schizophrenia* (NICE, 2009a).

Interventions for children and young people whose illness has not responded adequately to treatment

6.6.9.8 For children and young people with psychosis or schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions:

- review the diagnosis
- establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration
- review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families
- consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.[88,89]

6.7 EPPIC TREATMENT AS USUAL

6.7.1 Introduction

The Early Psychosis Prevention and Intervention Centre (EPPIC) is a mental health service aimed at addressing the needs of people aged 15 to 25 years with emerging psychotic disorders in the western and north-western regions of Melbourne, Australia.[90] The core of the EPPIC clinical programme is the EPPIC continuing care team, which consists of consultant psychiatrists, qualified nurses, clinical psychologists, occupational therapists and social workers. A range of treatments and services are offered to the young people and their families and carers for up to 2 years, including individual and group interventions. Given the highly comprehensive nature of the treatment as usual approach delivered at EPPIC, the GDG considered it an important intervention to consider in the psychological treatment and management of schizophrenia in children and young people.

The aims of EPPIC are:

- early identification and treatment of the primary symptoms of psychotic illness
- improved access to, and reduced delays, in initial treatment
- reducing frequency and severity of relapse, and increasing time to first relapse
- reducing secondary morbidity in the post-psychotic phase of illness

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[88] Adapted from *Schizophrenia* (NICE, 2009a).

[89] This recommendation also appears in Section 6.5.13 where CBT is reviewed.

[90] See: http://www.eppic.org.au/

- reducing disruption to social and vocational functioning and psychosocial development in the critical period following onset of illness when most disability tends to accrue
- promoting wellbeing among family members and reducing the burden for carers.

The aims of EPPIC treatment as usual are:

- explore the possible causes of psychotic symptoms and treat them
- educate the young person and their family about the illness
- reduce disruption in a young person's life caused by the illness
- support the young person and their carers through the recovery process
- restore normal developmental trajectory and psychosocial functioning
- reduce the young person's chances of having another psychotic experience.

6.7.2 Studies considered

Four studies (EDWARDS2011, GLEESON2009, JACKSON2008, POWER2003) (N = 225) compared a CBT-based psychological intervention plus EPPIC treatment as usual with EPPIC treatment as usual. They were combined in a meta-analysis to establish whether there is any benefit in providing a psychological intervention in addition to what is already very comprehensive treatment as usual (see Table 44 for a summary of the study characteristics).

6.7.3 Clinical evidence for any psychological intervention in addition to EPPIC treatment as usual versus EPPIC treatment as usual

All studies reported mean endpoint scores. At post-treatment the combined effects of up to three studies revealed no significant differences between groups on symptoms of psychosis, depression, quality of life and social functioning. The number of participants who died by suicide was low and similar between groups (RR = 2.06, 0.28 to 15.34) as was dropout (RR = 0.91, 0.38 to 2.19). Evidence from each reported outcome and overall quality of evidence are presented in Table 45. The full evidence profiles can be found in Appendix 17b.

6.7.4 Clinical evidence summary

There is no evidence to suggest that providing a psychological intervention in addition to EPPIC treatment as usual has any added benefits on improving psychotic symptoms, quality of life, social functioning and suicide. EPPIC, unlike UK services, is a highly specialised treatment centre designed specifically for young people (aged 15 to 25 years) experiencing first episode psychosis.

Table 44: Study information table for trials of any psychological intervention in addition to EPPIC treatment as usual

	CBT (individual) + EPPIC treatment as usual versus EPPIC treatment as usual	**CBT (individual) + EPPIC treatment as usual versus EPPIC treatment as usual in acutely suicidal participants**	**CBT (individual + family) + EPPIC treatment as usual versus EPPIC treatment as usual**	**CBT (individual) + clozapine + EPPIC treatment as usual versus clozapine + EPPIC treatment as usual**
Total no. of studies (N)	1 (N = 62)	1 (N = 56)	1 (N = 82)	1 (N = 25)[1]
Study ID	JACKSON2008*	POWER2003*	GLEESON2009*	EDWARDS2011*
Diagnosis	First episode psychosis (including bipolar disorder)	Acutely suicidal first episode psychosis mixed (bipolar disorder not specified)	First episode psychosis in remission (including bipolar disorder)	First episode psychosis (excluding bipolar disorder) that had not adequately responded to treatment
Mean age/range	22.3	Range: 15 to 29	20.1	21.4
Sex (% male)	73	Not reported	63	71
Ethnicity (% white)	Not reported	Not reported	Not reported	Not reported
Treatment length (weeks)	14	10	30.33	12
Length of follow-up (weeks)	52	26	30.33	24
Country	Australia	Australia	Australia	Australia

Note. *Extractable outcomes.
[1]EDWARDS2011 had four treatment arms: clozapine, clozapine + CBT, thioridazine, and thioridazine + CBT (N = 48), however, thioridazine was not included in the review protocol.

Table 45: Summary of findings table for outcomes reported for any psychological intervention in addition to EPPIC treatment as usual versus EPPIC treatment as usual at post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Positive symptoms (SMD)	EDWARDS2011 GLEESON2009 JACKSON2008	K = 3, N = 150	–0.11 [–0.43, 0.21]	(P = 0.59); I^2 = 0%	Very low[1,2,3]	Appendix14b (11.1)
Negative symptoms (SMD)	EDWARDS2011 GLEESON2009 JACKSON2008	K = 3, N = 150	–0.25 [–0.57, 0.08]	(P = 0.49); I^2 = 0%	Very low[1,2,3]	Appendix14b (11.2)
Depression (SMD)	EDWARDS2011 GLEESON2009	K = 2, N = 63	0.10 [–0.68, 0.87]	(P = 0.10); I^2 = 64%	Very low[1,2,3,4]	Appendix14b (11.3)
Quality of life (SMD)	EDWARDS2011 GLEESON2009 POWER2003	K = 3, N = 148	–0.02 [–0.34, 0.30]	(P = 0.99); I^2 = 0%	Very low[1,2,3]	Appendix14b (11.4)
Social functioning (SMD)	EDWARDS2011 GLEESON2009 JACKSON2008	K = 3, N = 150	–0.10 [–0.45, 0.24]	(P = 0.33); I^2 = 10%	Very low[1,2,3]	Appendix14b (11.5)
Suicide (number of participants; assuming dropouts did not die by suicide) (RR)	JACKSON2008 POWER2003	K = 2, N = 104	2.06 [0.28, 15.34]	(P = 0.43); I^2 = 0%	Very low[1,2,3]	Appendix14b (11.6)
Leaving the study early for any reason (RR)	GLEESON2009 JACKSON2008	K = 2, N = 144	0.91 [0.38, 2.19]	(P = 0.26); I^2 = 22%	Very low[1,2,3]	Appendix14b (11.7)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, unclear rater blinding trial registration not found, missing data, average daily dose of clozapine was 44.8 mg/day).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (including acutely suicidal participants, participants with bipolar disorder and participants receiving ECT).
[4]$I^2 \geq 50\%$, $p < .05$.

6.8 PRINCIPLES FOR DELIVERING PSYCHOLOGICAL INTERVENTIONS

6.8.1 Introduction

The GDG considered whether there were further recommendations from the adult *Schizophrenia* guideline (NICE, 2009a) regarding principles for delivering psychological interventions that were relevant to the care of children and young people with psychosis and schizophrenia. The GDG identified several recommendations as being of particular importance.

6.8.2 From evidence to recommendations

In the development of recommendations for principles for delivering psychological interventions, the GDG considered recommendations from *Schizophrenia* (NICE, 2009a) and adapted them (see Table 46) based on the methodological principles outlined in Chapter 3. Where recommendations required adaptation, the rationale is provided in the third column. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in the *Schizophrenia* guideline (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 6.8.3 in this guideline.

In addition, after reviewing the adapted recommendations, the GDG wished to make a further recommendation, based on consensus and expert opinion, that professionals delivering psychological interventions should take into account the child or young person's developmental level, emotional maturity (see recommendation 6.8.3.1).

6.8.3 Recommendations

How to deliver psychological interventions

6.8.3.1 When delivering psychological interventions for children and young people with psychosis or schizophrenia, take into account their developmental level, emotional maturity and cognitive capacity, including any learning disabilities, sight or hearing problems or delays in language development.

Monitoring and reviewing psychological interventions

6.8.3.2 When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including the child or young person's satisfaction and, if appropriate, parents' or carers' satisfaction.[91]

[91] Adapted from *Schizophrenia* (NICE, 2009a).

Table 46: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for general principles for delivering psychological interventions

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.3.4.7 When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including service user satisfaction and, if appropriate, carer satisfaction.	When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including the child or young person's satisfaction and, if appropriate, parents' or carers' satisfaction. (6.8.3.2)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.4.8 Healthcare teams working with people with schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review: • access to and engagement with psychological interventions • decisions to offer psychological interventions and equality of access across different ethnic groups.	Healthcare teams working with children and young people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review: • access to and engagement with psychological interventions • decisions to offer psychological interventions and equality of access across different ethnic groups. (6.8.3.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, with no significant adaptation required.
1.3.4.9 Healthcare professionals providing psychological interventions should: • have an appropriate level of competence in delivering the intervention to people with schizophrenia	Healthcare professionals providing psychological interventions should: • have an appropriate level of competence in delivering the intervention to children and young people with psychosis or schizophrenia	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Continued

Table 46: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	**Recommendation following adaptation for this guideline**	**Reasons for adaptation**
• be regularly supervised during psychological therapy by a competent therapist and supervisor.	• be regularly supervised during psychological therapy by a competent therapist and supervisor. (6.8.3.4)	
1.3.4.10 Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological therapy interventions recommended in this guideline.	Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological interventions for children and young people recommended in this guideline. (6.8.3.5)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.4.11 When psychological treatments, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption.	When psychological interventions, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption. (6.8.3.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

6.8.3.3 Healthcare teams working with children and young people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review:

- access to and engagement with psychological interventions
- decisions to offer psychological interventions and equality of access across different ethnic groups.[92]

[92] Adapted from *Schizophrenia* (NICE, 2009a).

Competencies for delivering psychological interventions

6.8.3.4 Healthcare professionals delivering psychological interventions should:

- have an appropriate level of competence in delivering the intervention to children and young people with psychosis or schizophrenia
- be regularly supervised during psychological therapy by a competent therapist and supervisor.[93]

6.8.3.5 Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological interventions for children and young people recommended in this guideline.[94]

Psychological and psychosocial interventions for subsequent acute episodes of psychosis or schizophrenia

6.8.3.6 When psychological interventions, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption.[95]

6.9 RESEARCH RECOMMENDATION

What is the clinical and cost effectiveness of psychological treatment alone, compared with antipsychotic medication and compared with psychological treatment and antipsychotic medication combined, for young people with first episode psychosis? (See Appendix 12 for further details.)

[93] Adapted from *Schizophrenia* (NICE, 2009a).
[94] Adapted from *Schizophrenia* (NICE, 2009a).
[95] Adapted from *Schizophrenia* (NICE, 2009a).

7 PHARMACOLOGICAL INTERVENTIONS

7.1 INTRODUCTION

Antipsychotic medication has long been seen as playing an integral role in the treatment and management of psychosis and schizophrenia in children and young people. However the evidence base for the use of antipsychotic medication in this age group is relatively sparse (but growing) and is to a degree reliant upon clinical experience, consensus guidelines and extrapolation from studies in adults. Indeed, the starting point for this guideline was the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) and the question 'Are there grounds for believing that treatment and management should be any different in children and adolescents?'

The first antipsychotic medication to be developed was chlorpromazine in the early 1950s. A steady stream of further drugs followed during subsequent decades, all with relatively high dopaminergic receptor-blocking potency and characterised by a propensity to cause extrapyramidal movement disorders as side effects and particularly irreversible tardive dyskinesia – these were the so-called 'first generation' antipsychotics (FGAs). The late 20th century saw a second wave of drug developments ('second generation' antipsychotics [SGAs]) with mixed dopaminergic- and serotinergic-blocking properties. The hope was that these drugs might have similar or greater efficacy with fewer or less severe side effects, particularly EPS. Current evidence, however, suggests that with the exception of clozapine in the context of treatment resistance, there is little if any difference between FGAs and SGAs in efficacy, and also that side effects are no fewer or less severe in either but merely different in nature, with SGAs particularly affecting cardiometabolic functioning (Kendall, 2011).

The nature of adverse effects that can follow first exposure to antipsychotic medication is in essence similar in adults and children/young people. However, where the impact may differ is that the child/young person is being exposed to these disturbances at a vulnerable phase of physical growth and development and may be particularly vulnerable to rapid weight gain (Álvarez-Jiménez *et al*., 2008) and adverse cardiometabolic disturbance (Correll *et al*., 2009; Foley & Morley, 2011). Combining these disturbances with the high rates of tobacco smoking in this group (Myles *et al.,* 2012) provides a potent mix of cardiovascular risk. Greater susceptibility to antipsychotic-induced adverse effects (Kumra *et al*., 2008b) alongside evidence for rapid acquisition (within weeks) of weight gain and metabolic disturbances (Correll *et al*., 2009; Foley & Morley, 2011) underline the importance of addressing cardiovascular risk in the critical early treatment period for these young people. The level and importance of cardiovascular risk, its speed of acquisition, its relationship to antipsychotic medication and its exacerbation by known lifestyle factors, all operating in the early phase, collectively provide the potential for a shift towards a more preventive approach for this vulnerable group of young people.

Balancing the impacts and risks of a severe mental disorder against the potential benefits and risks of prescribed antipsychotic drug treatments is therefore complex. Untreated or inadequately treated illness is likely to lead to poorer long-term outcomes but side effects can be both distressing and impairing in both the short and long term. Medication, when used, should be prescribed judiciously with an emphasis on incremental changes and using the minimal necessary dose to achieve therapeutic effect. Many of the antipsychotic drugs, in common with most medications used for treating children and young people, will not have been granted a marketing authorisation (product licence) for use in that population and prescribers should be aware of the altered professional responsibility inherent in their use (Paediatric Formulary Committee, 2011; Royal College of Paediatrics and Child Health, 2010).

7.2 INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION FOR FIRST EPISODE PSYCHOSIS

7.2.1 Introduction

Evidence published before the updated adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) suggests that drug-naïve patients may respond to doses of antipsychotic medication at the lower end of the recommended range (Cookson *et al*., 2002; McEvoy *et al*., 1991; Oosthuizen *et al*., 2001; Tauscher & Kapur, 2001). This may have particular implications in the treatment of children and young people experiencing their first episode of psychosis and schizophrenia. Lehman and Steinwachs (1998) have suggested that the maximum dose for drug-naïve adult patients should be 500 mg chlorpromazine equivalents per day. This contrasts with a recommended optimal oral antipsychotic dose of 300 to 1000 mg chlorpromazine equivalents per day for the routine treatment of an acute episode in non-drug-naïve adult patients.

7.2.2 Clinical review protocol for initial treatment with antipsychotic medication in children and young people with first episode psychosis

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 47. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

7.2.3 Studies considered[96]

Nine RCTs (N = 1674) providing relevant clinical evidence met the eligibility criteria for the review of initial treatment with antipsychotic medication in children and young

[96]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 47: Clinical review protocol for the review of initial treatment with antipsychotic medication in children and young people with first episode psychosis

Review questions	**RQ B2:** Does the efficacy profile of continuous antipsychotic drug treatment, compared with alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children/young people and adults with psychosis and schizophrenia? **RQ B3:** Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared with adults with psychosis and schizophrenia (in particular, metabolic, neurological and cognitive impairments)? **RQ B5a:** Should the dose/duration (and, where relevant, frequency) be different compared with adults?
Objectives	To provide evidence-based recommendations regarding the pharmacological (antipsychotic) treatment and management of initial treatment in children and young people with psychosis and schizophrenia, including a review of the adult *Schizophrenia* guideline (NICE, 2009a; NCCMH, 2010) for its relevance to children and young people.
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	All antipsychotic medication licensed in the UK for the treatment of children and young people with psychosis and schizophrenia, including considerations related to the age of participants (for example, dose modifications). Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia). • Amisulpride • Aripiprazole • Benperidol

Continued

Table 47: (*Continued*)

	• Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol • Levomepromazine • Olanzapine • Pericyazine • Pimozide • Prochlorperazine • Promazine hydrochloride • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate
Comparison	Alternative management strategies: • Placebo • Psychological intervention • Any of the above interventions offered as an alternative management strategy
Critical outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes and cardiotoxicity) • Remission
Electronic databases	**RQ B2 and RQ B5:** Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases and grey literature (see Appendix 8) **RQ B3:** Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases (see Appendix 8)

Continued

Table 47: (*Continued*)

Date searched	Systematic reviews: 1995 to May 2012 RCTs: inception of databases to May 2012
Study design	RCTs; systematic reviews
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • In order to assess the possible side effects of antipsychotic medication, children and young people with psychosis and schizophrenia will be included. In order to assess the efficacy of antipsychotic medication, children and young people with a formal diagnosis of schizophrenia will be included. • The main review will focus on children and young people between the ages of 14 and 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

people with first episode psychosis (ARANGO2009 [Arango *et al.*, 2009], BERGER2008 [Berger *et al.*, 2008], LIEBERMAN2003 [Lieberman *et al.*, 2003], MCEVOY2007 [McEvoy *et al.*, 2007], ROBINSON2006 [Robinson *et al.*, 2006], SCHOOLER2005 [Schooler *et al.*, 2005], SIKICH2008 [Sikich *et al.*, 2008], SWADI2010 [Swadi *et al.*, 2010], VANBRUGGEN2003 [Van Bruggen *et al.*, 2003]). All included RCTs were published in peer-reviewed journals between 2003 and 2010. Additional unpublished data were also obtained from one study (ROBINSON2006). Only one study investigated

antipsychotic medication use in first episode psychosis in children and young people aged 18 years and younger (ARANGO2009). Data were extrapolated from eight remaining studies that provided relevant clinical data in first episode psychosis populations that included young people over the age of 18, but had an overall mean age of 25 years and younger (BERGER2008, LIEBERMAN2003, MCEVOY2007, ROBINSON2006, SIKICH2008, SCHOOLER2005, SWADI2010, VANBRUGGEN2003).

All studies reported at least one outcome in sufficient detail to allow for extraction and analysis. In addition, 814 studies were considered irrelevant to the pharmacological treatment and management of psychosis and schizophrenia in children and young people and excluded from the review.

All included studies were head-to-head comparisons of antipsychotic medication, including two three-arm trials (MCEVOY2007, SIKICH2008). The trial by SIKICH2008 included a third arm of molindone; however as molindone was discontinued by its sole supplier, Endo Pharmaceuticals in 2010, only data for risperidone and olanzapine are reviewed in this guideline. There was a total of six evaluations: two studies comparing olanzapine with quetiapine (N = 317) (ARANGO2009, MCEVOY2007); two studies comparing risperidone with quetiapine (N = 289) (MCEVOY2007, SWADI2010); one study comparing haloperidol with olanzapine (N = 263) (LIEBERMAN2003); one study comparing haloperidol with risperidone (N = 559) (SCHOOLER2005); four studies comparing risperidone with olanzapine (MCEVOY2007, ROBINSON2006, SIKICH2008, VANBRUGGEN2003) (N = 506); and one study comparing two difference doses of antipsychotic medication (quetiapine 200.0 mg per day versus quetiapine 400.0 mg per day) (N = 141) (BERGER2008).

A summary of study characteristics is presented in Table 48. Further information about both included and excluded studies can be found in Appendix 13c.

7.2.4 Clinical evidence for olanzapine versus quetiapine as initial treatment for first episode psychosis

Two studies (ARANGO2009, MCEVOY2007) (N = 317) compared olanzapine and quetiapine in children and young people with first episode psychosis, with whom at least half (50% and 96% respectively) were antipsychotic naïve prior to receiving the study intervention. The studies differed regarding the age groups of the populations under investigation. All participants in the ARANGO2009 study were under 18 years, with a mean age of 15.9 years; however the sample in the MCEVOY2007 study were between 16.4 and 44.4 years, with a mean age of 24.5 years.

Efficacy

Both studies (N = 317) reported data for symptoms, depression and global state and ARANGO2009 reported psychosocial functioning data. ARANGO2009 reported mean endpoint scores and MCEVOY2007 reported mean change scores; however given the limited amount of data identified both studies were included in one analysis (sensitivity analysis is not considered appropriate in an analysis including only two studies).

Table 48: Study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis

	Olanzapine versus quetiapine	Risperidone versus quetiapine	Haloperidol versus olanzapine	Haloperidol versus risperidone	Risperidone versus olanzapine	Quetiapine (200 mg per day) versus quetiapine (400 mg per day)
Total no. of studies (N)	K = 2 (N for comparison = 317; N for included studies = 450)	K = 2 (N for comparison = 289; N for included studies = 422)	K = 1 (N = 263)	K = 1 (N = 559)	K = 4 (N for comparison = 506; N for included study = 6,833)	K = 1 (N = 141)
Study ID	(1) ARANGO2009[1] (2) MCEVOY2007[1]	(1) MCEVOY2007[1] (2) SWADI2010[1]	LIEBERMAN 2003[1]	SCHOOLER 2005[1]	(1) MCEVOY2007[1] (2) ROBINSON2006[1] (3) SIKICH2008[1,3] (4) VANBRUGGEN2003[1]	BERGER2008[1]
Diagnosis[2]	First episode psychosis	First episode psychosis	First episode psychosis	First episode psychosis	First episode psychosis: 93% in SIKICH2008; 89% and 85% in the risperidone and olanzapine groups in VANBRUGGEN2003	First episode psychosis
Prior antipsychotic use (% naïve prior to intervention)[2]	(1) 50 (2) 96	(1) 96 (2) Not reported (participants who had earlier treatment with an atypical antipsychotic excluded)	26	47	(1) 96 (2) 78 (3) 33 (4) Not reported	0

Continued

Table 48: (*Continued*)

	Olanzapine versus quetiapine	**Risperidone versus quetiapine**	**Haloperidol versus olanzapine**	**Haloperidol versus risperidone**	**Risperidone versus olanzapine**	**Quetiapine (200 mg per day) versus quetiapine (400 mg per day)**
Mean age (range)[2]	(1) 16.0 (not reported) (2) 24.5 (16.4 to 44.4)	(1) 24.5 (16.4 to 44.4) (2) 16.74 (16 to 19)	23.8 (not reported)	25.4 (not reported)	(1) 24.5 (16.4 to 44.4) (2) 23.3 (not reported) (3) 13.8 (8.0 to 19.0) (4) 20.8 (not reported)	19.4 (not reported)
Sex (% male)[2]	(1) 78 (2) 73	(1) 73 (2) Not reported	82	71	(1) 73 (2) 70 (3) 65 (4) 80	68
Ethnicity (% white)[2]	(1) 78 (2) 51	(1) 51 (2) Not reported	53	74	(1) 51 (2) 20 (3) 64 (4) Not reported	Not reported
Mean (range) medication dose (mg per day[2]	(1) Olanzapine: 12.1 (not reported); quetiapine: 438.8 (not reported) (2) Olanzapine: 11.7 (2.5 to 20.0); quetiapine: 506.0 (100.0 to 800.0)	(1) Risperidone: 2.4 (0.5 to 4.0); quetiapine: 506.0 (100.0 to 800.0) (2) Risperidone: 2.9 (1.5 to 5.0; quetiapine: 607.0 (100.0 to 800.0)	Haloperidol: 4.4 (2.0 to 20.0); olanzapine: (9.1 (5.0 to 20.0)	Haloperidol: 2.9 (not reported); risperidone: 3.3 (not reported)	(1) Risperidone: 2.4 (0.5 to 4.0); olanzapine: 11.7 (2.5 to 20.0) (2) Risperidone: 3.9 (1.0 to 6.0); olanzapine: 11.8 (2.5 to 20.0) (3) Risperidone: 2.8 (0.5 to 6.0); olanzapine: 11.4 (2.5 to 20.0) (4) Risperidone: 4.4 (1.0 to 8.0); olanzapine: 15.6 (5.0 to 30.0)	Quetiapine 200.0 mg per day versus quetiapine 400.0 mg per day

Treatment length (weeks)[2]	(1) 26 (2) 52	(1) 52 (2) 6	104[4]	106	(1) 52 (2) 156[5] (3) 52[6] (4) 6 to 1	12
Length of follow-up (weeks)[2]	(1) 26 (2) 52	(1) 52 (2) 6	104	Not reported	(1) 52 (2) 156 (3) 52 (4) 6 to 10	12
Setting[2]	(1) General hospital (2) Inpatient and outpatient	(1) Inpatient and outpatient (2) Inpatient	Inpatient and outpatient	Not reported	(1)–(3) Inpatient and outpatient (4) Inpatient	Inpatient and outpatient specialist clinic
Country[2]	(1) Spain (2) US and Canada	(1) US and Canada (2) New Zealand	North America and Western Europe	Eleven countries – details not reported	(1) US and Canada (2) Denmark (3) US (4) The Netherlands	Australia
Funding[2]	(1)–(2) AstraZeneca	(1)–(2) AstraZeneca	Lilly Research Laboratories	Johnson & Johnson	(1) AstraZeneca (2)–(3) Non-industry (4) Eli Lily and non-industry	AstraZeneca

Note. [1]Extractable outcomes.
[2]Data are reported for the population characteristics of each study, not the population characteristics of each treatment group.
[3]Molindone was the third arm (n = 40) in the trial conducted by SIKICH2008, however as it was discontinued by its sole supplier, Endo Pharmaceuticals, in 2010 only data for risperidone and olanzapine are reviewed in this guideline.
[4]Design included a 12-week acute phase.
[5]Design included a 16-week acute phase.
[6]Design included an 8-week acute phase.

The only significant difference between groups was found for positive symptoms with olanzapine favoured over quetiapine (SMD = −0.42; 95% CI, −0.77 to −0.08). A small, significant difference between treatment groups, favouring olanzapine was found for quality of life (SMD = −0.18; 95% CI, −0.36 to −0.00). Evidence from each reported outcome and overall quality of evidence are presented in Table 49; the full evidence profiles can be found in Appendix 17c.

Side effects

ARANGO2009 reported mean endpoint scores and MCEVOY2007 reported mean change scores; however given the limited amount of data identified both studies were included in one analysis (sensitivity analysis is not considered appropriate in an analysis including only two studies). The risk of gaining weight was significantly greater in olanzapine-treated participants compared with quetiapine-treated participants (RR = 2.05; 95% CI, 1.41 to 2.97). Similarly a large, significant difference in mean weight (lbs) change between treatment groups was found, with olanzapine-treated participants gaining more weight than quetiapine-treated participants (SMD = 1.06; 95% CI, 0.59 to 1.53). In addition, body mass index (BMI) was significantly different between groups, with a greater increase in BMI demonstrated in olanzapine-treated participants compared with quetiapine-treated participants (SMD = 1.08; 95% CI, 0.61 to 1.54). A small, significant difference was found between treatment groups on mean change in high-density lipoprotein cholesterol, with olanzapine favoured over quetiapine (SMD = −0.48; 95% CI, −0.9 to −0.04). No significant differences were found on any other side effect outcome assessed in the study. Evidence from each reported outcome and overall quality of evidence are presented in Table 50; the full evidence profiles can be found in Appendix 17c.

7.2.5 Clinical evidence for risperidone versus quetiapine as initial treatment for first episode psychosis

Two studies (MCEVOY2007, SWADI2010) (N = 289) compared risperidone and quetiapine in children and young people with first episode psychosis, with the majority of the participants in the MCEVOY2007 trial being antipsychotic naïve at baseline (96%). SWADI2010 did not report participants' antipsychotic use before entering the study. The mean (range) age of participants was 24.5 (16.4 to 44.4) years in the MCEVOY2007 trial and 16.74 (16 to 19) years in the SWADI2010 trial.

Efficacy

Data obtained from the MCEVOY2007 trial suggests a small, significant difference favouring risperidone over quetiapine on quality of life (SMD = −0.30; 95% CI, −0.60 to −0.00). No significant differences between treatment groups for any of the other measured efficacy outcomes were found in either study. Evidence from each reported outcome and overall quality of evidence are presented in Table 51; the full evidence profiles can be found in Appendix 17c.

Table 49: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with olanzapine versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	ARANGO2009 MCEVOY2007	K = 2; N = 131	–0.04 [–0.54, 0.46]	(P = 0.16); I^2 = 50%	Very low[1,2,3,4,5]	Appendix 14c (i) (1.1)
Positive symptoms (SMD)	ARANGO2009 MCEVOY2007	K = 2; N = 131	–0.42 [–0.77, –0.08]*	(P = 0.38); I^2 = 0%	Very low[1,2,3,5]	Appendix 14c (i) (1.2)
Negative symptoms (SMD)	ARANGO2009 MCEVOY2007	K = 2; N = 131	–0.53 [–1.22, 0.15]	(P = 0.06); I^2 = 72%	Very low[1,2,3,4,5]	Appendix 14c (i) (1.3)
Global state (severity) (SMD)	ARANGO2009 MCEVOY2007	K = 2; N = 131	0.11 [–0.44, 0.66]	(P = 0.12); I^2 = 59%	Very low[1,2,3,4,5]	Appendix 14c (i) (1.4)
Depression (SMD)	ARANGO2009 MCEVOY2007	K = 2; N = 124	0.31 [–0.04, 0.67]	(P = 0.46); I^2 = 0%	Very low[1,2,3,5]	Appendix 14c (i) (1.5)
Mania (SMD)	ARANGO2009	K = 1; N = 60	0.10 [–0.45, 0.66]	N/A	Very low[1,2,3,5]	Appendix 14c (i) (1.6)
Quality of life (SMD)	MCEVOY2007	K = 1; N = 81	–0.18 [–0.36, –0.00]*	N/A	Very low[1,2,3,5]	Appendix 14c (i) (1.7)
Psychosocial functioning	ARANGO2009	K = 1; N = 50	–0.35 [–0.91, 0.20]	N/A	Very low[1,2,3]	Appendix 14c (i) (1.8)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours olanzapine.
[1]Serious risk of bias (including unclear sequence generation and/or allocation concealment; one open-label trial (no blinding) or unclear rater blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified ITT population; last observation carried forward (LOCF) reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]$I^2 \geq 50\%$, $p < .05$.
[5]Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Table 50: Summary of findings table for side effect outcomes reported at treatment endpoint associated with olanzapine versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Studies/number of participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (RR)	ARANGO2009 MCEVOY2007	K = 2; N = 131	2.05 [1.41, 2.97]**	(P = 0.54); I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (2.1)
Metabolic: weight lbs (SMD)	MCEVOY2007	K = 1; N = 81	1.06 [0.59, 1.53]**	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.2)
Metabolic: BMI (SMD)	MCEVOY2007	K = 1; N = 81	1.08 [0.61, 1.54]**	N/A	Very low[1,2,3]	Appendix 14c (i) (2.3)
Metabolic: fasting serum glucose level mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	0.23 [–0.21, 0.67]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.4)
Metabolic: fasting total cholesterol mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	–0.34 [–0.78, 0.11]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.5)
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	–0.48 [–0.93, –0.04]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.6)
Metabolic: fasting triglycerides mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	–0.02 [–0.46, 0.42]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.7)
Cardio: systolic BP (SMD)	MCEVOY2007	K = 1; N = 81	0.13 [–0.31, 0.57]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.8)

Cardio: diastolic BP (SMD)	MCEVOY2007	K = 1; N = 81	0.13 [−0.31, 0.57]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.9)
Cardio: tachycardia (RR)	ARANGO2009	K = 1; N = 60	0.92 [0.06, 13.95]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.10)
Hormonal: prolactin	MCEVOY2007	K = 1; N = 81	0.17 [−0.27, 0.60]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.11)
Neurological: tremor (RR)	ARANGO2009	K = 1; N = 60	0.92 [0.26, 3.29]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.12)
Neurological: akathisia (RR)	ARANGO2009	K = 1; N = 60	6.48 [0.35, 119.32]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (2.13)
Leaving the study early for any reason (RR)	ARANGO2009 MCEVOY2007	K = 2; N = 317	0.97 [0.83, 1.13]	(P = 0.85); I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (2.14)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.

* Favours olanzapine.

**Favours quetiapine.

[1]Serious risk of bias (including unclear sequence generation and/or allocation concealment; one open-label trial (no blinding) or unclear rater blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified ITT population; LOCF reported but high dropout).

[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

[3]Serious risk of reporting bias.

[4]Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Table 51: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCEVOY2007 SWADI2010	K = 2; N = 103	−0.28 [−0.67, 0.11]	(P = 0.98), I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (3.1)
Total symptoms (RR: response)	SWADI2010	K = 1; N = 22	1.25 [0.45, 3.45]	N/A	Very low[1,2,3]	Appendix 14c (i) (3.2)
Positive symptoms (SMD)	MCEVOY2007 SWADI2010	K = 2; N = 103	−0.43 [−0.82, −0.03]	(P = 0.74), I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (3.3)
Negative symptoms (SMD)	MCEVOY2007 SWADI2010	K = 2; N = 103	−0.22 [−0.61, 0.17]	(P = 0.86), I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (3.4)
Global state (severity) (SMD)	MCEVOY2007 SWADI2010	K = 2; N = 103	−0.14 [−0.53, 0.25]	(P = 0.86), I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (3.5)
Global state (severity) (RR: response)	SWADI2010	K = 1; N = 22	0.83 [0.36, 1.94]	N/A	Very low[1,2,3]	Appendix 14c (i) (3.6)
Depression (SMD)	MCEVOY2007	K = 1; N = 81	0.38 [−0.07, 0.82]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (3.7)
Depression (RR: response)	SWADI2010	K = 1; N = 22	0.71 [0.33, 1.57]	N/A	Very low[1,2,3]	Appendix 14c (i) (3.8)
Mania (RR: response)	SWADI2010	K = 1; N = 22	0.70 [0.43, 1.14]	N/A	Very low[1,2,3]	Appendix 14c (i) (3.9)
Quality of life (SMD)	MCEVOY2007	K = 1; N = 81	−0.30 [−0.60, −0.00]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (3.10)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours risperidone.
[1]Downgraded due to risk of bias (including: unclear sequence and/or allocation concealment; one open-label trial (no blinding) or unclear blinding; one analysis of a modified ITT population; LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Side effects

A small to moderate significant difference was found between treatment groups, favouring risperidone over quetiapine on total cholesterol (SMD = −0.47; 95% CI, −0.91 to −0.03), fasting triglycerides (SMD = −0.56; 95% CI, −1.00 to −0.11) and systolic blood pressure (SMD = −0.60; 95% CI, −1.05 to −0.15). No other significant differences in side effect outcomes between treatment groups were found. Evidence from each reported outcome and overall quality of evidence are presented in Table 52; the full evidence profiles can be found in Appendix 17c.

7.2.6 Clinical evidence for olanzapine versus haloperidol as initial treatment for first episode psychosis

One study (LIEBERMAN2003) (N = 262) compared haloperidol and olanzapine in children and young people with first episode psychosis in whom 26% were antipsychotic naïve at baseline, with a mean age of 23.8 years. The design of the 104-week trial included a 12-week acute phase, followed by a 92-week continuation phase in which dose ranges for each treatment group increased by up to 10 mg/day for olanzapine and 14 mg/day for haloperidol.

Efficacy

Efficacy outcomes were reported in sufficient detail to allow extraction and analysis at the end of the 12-week acute phase only. A small effect was found for negative symptoms (SMD = −0.25; 95% CI −0.50 to −0.00). No significant differences were found between treatment groups for other efficacy outcomes measured. Evidence from each reported outcome and overall quality of evidence are presented in Table 53; the full evidence profiles can be found in Appendix 17c.

Side effects

The only outcomes reported in sufficient detail to allow for extraction and analysis included weight, prolactin level and the number of people leaving the study early for any reason. Following the acute phase of treatment (12 weeks) olanzapine was favoured over haloperidol on change in prolactin level (SMD = −0.34; 95% CI, −0.59 to −0.10). Data for this outcome were not reported in sufficient detail at study endpoint (104 weeks) to allow for extraction and analysis. Both treatment groups gained weight during the study. A moderate and significant difference, favouring haloperidol over olanzapine on weight gain, was found at 104 weeks (SMD = 0.70; 95% CI, 0.45 to 0.95) and significantly fewer olanzapine-treated participants left the study early for any reason compared with haloperidol-treated participants (RR = 0.87; 95% CI, 0.77 to 0.97) (data at 104 weeks). Evidence from each reported outcome and overall quality of evidence are presented in Table 54; the full evidence profiles can be found in Appendix 17c.

Table 52: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone versus quetiapine as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	MCEVOY2007 SWADI2010	K = 2; N = 103	0.13 [–0.26, 0.52]	(P = 0.62), I^2 = 0%	Very low[1,2,3,5]	Appendix 14c (i) (4.1)
Metabolic: weight (RR)	MCEVOY2007 SWADI2010	K = 2; N = 103	1.88 [1.22, 2.89]**	(P = 0.08), I^2 = 68%	Very low[1,2,3,4,5]	Appendix 14c (i) (4.2)
Metabolic: BMI (SMD)	MCEVOY2007	K = 1; N = 81	0.24 [–0.20, 0.67]	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.3)
Metabolic: fasting serum glucose level mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	–0.13 [–0.57, 0.31]	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.4)
Metabolic: fasting total cholesterol mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	–0.47 [–0.91, –0.03]*	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.5)
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	MCEVOY2007	K = 1; N = 81	0.16 [–0.28, 0.60]	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.6)
Metabolic: fasting triglycerides	MCEVOY2007	K = 1; N = 81	–0.56 [–1.00, –0.11]*	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.7)
Cardio: systolic BP (SMD)	MCEVOY2007	K = 1; N = 81	–0.60 [–1.05, –0.15]*	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.8)
Cardio: diastolic BP (SMD)	MCEVOY2007	K = 1; N = 81	–0.43 [–0.87, 0.02]	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.9)
Hormonal: prolactin (SMD)	MCEVOY2007	K = 1; N = 81	1.81 [1.29, 2.33]**	N/A	Very low[1,2,3,5]	Appendix 14c (i) (4.10)

Continued

Table 52: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Hormonal: prolactin (RR)	SWADI2010	K = 1; N = 22	10.00 [1.53, 65.41]**	N/A	Very low[1,2,3]	Appendix 14c (i) (4.11)
Neurological: Abnormal Involuntary Movement Scale (AIMS) (RR)	SWADI2010	K = 1; N = 22	3.00 [0.37, 24.58]	N/A	Very low[1,2,3]	Appendix 14c (i) (4.12)
Neurological: Simpson-Angus Extrapyramidal Side Effects Scale (SAS) (RR)	SWADI2010	K = 1; N = 22	2.00 [0.66, 6.04]	N/A	Very low[1,2,3]	Appendix 14c (i) (4.13)
Neurological: Barnes Akathisia Rating Scale (BARS) (RR)	SWADI2010	K = 1; N = 22	1.00 [0.40, 2.50]	N/A	Very low[1,2,3]	Appendix 14c (i) (4.14)
Leaving the study early for any reason (RR)	MCEVOY2007 SWADI2010	K = 2; N = 189	0.51 [0.06, 4.08]	(P = 0.11), I^2 = 61%	Very low[1,2,3,4]	Appendix 14c (i) (4.15)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours risperidone.
**Favours quetiapine.
[1]Serious risk of (including: unclear sequence and/or allocation concealment; one open-label trial (no blinding) or unclear blinding; one analysis of a modified ITT population; LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]$I^2 \geq 50\%$, $p < .05$.
[5]Serious risk of indirectness (upper age range 44.4 years may not be representative of children and young people).

Table 53: Summary of findings table for efficacy outcomes reported at 12 weeks associated with olanzapine versus haloperidol as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	LIEBERMAN2003	K = 1; N = 251	−0.21 [−0.46, 0.04]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (5.1)
Positive symptoms	LIEBERMAN2003	K = 1; N = 252	−0.04 [−0.29, 0.20]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (5.2)
Negative symptoms	LIEBERMAN2003	K = 1; N = 252	−0.25 [−0.50, −0.00]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (5.3)
Global state (severity) (SMD)	LIEBERMAN2003	K = 1; N = 254	−0.16 [−0.41, 0.08]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (5.4)
Depression (SMD)	LIEBERMAN2003	K = 1; N = 251	−0.19 [−0.43, 0.06]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (5.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours olanzapine.
[1]Serious risk of bias (including: unclear sequence generation and allocation concealment; unclear rater blinding, trial registration could not be found, LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]Serious risk of indirectness (upper age range of 40 may not be representative of children and young people).

Table 54: Summary of findings table for side effect outcomes reported at 12 weeks associated with olanzapine versus haloperidol as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	LIEBERMAN2003	K = 1; N = 263	0.70 [0.45, 0.95]**	N/A	Very low[1,2,3,4]	Appendix 14c (i) (6.1)
Hormonal: prolactin (RR)	LIEBERMAN2003	K = 1; N = 263	−0.34 [−0.59, −0.10]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (6.2)
Leaving the study early for any reason (RR)	LIEBERMAN2003	K = 1; N = 263	0.87 [0.77, 0.97]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (6.3)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours olanzapine.
**Favours haloperidol.
[1]Serious risk of bias (including: unclear sequence generation and allocation concealment, unclear rater blinding, trial registration could not be found, LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]Serious risk of indirectness (upper age range of 40 may not be representative of children and young people).

7.2.7 Clinical evidence for haloperidol versus risperidone as initial treatment for first episode psychosis

One study (SCHOOLER2005) (N = 559) compared haloperidol and risperidone in children and young people with first episode psychosis, of whom 47% were antipsychotic naïve at baseline with a mean age of 25.5 years.

Efficacy
SCHOOLER2005 assessed change in symptoms and global state (however, timepoints were not clearly reported). No significant differences between treatment groups were found on either of these outcomes. Evidence from each reported outcome and overall quality of evidence are presented in Table 55; the full evidence profiles can be found in Appendix 17c.

Side effects
A small significant difference was found between treatment groups on prolactin level favouring haloperidol over risperidone (SMD = 0.51; 95% CI, 0.33 to 0.69); however the timepoint at which these data were collected is unclear. No significant differences were found between the treatment groups on weight or leaving the study early for any reason. Evidence from each reported outcome and overall quality of evidence are presented in Table 56; the full evidence profiles can be found in Appendix 17c.

7.2.8 Clinical evidence for risperidone versus olanzapine as initial treatment for first episode psychosis

Four studies (MCEVOY2007; ROBINSON2006; SIKICH2008; VANBRUGGEN2003) (N = 506) compared olanzapine and risperidone in children and young people for whom the majority were experiencing their first episode of psychosis. Prior antipsychotic use varied across trials with 96.0% in MCEVOY2007, 78.0% in ROBINSON2006 and 33.0% in SIKICH2008 being antipsychotic naïve at baseline (VANBRUGGEN2003 did not report prior antipsychotic use). All trials included participants aged 25 years and younger; however, the mean age of the participants in the SIKICH2008 trial was significantly younger than the other included trials (13.8 years). The design of the SIKICH2008 trial included an 8-week acute phase and a 52-week maintenance phase (post-treatment) in which participants were maintained in their randomised groups and administered doses within the same range as the acute phase. The ROBINSON2006 trial was conducted over 156 weeks, with a 16-week acute phase. Data are reported at the end of the acute phase only.

Efficacy
No significant differences between risperidone and olanzapine in symptoms, global state, depression, quality of life, response or remission were found. Evidence from each reported outcome and overall quality of evidence are presented in Table 57; the full evidence profiles can be found in Appendix 17c.

Table 55: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with haloperidol versus risperidone as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	SCHOOLER2005	K = 1; N = 528	−0.02 [−0.19, 0.15]	N/A	Very low[1,2,3]	Appendix 14c (i) (7.1)
Positive symptoms	SCHOOLER2005	K = 1; N = 528	0.05 [−0.12, 0.22]	N/A	Very low[1,2,3]	Appendix 14c (i) (7.2)
Negative symptoms	SCHOOLER2005	K = 1; N = 528	−0.08 [−0.25, 0.09]	N/A	Very low[1,2,3]	Appendix 14c (i) (7.3)
Global state (severity) (SMD)	SCHOOLER2005	K = 1; N = 528	0.06 [−0.11, 0.23]	N/A	Very low[1,2,3]	Appendix 14c (i) (7.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, unclear rater blinding, unable to find trial registration, unclear at what timepoint data were taken, high dropout).
[2]Serious risk of indirectness (48% population had bipolar disorder).
[3]Serious risk of reporting bias.

Table 56: Summary of findings table for side effect outcomes reported at treatment endpoint associated with haloperidol versus risperidone as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	SCHOOLER2005	K = 1; N = 415	0.11 [−0.08, 0.30]	N/A	Very low[1,3,4]	Appendix 14c (i) (8.1)
Hormonal: prolactin (RR)	SCHOOLER2005	K = 1; N = 507	0.51 [0.33, 0.69]*	N/A	Very low[1,3,4]	Appendix 14c (i) (8.2)
Leaving the study early for any reason (RR)	SCHOOLER2005	K = 1; N = 218	1.15 [0.94, 1.42]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (8.3)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours haloperidol.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment, unclear rater blinding, unable to find trial registration, unclear at what timepoint data were taken, high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (48% population had bipolar disorder).
[4]Serious risk of reporting bias.

Table 57: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone versus olanzapine as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	K = 3; N = 150	–0.09 [–0.41, 0.24]	(P = 0.58); I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (9.1)
Positive symptoms (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	K = 3; N = 150	–0.72 [–1.87, 0.43]	(P = 0.02); I^2 = 82%	Very low[1,2,3,4,5]	Appendix 14c (i) (9.2)
Negative symptoms (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	K = 3; N = 150	0.22 [–0.53, 0.98]	(P = 0.008); I^2 = 79%	Very low[1,2,3,4,5]	Appendix 14c (i) (9.3)
Global state (severity) (SMD)	MCEVOY2007 SIKICH2008	K = 2; N = 108	–0.06 [–0.44, 0.32]	N/A	Very low[1,2,3]	Appendix 14c (i) (9.4)
Depression (SMD)	MCEVOY2007 VANBRUGGEN2003	K = 2; N = 116	–0.60 [–1.74, 0.53]	N/A	Very low[1,2,3]	Appendix 14c (i) (9.5)
Quality of life (SMD)	MCEVOY2007	K = 1; N = 74	–0.13 [–0.45, 0.19]	N/A	Very low[1,2,3]	Appendix 14c (i) (9.6)
Response (RR)	ROBINSON2006	K = 1; N = 120	1.25 [0.84, 1.86]	N/A	Low[1,2]	Appendix 14c (i) (9.7)
Remission (RR)	VANBRUGGEN2003	K = 1; N = 44	0.55 [0.17, 1.78]	N/A	Very low[1,2,3]	Appendix 14c (i) (9.8)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including serious or unclear sequence generation and allocation concealment, unclear rater blinding, trial registration could not be found, analysis included modified ITT population, large discrepancies in length of untreated psychosis in each treatment group and antipsychotic use, unclear treatment of participants considered to be in remission and actively symptomatic during treatment, LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]Serious risk of indirectness (upper age limit includes adults over 44.4 years and therefore may not be representative of a population of children and young people).
[5]$I^2 \geq 50\%$, $p < .05$.

Side effects

ROBINSON2006 reported mean endpoint scores and MCEVOY2007, SIKICH2008 and VANBRUGGEN2003 reported mean change scores. Sensitivity analyses were conducted for outcomes measured using mean endpoint and mean change scores and where more than one study was included. Moderate and significant differences were found between treatment groups, favouring risperidone on the number of participants gaining 7% or more of their baseline weight (SMD = 0.68; 95% CI, 0.47 to 0.98) and BMI increase was significantly greater in olanzapine-treated participants compared with risperidone-treated participants (SMD = −0.66; 95% CI, −0.98 to −0.33). In addition, risperidone was favoured over olanzapine on triglyceride level (SMD = −0.57; 95% CI, −1.04 to −0.11). Risperidone was also favoured over olanzapine on diastolic and systolic blood pressure, with a small effect for diastolic blood pressure (SMD = −0.44; 95% CI, −0.84 to −0.04) and a moderate effect seen for systolic blood pressure (SMD = −0.76; 95% CI, −1.23 to −0.28). A moderate, significant effect for high-density lipoprotein cholesterol level (mg per dl) was found, favouring olanzapine over risperidone (SMD = 0.67; 95% CI, 0.20 to 1.14) and a large effect favouring olanzapine for prolactin level (mg per dl) (SMD = 1.67; 95% CI, 1.22 to 2.11) was found. Evidence from each reported outcome and overall quality of evidence are presented in Table 58; the full evidence profiles can be found in Appendix 17c.

7.2.9 Clinical evidence for quetiapine administered at different doses as initial treatment for first episode psychosis

One study (BERGER2008) (N = 141) compared quetiapine at different doses in children and young people with first episode psychosis, all of whom had previous experience with antipsychotic medication prior to the study and had a mean age of 19.4 years.

Efficacy

Extractable data were reported for the end of part one of the study (4 weeks) only. A small, significant difference favouring 400 mg of quetiapine per day over 200 mg per day was found for global state (SMD = 0.44; 95% CI, 0.02 to 0.85). No other significant differences between dosing schedules were found for the other efficacy outcomes reported. Evidence from each reported outcome and overall quality of evidence are presented in Table 59; the full evidence profiles can be found in Appendix 17c.

Side effects

No significant differences were found between treatment groups on any of the side effect outcomes reported at 4 weeks post-treatment. Evidence from each reported outcome and overall quality of evidence are presented in Table 60; the full evidence profiles can be found in Appendix 17c.

Table 58: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone versus olanzapine as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	MCEVOY2007 SIKICH2008 VANBRUGGEN2003	K = 3; N = 139	−0.29 [−1.02, 0.45]	(P = 0.02); I^2 = 76%	Very low[1,2,3,4,5]	Appendix 14c (i) (10.1)
Metabolic: weight (RR) (N = patients with >7% gain)	MCEVOY2007	K = 1; N = 74	0.68 [0.47, 098]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.2)
Metabolic: BMI (SMD)	MCEVOY2007 ROBINSON2006	K = 2; N = 186	−0.66 [−0.98, −0.33]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.3)
Metabolic: fasting serum glucose level mg per dl (SMD)	MCEVOY2007 SIKICH2008	K = 2; N = 108	−0.11 [−0.73, 0.52]	(P = 0.13); I^2 = 57%	Very low[1,2,3,4,5]	Appendix 14c (i) (10.4)
Metabolic: fasting total cholesterol mg per dl (SMD)	MCEVOY2007	K = 1; N = 74	−0.16 [−0.61, 0.30]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.5)
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	MCEVOY2007	K = 1; N = 74	0.67 [0.20, 1.14]**	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.6)

Continued

Table 58: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: fasting triglycerides (SMD)	MCEVOY2007	K = 1; N = 74	–0.57 [–1.04, –0.11]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.7)
Cardio: systolic BP (SMD)	MCEVOY2007	K = 1; N = 74	–0.76 [–1.23, –0.28]*	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.8)
Cardio: diastolic BP (SMD)	MCEVOY2007 SIKICH2008	K = 1; N = 74	–0.44 [–0.84, –0.04]*	(P = 0.30); I^2 = 6%	Very low[1,2,3,4]	Appendix 14c (i) (10.9)
Hormonal: prolactin (SMD)	MCEVOY2007 SIKICH2008	K = 2; N = 108	1.67 [1.22, 2.11]**	(P = 0.55); I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (10.10)
Neurological: AIMS (RR)	SIKICH2008	K = 1; N = 33	0.04 [–0.65, 0.73]	N/A	Very low[1,2,3]	Appendix 14c (i) (10.11)
Neurological: SAS (RR)	ROBINSON2006 SIKICH2008 VANBRUGGEN2003	K = 3; N = 168	0.34 [0.00, 0.67]	(P = 0.33); I^2 = 9%	Very low[1,2,3]	Appendix 14c (i) (10.12)
Sensitivity analysis: neurological: SAS (SMD)	SIKICH2008 VANBRUGGEN2003	K = 2; N = 56	0.03 [–0.50, 0.56]	(P = 0.93); I^2 = 0%	Very low[1,2,3]	Appendix 14c (i) (10.13)
Neurological: BARS (RR)	SIKICH2008	K = 1; N = 33	0.36 [–0.34, 1.06]	N/A	Very low[1,2,3]	Appendix 14c (i) (10.14)

Neurological: parkinsonism (RR)	ROBINSON2006	K = 1; N = 112	0.56 [0.20, 1.55]	N/A	Very low[1,2,3]	Appendix 14c (i) (10.15)
Neurological: akathisia (RR)	VANBRUGGEN2003	K = 1; N = 31	0.95 [0.34, 2.68]	N/A	Very low[1,2,3,4]	Appendix 14c (i) (10.16)
Leaving the study early for any reason (RR)	MCEVOY2007 ROBINSON2006 VANBRUGGEN2003	K = 3; N = 430	1.04 [0.89, 1.21]	(P = 0.68); I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (i) (10.17)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours risperidone.
**Favours olanzapine.
[1]Serious risk of bias (including serious or unclear sequence generation and allocation concealment, unclear rater blinding, trial registration could not be found, analysis included modified ITT population, large discrepancies in length of untreated psychosis in each treatment group and antipsychotic use, unclear treatment of participants considered to be in remission and actively symptomatic during treatment, LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.
[4]Serious risk of indirectness (upper age limit includes adults over 44.4 years and therefore may not be representative of a population of children and young people).
[5]$I^2 \geq 50\%$, $p < .05$.

Table 59: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with quetiapine 200 mg per day versus quetiapine 400 mg per day as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	BERGER2008	K = 1; N = 91	0.35 [–0.06, 0.77]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.1)
Positive symptoms	BERGER2008	K = 1; N = 91	0.37 [–0.04, 0.79]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.2)
Negative symptoms	BERGER2008	K = 1; N = 91	0.32 [–0.10, 0.73]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.3)
Global state (severity) (SMD)	BERGER2008	K = 1; N = 91	0.44 [0.02, 0.85]*	N/A	Very low[1,2,3]	Appendix 14c (i) (11.4)
Depression (SMD)	BERGER2008	K = 1; N = 91	–0.08 [–0.49, 0.33]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.5)
Mania	BERGER2008	K = 1; N = 91	0.34 [–0.07, 0.76]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.6)
Psychosocial functioning	BERGER2008	K = 1; N = 91	0.19 [–0.22, 0.60]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.7)
Social functioning	BERGER2008	K = 1; N = 91	–0.01 [–0.42, 0.40]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.8)
Response (RR)	BERGER2008	K = 1; N = 141	1.39 [0.78, 2.49]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.9)
Remission (RR)	BERGER2008	K = 1; N = 141	0.43 [0.16, 1.17]	N/A	Very low[1,2,3]	Appendix 14c (i) (11.10)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours 400 mg/day.
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained, available case analysis used).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Table 60: Summary of findings table for side effect outcomes reported at treatment endpoint associated with quetiapine 200 mg per day versus quetiapine 400 mg per day as initial treatment in children and young people with first episode psychosis

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	BERGER2008	K = 1; N = 106	−0.04 [−0.54, 0.47]	N/A	Very low[1,2,3]	Appendix 14c (i) (12.1)
Neurological: UKU	BERGER2008	K = 1; N = 91	−0.37 [−0.78, 0.04]	N/A	Very low[1,2,3]	Appendix 14c (i) (12.2)
Leaving the study early for any reason	BERGER2008	K = 1; N = 141	0.91 [0.35, 2.38]	N/A	Very low[1,2,3]	Appendix 14c (i) (12.3)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained, available case analysis used).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

7.2.10 Clinical evidence summary for initial treatment with antipsychotic medication in first episode psychosis in children and young people

In nine head-to-head RCTs, with a total of 1,674 participants with first episode psychosis, the evidence suggests minimal differences in efficacy between individual antipsychotic medications and doses. Some differences were seen in side effects associated with different individual antipsychotic medications. All antipsychotics examined for weight resulted in weight gain, however moderate to large, significant differential effects were found between olanzapine and active comparators (quetiapine, haloperidol and risperidone) favouring the active comparator on weight gain and BMI increase between olanzapine and risperidone (favouring risperidone). In addition, in one trial a large differential effect was found favouring quetiapine over risperidone on prolactin level. However, the results need to be considered in the context of the quality of the evidence. In general, the evidence for antipsychotics as initial treatment in children and young people was rated as low to very low due to imprecision, a high risk of publication bias, low internal validity of included trials and, where trial data were pooled, some evidence of heterogeneity. Therefore no robust conclusions can be drawn regarding the relative efficacy of individual antipsychotics and different doses of antipsychotics in initial treatment. Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence identified in children and young people, the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below in Section 7.2.11.

7.2.11 Clinical evidence summary – evidence for adults for initial treatment with antipsychotic medication

The review of initial treatment with antipsychotic medication in the adult *Schizophrenia* guideline (NCCMH, 2010) contained nine RCTs with a total of 1,801 participants with first episode or early schizophrenia (including people with a recent onset of schizophrenia and people who have never been treated with antipsychotic medication). The evidence suggested there were no clinically significant differences in efficacy between the antipsychotic drugs examined (see Section 6.2 of *Schizophrenia*). Most of the trials were not designed to examine differences in adverse effects of treatment, but metabolic and neurological side effects reported were consistent with those identified in the summary of product characteristics (SPC) for each drug.

7.3 ANTIPSYCHOTICS IN THE TREATMENT OF SUBSEQUENT ACUTE EPISODES OF PSYCHOSIS AND SCHIZOPHRENIA

7.3.1 Introduction

Early clinical studies established that antipsychotic medications are effective in the treatment of acute schizophrenic episodes (Davis & Garver, 1978), although they

proved to be more effective at alleviating positive symptoms than negative symptoms, such as alogia or affective blunting. However, no consistent difference between the FGAs was demonstrated in terms of antipsychotic efficacy or effects on individual symptoms, syndromes or schizophrenia subgroups. Accordingly, the choice of drug for an individual was largely dependent on differences in side effect profiles (Hollister, 1974; Davis & Garver, 1978). The limitations of these FGAs included heterogeneity of response in acute episodes, with a proportion of individuals showing little improvement (Kane, J. M., 1987), and a range of undesirable acute and long-term side effects. The search for better tolerated and more effective drugs eventually generated a series of second-generation drugs, which were thought to carry a lower potential risk of EPS (Barnes & McPhillips, 1999; Geddes *et al.*, 2000; Cookson *et al.*, 2002). However, the clinical evidence presented in the adult *Schizophrenia* guideline (NCCMH, 2010; which incorporated the recommendations from the NICE technology appraisal of SGAs [NICE, 2002]), particularly with regard to other adverse effects such as metabolic disturbance, and evidence from effectiveness (pragmatic) trials, suggested that choosing the most appropriate drug and formulation for an individual may be more important than the drug group (FGA or SGA).

7.3.2 Clinical review protocol for antipsychotics in the treatment of subsequent acute episodes of psychosis and schizophrenia in children and young people

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 61. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

7.3.3 Studies considered[97]

Thirteen RCTs (N = 1,524) providing relevant clinical evidence met the eligibility criteria for the review of antipsychotic medication as treatment in the acute episode (AstraZenecaD1441C00112 [AstraZeneca D1441C00112, unpublished], FINDLING2008A [Findling *et al.*, 2008], HAAS2009 [Haas *et al.*, 2009a], HAAS2009B [Haas *et al.*, 2009b], JENSEN2008 [Jensen *et al.*, 2008], KRYZHANOVSKAYA2009B [Kryzhanovskaya *et al.*, 2009], MOZES2006 [Mozes *et al.*, 2006], PAILLERE-MARTINOT1995 [Paillère-Martinot *et al.*, 1995], POOL1976 [Pool *et al.*, 1976], SIKICH2004 [Sikich *et al.*, 2004], SINGH2011 [Singh, J., *et al.*, 2011], XIONG2004/KENNEDY2012 [Kennedy *et al.*, 2007, updated 2012], YAO2003/KENNEDY2012 [Kennedy *et al.*, 2007, updated 2012]). The latter two

[97]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 61: Clinical review protocol for the review of antipsychotics in the treatment of the acute episode in children and young people

Review questions	**RQ B2:** Does the efficacy profile of continuous antipsychotic drug treatment, compared with alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children/young people and adults with psychosis and schizophrenia? **RQ B3:** Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared with adults with psychosis and schizophrenia (in particular, metabolic, neurological and cognitive impairments)?
Objectives	To provide evidence-based recommendations regarding the pharmacological (antipsychotic) treatment and management of the acute episode in children and young people with psychosis and schizophrenia, including a review of the adult *Schizophrenia* guideline (NICE, 2009a; NCCMH, 2010) for its relevance to children and young people.
Population	**Inclusion:** Children and young people (aged 18 years and younger) with an acute episode of psychosis and schizophrenia. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	All antipsychotic medication licensed in the UK for the treatment of children and young people with psychosis and schizophrenia, including considerations related to the age of participants (for example, dose modifications). Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia). • Amisulpride • Aripiprazole • Benperidol • Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol

Continued

Table 61: (*Continued*)

	• Levomepromazine • Olanzapine • Pericyazine • Pimozide • Prochlorperazine • Promazine hydrochloride • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate
Comparison	Alternative management strategies: • Placebo • Psychological intervention • Any of the above interventions offered as an alternative management strategy
Critical outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes, cardiotoxicity) • Remission
Electronic databases	**RQ B2:** Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, ERIC, HTA, IBSS, Sociological Abstracts, SSA, SSCI Grey literature databases: HMIC, PsycBOOKS, PsycEXTRA **RQ B3:** Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: CDSR, CENTRAL, DARE

Continued

Table 61: (*Continued*)

Date searched	Systematic reviews: 1995 to May 2012 RCTs: inception of databases to May 2012
Study design	Systematic review, RCT
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and at or under 18 years. The review will seek to identify whether modifications in treatment and management of children aged at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger are available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

studies were not published in English and were identified via a systematic review of antipsychotic medication for childhood-onset schizophrenia (Kennedy *et al*., 2007, updated 2012). The remaining 12 included RCTs were published in peer-reviewed journals between 1976 and 2012. Additional unpublished data were also obtained from one placebo controlled trial of quetiapine (AstraZenecaD1441C00112). All studies reported at least one outcome in sufficient detail to allow for extraction and analysis. Eleven studies investigated antipsychotic medication use in children and young people experiencing an acute episode of psychosis and schizophrenia aged 18 years and younger (AstraZenecaD1441C00112, FINDLING2008A, HAAS2009, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011, POOL1976, MOZES2006, JENSEN2008 XIONG2004/KENNEDY2012, YAO2003/KENNEDY2012). Data were extrapolated

from two remaining studies providing relevant clinical evidence in populations of young people experiencing an acute episode of psychosis and schizophrenia, which included children and young people aged over and under 18 years, but with an overall mean age 25 years and younger (PAILLIERE-MARTINOT1995, SIKICH2004). In addition, 583 studies were considered irrelevant to the pharmacological management of psychosis and schizophrenia in children and young people and excluded from the review. Further information about both included and excluded studies can be found in Appendix 13c.

There were a total of 22 evaluations across three comparison groups: antipsychotic medication versus placebo (Section 7.3.4); antipsychotic medication in head-to-head trials (Section 7.3.5); and antipsychotic medications administered at different doses (Section 7.3.6). Characteristics of the included studies within each comparison group can be found in Table 62, Table 69 (page 272) and Table 80 (page 285). (Further information about both included and excluded studies can be found in Appendix 13c.) Forest plots and evidence profiles for each outcome can be found in Appendix 14c and Appendix 17c, respectively.

7.3.4 Clinical evidence for antipsychotic medication versus placebo

Studies considered

Seven included RCTs (N = 1067) provided relevant clinical evidence for antipsychotic medication compared with placebo in the treatment of the acute episode (AstraZenecaD1441C00112, FINDLING2008A, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011, PAILLERE-MARTINOT1995, POOL1976) (see Table 62 for a summary of study characteristics). Included studies reported at least one outcome in sufficient detail to allow for extraction and analysis. There was a total of 12 comparisons against placebo: quetiapine 400 mg per day (AstraZenecaD1441C00112); quetiapine 800 mg per day (AstraZenecaD1441C00112); aripiprazole 10 mg per day (FINDLING2008A); aripiprazole 30 mg per day (FINDLING2008A); risperidone 1 to 3 mg per day (HAAS2009B); risperidone 4 to 6 mg per day (HAAS2009B); olanzapine 11.1 mg per day (KRYZHANOVSKAYA2009B); paliperidone 1.5 mg per day (SINGH2011); paliperidone 3 mg per day (SINGH2011); paliperidone 6 mg per day (SINGH2011); amisulpride 50 to 100 mg per day (PAILLERE-MARTINOT1995); and haloperidol 11.9 mg per day (POOL1976). To assess the efficacy of antipsychotics versus placebo, the GDG used the dose ranges identified by the UK Prescribing Observatory for Mental Health (POMH-UK) benchmarking exercise of antipsychotic prescribing in children and young people in practice (POMH-UK, 2012) to categorise doses administered in the included trials as either 'lower' or 'higher' doses. 'Lower dose' and 'higher dose' antipsychotic medications were compared with placebo. Because of the known differential side effect profiles of the included antipsychotics the GDG decided it was not meaningful to pool data from all included antipsychotics against placebo in an analysis of side effects. Side effects were therefore assessed according to individual antipsychotic and respective dose.

Table 62: Study information table for trials comparing an antipsychotic medication with placebo in the treatment of an acute episode in children and young people with psychosis and schizophrenia

	Placebo is the comparator across trials						
	Quetiapine	**Aripiprazole**	**Risperidone**	**Olanzapine**	**Paliperidone**	**Amisulpride**	**Haloperidol**
Total no. of studies (N)	K = 1 (N = 222)	K = 1 (N = 302)	K = 1 (N = 160)	K = 1 (N = 107)	K = 1 (N = 200)	K = 1 (N = 27)	K = 1 (N = 49)
Study ID	AstraZeneca D144IC00112	FINDLING 2008A	HAAS 2009B	KRYZHANOV-SKAYA2009B	SINGH2011	PAILLERE-MARTINOT1995	POOL1976
Diagnosis	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenic disorder	Schizophrenia
Prior antipsychotic use (% naïve prior to intervention)	Not reported	51.7	Not reported	56.5	36% and 60% atypical and typical, respectively	Not reported	Not reported
Mean age (range)	15.4 (13.0 to 17.0)	15.5 (not reported)	15.6 (13.0 to 17.0)	16.2 (not reported)	15.4 (not reported)	20.0 (not reported)	15.5 (not reported)
Sex (% male)	59	57	64	70	59	Not reported	95
Ethnicity (% white)	61	37	53	72	68	Not reported	Not reported

Mean (range) medication dose (mg per day)	'Lower dose': 400.0 (not reported); 'higher dose': 800.0 (not reported)	'Lower dose': 10.0 (2.0 to 10.0); 'higher dose': 30.0 (2.0 to 30.0)	'Lower dose': (not reported) 1.0 to 3.0; 'higher dose': (not reported) 4.0 to 6.0	'Lower dose': 11.1 (2.5 to 20.0)	'Lower dose': 1.5 (not reported); 'higher dose': 3.0 (3.0 to 6.0) (additional dose arm: 6.0 [6.0 to 12.0])	'Lower dose': not reported (50.0 to 100.0)	'Higher dose': 11.9 (2.0 to 12.0)
Treatment length (weeks)	6	6	6	6	6	6	4
Length of follow-up (weeks)	6	6	6	6	6	6	4
Setting	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Adolescent hospital
Country	43 international sites, including the US and Asia	US, Europe, South America, Asia, the Caribbean, South Africa	India, Russia, Ukraine, US	US and Russia	Russia, India, Ukraine, US, Romania	France	US
Funding	AstraZeneca	Otsuka Pharmaceuticals	Johnson & Johnson	Eli Lilly and Company	Johnson & Johnson	Laboratories Synthèlabo (now Sanofi-Aventis)	Non-industry

Clinical evidence for 'lower dose' antipsychotic medication versus placebo for treatment of the acute episode

Six included RCTs (N = 696) provided relevant clinical evidence for an analysis of 'lower dose' antipsychotic medication compared with placebo in the treatment of the acute episode (AstraZenecaD1441C00112, FINDLING2008A, HAAS2009B, KRYZHANOVSKAYA2009B, PAILLERE-MARTINOT1995, SINGH2011). Antipsychotic medications and respective mean (range) doses included were: quetiapine 400 mg per day (not reported); aripiprazole 10 mg per day (2 to 10); risperidone (mean not reported) 1 to 3 mg per day; olanzapine 11.1 mg per day (2.5 to 20.0); paliperidone 1.5 mg per day (not reported); and amisulpride (mean not reported) 50 to 100 mg per day. Five studies were conducted in children and young people aged 18 years and younger (AstraZenecaD1441C00112, FINDLING2008A, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011) and one study was conducted in a population that included young people aged over 18, but with an overall mean age of 25 years and younger (PAILLERE-MARTINOT1995). The median of the mean ages is 15.5 years.

Efficacy

KRYZHANOVSKAYA2009B and PAILLIERE-MARTINOT1995 reported mean endpoint scores, while all remaining studies reported mean change scores. Sensitivity analyses were conducted for all outcomes measured using both mean endpoint and mean change scores and where more than one study had been included in the analysis. Small, significant differences were found favouring 'lower dose' antipsychotics over placebo for total symptoms (SMD = −0.32; 95% CI, −0.51 to −0.14), negative symptoms (SMD = −0.33; 95% CI, −0.49 to −0.16) and global state (SMD = −0.38; 95% CI, −0.57 to −0.18); and sensitivity analyses showed no significant changes to the overall effects when mean endpoint scores (KRYZHANOVSKAYA2009B) were removed. A small significant difference, favouring 'lower dose' antipsychotic over placebo was found for positive symptoms (SMD = −0.31; 95% CI, −0.59 to −0.02), however when mean endpoint scores were removed (KRYZHANOVSKAYA2009B; PAILLERE-MARTINOT1995) in a sensitivity analysis, the effect did not remain significant (SMD = −0.26; 95% CI, −0.56 to 0.04). No significant difference was found between treatment groups for depression and this remained non-significant in a sensitivity analysis. A small significant difference favouring 'lower dose' antipsychotic over placebo was found for psychosocial functioning (SMD = −0.29; 95% CI, −0.51 to −0.06). No significant differences were found between 'lower dose' antipsychotics and placebo on quality of life or number of participants considered to have responded (measured using the CGI). Evidence from each reported outcome and overall quality of evidence are presented in Table 63; the full evidence profiles can be found in Appendix 17c.

Side effects

Because of the known differential side effect profiles of the included antipsychotics, the GDG decided it was not meaningful to pool data from all included antipsychotics against placebo in an analysis of side effects. Side effects are therefore

Table 63: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with a 'lower dose' antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A KRYZHANOVSKAYA2009B SINGH2011	K = 4; N = 557	−0.32 [−0.51, −0.14]*	(P = 0.31); I^2 = 16%	Low[1,2]	Appendix 14c (ii) (1.1)
Sensitivity analysis: total symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A SINGH2011	K = 3; N = 450	−0.26 [−0.44, −0.07]*	(P = 0.64); I^2 = 0%	–	Appendix 14c (ii) (1.2)
Positive symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A KRYZHANOVSKAYA2009B HAAS2009B PAILLERE-MARTINOT1995 SINGH2011	K = 6; N = 685	−0.31 [−0.59, −0.02]*	(P < 0.0001); I^2 = 83%	Very low[1,2,4]	Appendix 14c (ii) (1.3)
Sensitivity analysis: positive symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B SINGH2011	K = 4; N = 558	−0.26 [−0.56, 0.04]	(P = 0.0003); I^2 = 84%	–	Appendix 14c (ii) (1.4)
Negative symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B KRYZHANOVSKAYA2009B PAILLERE-MARTINOT1995 SINGH2011	K = 6; N = 685	−0.33 [−0.49, −0.16]*	(P = 0.33); I^2 = 14%	Very low[1,2,4]	Appendix 14c (ii) (1.5)

Continued

Table 63: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Sensitivity analysis: negative symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B SINGH2011	K = 4; N = 558	–0.30 [–0.51, –0.10]*	(P = 0.22); I^2 = 31%	–	Appendix 14c (ii) (1.6)
Global state (severity) (SMD)	AstraZenecaD1441C00112 FINDLING2008A KRYZHANOVSKAYA2009B	K = 3; N = 452	–0.38 [–0.57, –0.18]*	(P = 0.43); I^2 = 0%	Low[1,2]	Appendix 14c (ii) (1.7)
Sensitivity analysis: global state (severity) (SMD)	AstraZenecaD1441C00112 FINDLING2008A	K = 2; N = 245	–0.31 [–0.53, –0.10]	(P = 0.89); I^2 = 0%	–	Appendix 14c (ii) (1.8)
Depression (SMD)	AstraZenecaD1441C00112 PAILLERE-MARTINOT1995 SINGH2011	K = 3; N = 173	–0.20 [–0.44, 0.04]	(P = 0.63); I^2 = 0%	Very low[1,2,3]	Appendix 14c (ii) (1.9)
Sensitivity analysis: depression (SMD)	AstraZenecaD1441C00112 SINGH2011	K = 2; N = 253	–0.17 [–0.42, 0.08]	(P = 0.75); I^2 = 0%	–	Appendix 14c (ii) (1.10)
Quality of life (SMD)	FINDLING2008A	K = 1; N = 197	–0.29 [–0.71, 0.13]	(P = 0.15); I^2 = 43%	Very low[1,2,3]	Appendix 14c (ii) (1.11)
Psychosocial functioning (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B SINGH2011	K = 4; N = 553	–0.29 [–0.51, –0.06]*	(P = 0.15); I^2 = 43%	Low[1,2]	Appendix 14c (ii) (1.12)
Response (RR)	AstraZenecaD1441C00112	K = 1; N = 149	1.98 [1.28, 3.05]	N/A	Very low[1,2,3]	Appendix 14c (ii) (1.13)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 'lower dose'.
[1]Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rater blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differs between groups, study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]$I^2 \geq 50\%$, $p < .05$.

assessed according to individual antipsychotic and respective dose. Three out of four studies found a significant difference between treatment groups, favouring placebo on weight gain (AstraZenecaD1441C00112, FINDLING2008A, KRYZHANOVSKAYA2009B). The largest effect found was between olanzapine and placebo (SMD = 1.33; 95% CI, 0.88 to 1.77). Similarly, significant differences favouring placebo were found between treatment groups on BMI increase with the largest effect between olanzapine and placebo (SMD = 1.31; 95% CI, 0.87 to 1.75). For other metabolic outcomes, small to moderate significant effects were found favouring placebo compared with aripiprazole 10 mg per day on fasting serum glucose level (SMD = 0.38; 95% CI, 0.03 to 0.74), quetiapine 400 mg per day on fasting low-density lipoprotein cholesterol levels (SMD = 0.58; 95% CI, 0.22 to 0.93) and total cholesterol (SMD = 0.58; 95% CI, 0.22 to 0.94), and olanzapine on fasting triglycerides (SMD = 0.54; 95% CI, 0.05 to 1.02). Placebo was also favoured over quetiapine 400 mg per day on systolic and diastolic blood pressure (SMD = 0.40; 95% CI, 0.07 to 0.73 for both outcomes) and standing pulse (SMD = 0.67; 95% CI, 0.33 to 1.00). Large differential effects between placebo and olanzapine (11.1 mg per day) and risperidone (1 to 3 mg per day) were found for prolactin level increase (SMD = 0.71; 95% CI, 0.26 to 1.15 and 1.05, 0.65 to 1.45 respectively). The number of participants treated with olanzapine (11.1 mg per day) leaving the study early for any reason was significantly fewer than the number of participants in the placebo group (SMD = 0.56; 95% CI, 0.36 to 0.87). No further significant differences were found for any other side effect outcomes measured. Evidence from each reported outcome and overall quality of evidence are presented in Table 64; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for 'higher dose' antipsychotic medication versus placebo for treatment of the acute episode

Five included RCTs (N = 604) provided relevant clinical evidence for an analysis of 'higher dose' antipsychotic medication compared with placebo in the treatment of the acute episode (AstraZenecaD1441C00112, FINDLING2008A, HAAS2009B, POOL1976, SINGH2011). Antipsychotic medications and respective mean (range) doses included: quetiapine 800 mg per day (not reported); aripiprazole 30 mg per day (2 to 30 mg); risperidone (mean not reported) 4 to 6 mg per day; paliperidone 3 to 6 mg per day (mean not reported); and haloperidol 11.9 mg per day (2 to 12 mg). All studies were conducted in children and young people aged 18 years and younger with a median of the mean of 15.5 years.

Efficacy

Small to moderate significant effects were found between a 'higher dose' antipsychotic and placebo on total symptoms (SMD = −0.48; 95% CI, −0.66 to −0.29), positive symptoms (SMD = −0.49; 95% CI, −0.66 to −0.32), negative symptoms (SMD = −0.34; 95% CI, −0.53 to −0.15), global state (SMD = −0.44; 95% CI, −0.65 to −0.22), depression (SMD = −0.28; 95% CI, −0.53 to −0.03), quality of life (SMD = −0.42, −0.83 to −0.01) and psychosocial functioning (SMD = −0.48; 95% CI, −0.65 to −0.31).

Table 64: Summary of findings table for side effect outcomes reported at treatment endpoint associated with a 'lower dose' antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Antipsychotic (dose)	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 197	0.34 [0.06, 0.62]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.1)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 107	1.33 [0.88, 1.77]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.1)
	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 146	0.75 [0.41, 1.08]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.1)
	SINGH2011	Paliperidone (1.5 mg per day)	K = 1; N = 105	0.19 [–0.20, 0.57]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.1)
Metabolic: BMI (SMD)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 197	0.33 [0.05, 0.61]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.2)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 107	1.31 [0.87, 1.75]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.2)
Metabolic: fasting serum glucose level mg/dl (SMD)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 127	0.38 [0.03, 0.74]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.3)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 80	0.43 [–0.04, 0.91]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.3)
	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 135	0.14 [–0.20, 0.48]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.3)
Metabolic: fasting total cholesterol mg/dl	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 191	0.23 [–0.06, 0.51]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.4)
	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 125	0.58 [0.22, 0.94]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.4)

Metabolic: fasting high-density lipoprotein cholesterol mg/dl (SMD)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 92	0.39 [–0.02, 0.81]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.5)
	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 125	0.04 [–0.31, 0.39]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.5)
Metabolic: fasting low-density lipoprotein cholesterol mg/dl (SMD)	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 125	0.58 [0.22, 0.93]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.6)
Metabolic: fasting triglycerides	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 92	0.04 [–0.37, 0.45]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.7)
	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 125	0.36 [0.00, 0.71]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.7)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 80	0.54 [0.05, 1.02]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.7)
Cardio: QT interval (SMD)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 194	0.09 [–0.19, 0.37]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.8)
	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 129	–0.28 [–0.63, 0.06]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.8)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 92	0.09 [–0.35, 0.53]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.8)
Cardio: QT interval (RR) (incidence of prolonged QT)	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 148	3.08 [0.13, 74.43]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.9)
	SINGH2011	Paliperidone (1.5 mg per day)	K = 1; N = 105	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.9)
Cardio: systolic BP (SMD)	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 146	0.40 [0.07, 0.73]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.10)
Cardio: diastolic BP (SMD)	AstraZenecaD144IC00112	Quetiapine (400 mg per day)	K = 1; N = 146	0.40 [0.07, 0.73]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.11)

Continued

Table 64: (*Continued*)

Outcome or subgroup	Study ID	Antipsychotic (dose)	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Cardio: tachycardia (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	9.24 [0.51, 168.69]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.12)
	SINGH2011	Paliperidone (1.5 mg per day)	K = 1; N = 105	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.12)
	HAAS2009B	Risperidone (1 to 3 mg per day)	K = 1; N = 109	0.98 [0.21, 4.65]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.12)
Cardio: standing pulse	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 146	0.67 [0.33, 1.00]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.13)
Hormonal: prolactin	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 194	–0.15 [–0.43, 0.14]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.14)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 94	0.71 [0.26, 1.15]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.14)
	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 125	0.33 [–0.02, 0.68]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.14)
	SINGH2011	Paliperidone (1.5 mg per day)	K = 1; N = 92	0.06 [–0.35, 0.47]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.14)
	HAAS2009B	Risperidone (1 to 3 mg per day)	K = 1; N = 109	1.05 [0.65, 1.45]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.14)
Hormonal: insulin	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 122	0.28 [–0.08, 0.63]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.15)

Neurological: extrapyramidal disorder (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	3.08 [0.13, 74.43]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.16)
Neurological: AIMS	HAAS2009B	Risperidone (1 to 3 mg per day)	K = 1; N = 109	0.23 [–0.15, 0.61]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.17)
Neurological: SAS	HAAS2009B	Risperidone (1 to 3 mg per day)	K = 1; N = 109	0.00 [–0.38, 0.38]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.18)
Neurological: parkinsonism (RR)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 200	2.14 [0.91, 5.03]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.19)
Neurological: tremor (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	1.54 [0.27, 8.96]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.20)
Neurological: akathisia (RR)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 200	1.00 [0.33, 3.00]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.21)
	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	1.54 [0.27, 8.96]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.21)
Neurological: dystonia (RR)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 200	9.00 [0.49, 165.00]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.22)
Neurological: dyskinesia (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	5.14 [0.25, 105.17]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.23)
Neurological: extrapyramidal disorder (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	3.08 [0.13, 74.43]	N/A	Very low[1,2,3]	Appendix 14c (ii) 2.24
Mortality (RR)	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 200	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.25)
	HAAS2009B	Risperidone (1 to 3 mg per day)	K = 1; N = 109	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.25)

Continued

Table 64: (*Continued*)

Outcome or subgroup	Study ID	Antipsychotic (dose)	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Leaving the study early for any reason (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 148	0.62 [0.37, 1.04]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.26)
	FINDLING2008A	Aripiprazole (10 mg per day)	K = 1; N = 200	1.60 [0.76, 3.35]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.26)
	KRYZHANOVSKAYA2009B	Olanzapine (11.1 mg per day)	K = 1; N = 94	0.56 [0.36, 0.87]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.26)
	PAILLERE-MARTINOT1995	Amisulpride (50 to 100 mg per day)	K = 1; N = 17	1.11 [0.45, 2.78]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.26)
	HAAS2009B	Risperidone (1 to 3 mg per day)	K = 1; N = 109	0.55 [0.28, 1.07]	N/A	Very low[1,2,3]	Appendix 14c (ii) (2.26)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 'lower dose'.
** Favours placebo.
[1]Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rater blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differs between groups, LOCF analysis, but high dropout).
[2]Serious risk of publication bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 65: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with a 'higher dose' antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A SINGH2011	K = 3; N = 443	−0.48 [−0.66, −0.29]*	(P = 0.87); I^2 = 0%	Low[1,2]	Appendix 14c (ii) (3.1)
Positive symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B SINGH2011	K = 4; N = 547	−0.49 [−0.66, −0.32]*	(P = 0.87); I^2 = 0%	Low[1,2]	Appendix 14c (ii) (3.2)
Negative symptoms (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B SINGH2011	K = 4; N = 546	−0.34 [−0.53, −0.15]*	(P = 0.29); I^2 = 20%	Low[1,2]	Appendix 14c (ii) (3.3)
Global state (severity) (SMD)	AstraZenecaD1441C00112 FINDLING2008A	K = 2; N = 344	−0.44 [−0.65, −0.22]*	(P = 0.73); I^2 = 0%	Very low[1,2,3]	Appendix 14c (ii) (3.4)
Depression (SMD)	AstraZenecaD1441C00112 SINGH2011	K = 2; N = 248	−0.28 [−0.53, −0.03]*	(P = 0.94); I^2 = 0%	Very low[1,2,3]	Appendix 14c (ii) (3.5)

Continued

Table 65: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Quality of life (SMD)	FINDLING2008A	K = 1; N = 195	−0.42 [−0.83, −0.01]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (3.6)
Psychosocial functioning (SMD)	AstraZenecaD1441C00112 FINDLING2008A HAAS2009B SINGH2011	K = 4; N = 543	−0.48 [−0.65, −0.31]*	(P = 0.62); I^2 = 0%	Low[1,2]	Appendix 14c (ii) (3.7)
Response (RR)	AstraZenecaD1441C00112	K = 1; N = 148	1.85 [1.19, 2.88]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (3.8)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 'higher dose'.
[1]Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rate blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differs between groups, patients who did not complete 4 weeks of daily medication because of voluntary withdrawal or for administrative reasons were not included in the analyses for efficacy ratings and were replaced by new patients, study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met .

A large effect was found for response (measured using the CGI) (RR = 1.85; 95% CI, 1.19 to 2.88). Evidence from each reported outcome and overall quality of evidence are presented in Table 65; the full evidence profiles can be found in Appendix 17c.

SINGH2011 also reported data for a third dose of paliperidone (6.0 to 12.0 mg per day) versus placebo. A small, significant difference favouring 6 to 12 mg of paliperidone per day over placebo was found for negative symptoms (SMD = −0.40; 95% CI, −0.8 to −0.01), but no other significant differences were found on the other side effects measured (see Table 66).

Side effects

Three trials assessing weight gain found small to moderate significant effects favouring quetiapine 800.00 mg per day (SMD = 0.58; 95% CI, 0.25 to 0.91); aripiprazole 30.0 mg per day (SMD = 0.41; 95% CI, 0.12 to 0.69); and paliperidone 3 to 6 mg per day (SMD = 0.57; 95% CI, 0.17 to 0.97). In addition, BMI was found to increase significantly more in participants treated with aripiprazole 30.0 mg per day compared with placebo (SMD = 0.33; 95% CI, 0.05 to 0.61). A moderate and significant difference, favouring placebo for triglycerides was also found for quetiapine 800.00 mg per day (SMD = 0.61; 95% CI, 0.25 to 0.98) and low-density lipoprotein cholesterol level (SMD = 0.41; 95% CI, 0.05 to 0.77). Other significant differences favouring placebo included cardiac, hormonal and neurological changes. QT interval was found to be significantly longer in participants treated with quetiapine 800.0 mg per day compared with placebo-treated participants (SMD = 0.37; 95% CI, 0.03 to 0.72). Prolactin level was found to increase significantly more in participants treated with quetiapine 800.0 mg per day (SMD = 0.37; 95% CI, 0.02 to 0.73) and a large effect favouring placebo was found for risperidone 4 to 6 mg per day (SMD = 1.38; 95% CI, 0.95 to 1.81). Participants treated with placebo scored significantly better than patients treated with risperidone 4 to 6.0 mg per day on the SAS (SMD = 0.45; 95% CI, 0.06 to 0.84) and participants treated with aripiprazole 30.0 mg per day experienced a significantly higher incidence of parkinsonism compared with placebo-treated patients (RR = 4.43; 95% CI, 2.05 to 9.58). A significant effect was also found favouring placebo over haloperidol 11.9 mg per day on EPS (RR = 17.28; 95% CI, 2.50 to 119.55), however the CIs are wide. Significantly fewer people treated with quetiapine 800.0 mg per day dropped out compared with placebo-treated participants (SMD = 0.47; 95% CI, 0.27 to 0.84). Evidence from each reported outcome and overall quality of evidence are presented in Table 67; the full evidence profiles can be found in Appendix 17c.

SINGH2011 also reported data for a third dose of paliperidone (6 to 12 mg per day) versus placebo (see Table 68). A moderate and significant difference favouring placebo versus 6 to 12 mg per day of paliperidone was found for weight increase (SMD = 0.72; 95% CI, 0.31 to 1.13), but no further significant differences were found on the other side effects measured.

Table 66: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with an additional (high) dose of paliperidone versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	SINGH2011	K = 1; N = 98	−0.32 [−0.72, 0.08]	N/A	Very low[1,2,3]	Appendix 14c (ii) (4.1)
Positive symptoms (SMD)	SINGH2011	K = 1; N = 98	−0.27 [−0.67, 0.13]	N/A	Very low[1,2,3]	Appendix 14c (ii) (4.2)
Negative symptoms (SMD)	SINGH2011	K = 1; N = 98	−0.41 [−0.80, −0.01]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (4.3)
Depression (SMD)	SINGH2011	K = 1; N = 98	−0.24 [−0.63, 0.16]	N/A	Very low[1,2,3]	Appendix 14c (ii) (4.4)
Psychosocial functioning (SMD)	SINGH2011	K = 1; N = 98	−0.28 [−0.68, 0.12]	N/A	Very low[1,2,3]	Appendix 14c (ii) (4.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours 6 to 12 mg per day paliperidone.
[1]Serious risk of bias (study reports LOCF analysis, but high dropout, each treatment group exposed to treatment for different lengths of time).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 67: Summary of findings table for side effect outcomes reported at treatment endpoint associated with a 'higher dose' antipsychotic medication versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Antipsychotic (dose)	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 146	0.58 [0.25, 0.91]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.1)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 195	0.41 [0.12, 0.69]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.1)
	SINGH2011	Paliperidone (3 to 6 mg per day)	K = 1; N = 100	0.57 [0.17, 0.97]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.1)
Metabolic: BMI (SMD)	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 195	0.33 [0.05, 0.61]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 137	0.03 [–0.30, 0.37]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.3)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 120	0.17 [–0.19, 0.53]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.3)
Metabolic: fasting total cholesterol mg per dl (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 119	0.12 [–0.24, 0.48]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.4)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 194	0.11 [–0.17, 0.39]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.4)

Continued

Table 67: (*Continued*)

Outcome or subgroup	Study ID	Antipsychotic (dose)	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 123	–0.16 [–0.51, 0.20]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.5)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 85	0.38 [–0.05, 0.81]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.5)
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 123	0.41 [0.05, 0.77]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.6)
Metabolic: fasting triglycerides	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 123	0.61 [0.25, 0.98]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.7)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 85	0.11 [–0.32, 0.53]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.7)
Cardio: QT interval (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 129	0.37 [0.03, 0.72]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.8)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 198	0.21 [–0.08, 0.49]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.8)
Cardio: QT interval (RR) (incidence of prolonged QT)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	3.04 [0.13, 73.44]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.9)
	SINGH2011	Paliperidone (3 to 6 mg per day)	K = 1; N = 99	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.9)

Cardio: systolic BP (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 147	0.13 [–0.19, 0.46]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.10)
Cardio: diastolic BP (SMD)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 147	0.25 [–0.07, 0.58]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.11)
Cardio: tachycardia (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	13.17 [0.76, 229.73]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.12)
	HAAS2009B	Risperidone (4 to 6 mg per day)	K = 1; N = 105	0.71 [0.12, 4.05]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.12)
	SINGH2011	Paliperidone (3 to 6 mg per day)	K = 1; N = 99	7.43 [0.39, 140.15]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.12)
Cardio: standing pulse	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 147	0.31 [–0.02, 0.63]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.13)
Hormonal: prolactin	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 123	0.37 [0.02, 0.73]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.14)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 188	–0.26 [–0.55, 0.03]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.14)
	HAAS2009B	Risperidone (4 to 6 mg per day)	K = 1; N = 105	1.38 [0.95, 1.81]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.14)
	SINGH2011	Paliperidone (3 to 6 mg per day)	K = 1; N = 83	0.09 [–0.34, 0.52]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.14)
Hormonal: insulin	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 119	0.12 [–0.24, 0.48]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.15)
Neurological: EPS (RR)	POOL1976	Haloperidol (11.9 mg per day)	K = 1; N = 59	17.28 [2.50, 119.55]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.16)
Neurological: AIMS	HAAS2009B	Risperidone (4 to 6 mg per day)	K = 1; N = 105	0.35 [–0.03, 0.74]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.17)

Continued

Table 67: (*Continued*)

Outcome or subgroup	Study ID	Antipsychotic (dose)	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Neurological: SAS	HAAS2009B	Risperidone (4 to 6 mg per day)	K = 1; N = 105	0.45 [0.06, 0.84]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.18)
Neurological: parkinsonism (RR)	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 200	4.43 [2.05, 9.58]**	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.19)
Neurological: tremor (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	1.52 [0.26, 8.84]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.20)
Neurological: akathisia (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	1.52 [0.26, 8.84]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.21)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 200	2.00 [0.78, 5.12]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.21)
Neurological: dystonia (RR)	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 200	5.00 [0.24, 102.85]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.22)
Neurological: dyskinesia (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.23)
Neurological: extrapyramidal disorder (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	3.04 [0.13, 73.44]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.24)

Mortality (RR)	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 200	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.25)
	HAAS2009B	Risperidone (4 to 6 mg per day)	K = 1; N = 105	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.25)
Leaving the study early for any reason (RR)	AstraZenecaD1441C00112	Quetiapine (400 mg per day)	K = 1; N = 149	0.47 [0.27, 0.84]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.26)
	FINDLING2008A	Aripiprazole (30 mg per day)	K = 1; N = 202	1.76 [0.86, 3.63]	N/A	Very low[1,2,3]	Appendix 14c (ii) (5.26)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours 'higher dose'.
**Favours placebo.
[1]Serious risk of bias (including unclear sequence generation and/or allocation concealment, unclear rate blinding procedures, participants excluded if they had a previous non-response to study treatment, treatment exposure [time] differs between groups, patients who failed to complete 4 weeks of daily medication because of voluntary withdrawal or for administrative reasons were not included in the analyses for efficacy ratings and were replaced by new patients, LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 68: Summary of findings table for side effect outcomes reported at treatment endpoint associated with an additional (high) dose of paliperidone versus placebo in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight (kg) (SMD)	SINGH2011	K = 1; N = 98	0.72 [0.31, 1.13]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (6.1)
Cardio: QT interval	SINGH2011	K = 1; N = 98	1.00 [0.00, 0.00]	N/A	Very low[1,2,3]	Appendix 14c (ii) (6.2)
Cardio: tachycardia (RR)	SINGH2011	K = 1; N = 98	9.75 [0.54, 176.36]	N/A	Very low[1,2,3]	Appendix 14c (ii) (6.3)
Hormonal: prolactin	SINGH2011	K = 1; N = 83	−0.10 [−0.53, 0.33]	N/A	Very low[1,2,3]	Appendix 14c (ii) (6.4)

Note.[a] The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours placebo.
[1]Serious risk of bias (study reports LOCF analysis, but high dropout and each treatment group exposed to treatment for different lengths of time).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.3.5 Clinical evidence for antipsychotic medications in head-to-head trials

Studies considered

Five RCTs (N = 242) providing relevant clinical evidence for antipsychotic medication in head-to-head trials in the treatment of the acute episode were identified (JENSEN2008, MOZES2006, SIKICH2004, XIONG2004/KENNEDY2012, YAO2003/KENNEDY2012) (see Table 69 for a summary of study characteristics). All studies were conducted in children and young people experiencing an acute episode of psychosis and schizophrenia who were aged 18 years and younger. MOZES2006, SIKICH2004, XIONG2004/ KENNEDY2012 and YAO2003/ KENNEDY2012 reported at least one outcome in sufficient detail to allow for extraction and analysis. The number of dropouts and unclear method of analysis reported by JENSEN2008 meant that it was not possible to include the risperidone arm of this three-arm trial, however it was possible to extract and analyse data for the olanzapine and quetiapine arms. SIKICH2004 also conducted a three-arm trial. There were therefore a total of five comparisons: two studies comparing risperidone with olanzapine (MOZES2006; SIKICH2004); two studies comparing risperidone with haloperidol (SIKICH2004, YAO2003/KENNEDY2012); one study comparing risperidone with chlorpromazine (XIONG2004/KENNEDY2012); one study comparing olanzapine with quetiapine (JENSEN2008); and one study comparing olanzapine with haloperidol (SIKICH2004).

Clinical evidence for risperidone versus olanzapine for treatment of the acute episode

Two studies (MOZES2006, SIKICH2004) compared risperidone and olanzapine in children and young people with psychosis and schizophrenia. The median of the mean ages across studies is 12.9 years.

Efficacy

No significant differences between treatment groups at treatment endpoint were found for any efficacy outcome measured. Evidence from each reported outcome and overall quality of evidence are presented in Table 70; the full evidence profiles can be found in Appendix 17c.

Side effects

Significantly fewer participants treated with olanzapine 11.1 mg per day left the study early for any reason compared with placebo-treated participants (RR = 3.90; 95% CI, 1.25 to 12.17), however the sample size is extremely small and CIs are wide. No further significant differences were found between treatment groups for side effect outcomes assessed; however both treatment groups gained weight, with the direction of the effect favouring risperidone over olanzapine.

Evidence from each reported outcome and overall quality of evidence are presented in Table 71; the full evidence profiles can be found in Appendix 17c.

Table 69: Study information table for trials comparing antipsychotic medication in head-to-head trials for the treatment of an acute episode in children and young people with psychosis and schizophrenia

	Risperidone versus olanzapine	Risperidone versus haloperidol	Risperidone versus chlorpromazine	Olanzapine versus quetiapine	Olanzapine versus haloperidol
Total no. of studies (N)	K = 2 (N for comparison = 61; N for the included studies = 76)	K = 2 (N for the comparison = 77; N for the included study = 93)	K = 1 (N = 60)	K = 1 (N for the comparison = 20; N for the included study = 30)	K = 1 (N for the comparison 31; N for the comparison = 51)
Study ID	(1) MOZES2006[2] (2) SIKICH2004[2]	(1) SIKICH2004[2] (2) YAO2003/ KENNEDY2012[2]	XIONG2004/ KENNEDY2012[2]	JENSEN2008[2]	SIKICH2004[2]
Diagnosis[1]	(1) Schizophrenic disorder (2) Psychosis, including schizophrenia spectrum disorders and affective disorders	(1) Psychosis, including schizophrenia spectrum disorders and affective disorders (2) Childhood-onset schizophrenia	Childhood-onset schizophrenia	Schizophrenic disorder	Psychosis, including schizophrenia spectrum disorders and affective disorders
Prior antipsychotic use (% naïve prior to intervention)[1]	(1) Not reported (2) 24.0	(1) 24.0 (2) Not reported	Not reported	76.7	24.0
Mean age (range)[1]	(1) 11.1 (9.0 to 14.0) (2) 14.8 (not reported)	(1) 14.8 (not reported) (2) 11 (not reported)	13.0 (7.0 to 16.0)	15.2 (10.0 to 18.0)	14.8 (not reported)

Sex (% male)[1]	(1) 40.0 (2) 60.0	(1) 60 (2) 56	57	66.7	60.0
Ethnicity (% white)[1]	(1) Not reported (2) 60.0	(1) 60 (2) Not reported	Not reported	60.0	60.0
Mean (range) medication dose (mg per day)[1]	(1) Risperidone: 1.62 (0.25 to 4.5); olanzapine: 8.18 (2.5 to 20) (2) Risperidone: 4.0 (0.5 to 6.0); olanzapine: 12.3 (2.5 to 20)	(1) Risperidone: 4.0 (0.5 to 6.0); haloperidol: 5.0 (1 to 8) (2) Risperidone: not reported (0.25 to 3.0); haloperidol: not reported (0.5 to 12)	Risperidone: not reported (0.5 to 5.0); chlorpromazine: not reported (50.0 to 400.0)	Olanzapine: 14.0 (5 to 20); quetiapine: 611.0 (100 to 800)	Olanzapine: 12.3 (2.5 to 20); haloperidol: 5.0 (1 to 8)
Treatment length (weeks)[1]	(1) 12 (2) 8	(1) 8 (2) 6	8	12	8
Length of follow-up (weeks)[1]	(1) 12 (2) 8	(1) 8 (2) 6	8	12	8
Setting[1]	(1) Inpatient (2) Inpatient and outpatient	(1)–(2) Inpatient and outpatient	Inpatient	Inpatient and outpatient	Inpatient and outpatient
Country[1]	(1) Israel (2) US	(1) US (2) China	China	US	US
Funding[1]	(1) Not reported (2) Eli Lily, Janssen and non-industry sponsors	(1) Eli Lily, Janssen and non-industry sponsors (2) Not reported	Not reported	AstraZeneca	Eli Lily, Janssen and non-industry sponsors

Note.[1]Extractable outcomes.
[2]Data are reported for the population characteristics of each study, not the population characteristics of each treatment group.

Table 70: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone versus olanzapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	MOZES2006 SIKICH2004	K = 2; N = 60	0.38 [–0.14, 0.89]	(P = 0.33); I^2 = 0%	Very low[1,2,3]	Appendix 14 c (ii) (7.1)
Positive symptoms (SMD)	MOZES2006 SIKICH2004	K = 2; N = 60	0.38 [–0.13, 0.89]	(P = 0.63); I^2 = 0%	Very low[1,2,3]	Appendix 14 c (ii) (7.2)
Negative symptoms (SMD)	MOZES2006 SIKICH2004	K = 2; N = 60	0.22 [–0.51, 0.96]	(P = 0.16); I^2 = 50%	Very low[1,2,3,4]	Appendix 14 c (ii) (7.3)
Global state (severity) (SMD)	SIKICH2004	K = 1; N = 35	0.15 [–0.52, 0.82]	N/A	Very low[1,2,3]	Appendix 14 c (ii) (7.4)
Psychosocial functioning (SMD)	MOZES2006	K = 1; N = 15	0.25 [–0.54, 1.04]	N/A	Very low[1,2,3]	Appendix 14 c (ii) (7.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (unclear sequence generation and allocation concealment, open-label trial, trial registration cannot be found, LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]$I^2 \geq 50\%$, $p < .05$.

Table 71: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone versus olanzapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	MOZES2006 SIKICH2004	K = 2; N = 60	–0.36 [–0.87, 0.16]	(P = 0.81); I^2 = 0%	Very low[1,2,3]	Appendix 14c (ii) (8.1)
Metabolic: BMI (SMD)	SIKICH2004	K = 1; N = 35	–0.09 [–0.75, 0.58]	N/A	Very low[1,2,3]	Appendix 14c (ii) (8.2)
Cardio: QT interval (SMD)	SIKICH2004	K = 1; N = 35	0.00 [–0.67, 0.67]	N/A	Very low[1,2,3]	Appendix 14c (ii) (8.3)
Neurological: SAS (SMD)	SIKICH2004	K = 1; N = 35	0.09 [–0.58, 0.75]	N/A	Very low[1,2,3]	Appendix 14c (ii) (8.4)
Neurological: EPS (SAS) (RR)	MOZES2006	K = 1; N = 25	0.95 [0.50, 1.80]	N/A	Very low[1,2,3]	Appendix 14c (ii) (8.5)
Neurological: BARS	MOZES2006	K = 1; N = 25	3.25 [0.39, 27.15]	N/A	Very low[1,2,3]	Appendix 14c (ii) (8.6)
Neurological: tremor (RR)	MOZES2006	K = 1; N = 15	1.38 [0.71, 2.71]	N/A	Very low[1,2,3]	Appendix 14c (ii) (8.7)
Leaving the study early for any reason (RR)	MOZES2006 SIKICH2004	K = 2; N = 61	3.90 [1.25, 12.17]*	(P = 0.95); I^2 = 0%	Very low[1,2,3]	Appendix 14c (ii) (8.8)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours olanzapine.
[1]Serious risk of bias (unclear sequence generation and allocation concealment, open-label trial, trial registration cannot be found, LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Pharmacological interventions

Clinical evidence for risperidone versus haloperidol for treatment of the acute episode
Two studies (SIKICH2004, YAO2003/KENNEDY2012) (N = 77) compared risperidone and haloperidol in children and young people with psychosis and schizophrenia with a median of the mean ages of 12.9 years.

Efficacy
No significant differences between risperidone and haloperidol treatment groups were found at treatment endpoint for efficacy outcomes. Evidence from each reported outcome and overall quality of evidence are presented in Table 72; the full evidence profiles can be found in Appendix 17c.

Side effects
YAO2003/KENNEDY2012 found a significant risk reduction of experiencing EPS favouring risperidone over haloperidol at treatment endpoint (RR = 0.12; 95% CI, 0.04, 0.37) for side effect outcomes, however the sample size in this trial was very small. No other significant differences between risperidone and haloperidol were found. Evidence from each reported outcome and overall quality of evidence are presented in Table 73; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for risperidone versus chlorpromazine for the treatment of the acute episode
One study (XIONG2004/KENNEDY2012) (N = 60) compared risperidone and chlorpromazine in children with psychosis and schizophrenia with a mean age of 13 years.

Efficacy
No significant differences between risperidone and chlorpromazine groups were found at treatment endpoint for efficacy outcomes. Evidence from each reported outcome and overall quality of evidence are presented in Table 74; the full evidence profiles can be found in Appendix 17c.

Side effects
No significant differences between risperidone and chlorpromazine groups were found at treatment endpoint for side effect outcomes. Evidence from each reported outcome and overall quality of evidence are presented in Table 75; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for olanzapine versus quetiapine for treatment of the acute episode
One study (JENSEN2008) (N = 20) compared olanzapine and quetiapine in children and young people with psychosis and schizophrenia, with a mean age of 15.2 years.

Efficacy
JENSEN2008 measured response using the PANSS. No significant difference between the olanzapine and quetiapine treatment groups at treatment endpoint (12 weeks) was found. Evidence from each reported outcome and overall quality of evidence are presented in Table 76; the full evidence profiles can be found in Appendix 17c.

Table 72: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	SIKICH2004 YAO2003/ KENNEDY2012	K = 2; N = 76	−0.33 [−0.79, 0.12]	P = 0.90; I^2 = 0%	Very low[1,2,3,4]	Appendix 14c (ii) (9.1)
Positive symptoms (SMD)	SIKICH2004	K = 1; N = 34	−0.25 [−0.93, 0.43]	N/A	Very low[1,2,3]	Appendix 14c (ii) (9.2)
Negative symptoms (SMD)	SIKICH2004	K = 1; N = 34	−0.11 [−0.79, 0.57]	N/A	Very low[1,2,3]	Appendix 14c (ii) (9.3)
Global state (severity) (SMD)	SIKICH2004	K = 1; N = 34	−0.54 [−1.23, 0.15]	N/A	Very low[1,2,3]	Appendix 14c (ii) (9.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found, LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]Sequence generation, analysis and selective outcome reporting not reported by YAO2003/ KENNEDY2012.

Table 73: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	SIKICH2004	K = 1; N = 34	−0.40 [−1.09, 0.28]	N/A	Very low[1,2,3]	Appendix 14c (ii) (10.1)
Metabolic: BMI (SMD)	SIKICH2004	K = 1; N = 34	−0.55 [−1.24, 0.14]	N/A	Very low[1,2,3]	Appendix 14c (ii) (10.2)
Cardio: QT interval (SMD)	SIKICH2004	K = 1; N = 34	0.00 [−0.68, 0.68]	N/A	Very low[1,2,3]	Appendix 14c (ii) (10.3)
Neurological: EPS (RR)	YAO2003/ KENNEDY2012	K = 1; N = 42	0.12 [0.04, 0.37]*	N/A	Low[1,3,4]	Appendix 14c (ii) (10.4)
Leaving the study early for any reason (RR)	SIKICH2004	K = 1; N = 34	1.07 [0.53, 2.15]	N/A	Very low[1,2,3]	Appendix 14c (ii) (10.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours risperidone.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]Sequence generation, analysis and selective outcome reporting not reported by YAO2003/KENNEDY2012.

Table 74: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone versus chlorpromazine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	XIONG2004/ KENNEDY 2012	K = 1; N = 60	–0.29 [–0.80, 0.22]	N/A	Low[1,2,3,4]	Appendix 14c (ii) (11.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]Sequence generation, analysis and selective outcome reporting not reported by XIONG2004/KENNEDY2012.

Table 75: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone versus chlorpromazine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Tremor (RR)	XIONG2004/ KENNEDY 2012	K = 1; N = 60	0.50 [0.05, 5.22]	N/A	Low[1,2,3,4]	Appendix 14c (ii) (12.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]Sequence generation, analysis and selective outcome reporting not reported by XIONG2004/KENNEDY2012.

Table 76: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with olanzapine versus quetiapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Response (RR)	JENSEN2008	K = 1; N = 20	0.60 [0.19, 1.86]	N/A	Very low[1,2,3]	Appendix 14c (ii) (13.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, open-label trial study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Side effects

No significant differences between the olanzapine and quetiapine treatment groups were found on side effects assessed at treatment endpoint. Evidence from each reported outcome and overall quality of evidence are presented in Table 77; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for olanzapine versus haloperidol for treatment of the acute episode

One study (SIKICH2004) (N = 20) compared olanzapine and haloperidol, as part of a three-arm trial (also including risperidone) in children and young people with psychosis and schizophrenia with a mean age of 14.8 years.

Efficacy

No significant differences between the olanzapine and haloperidol treatment groups on efficacy outcomes were found at treatment endpoint. Evidence from each reported outcome and overall quality of evidence are presented in Table 78; the full evidence profiles can be found in Appendix 17c

Side effects

A small, significant difference, favouring olanzapine over haloperidol was found for SAS scores (SMD = −0.73; 95% CI, −1.46 to −0.00). No further significant differences were found on any other side effect outcome assessed. Evidence from each reported outcome and overall quality of evidence are presented in Table 79; the full evidence profiles can be found in Appendix 17c.

Table 77: Summary of findings table for side effect outcomes reported at treatment endpoint associated with olanzapine versus quetiapine in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (RR)	JENSEN2008	K = 1; N = 20	1.20 [0.54, 2.67]	N/A	Very low[1,2,3]	Appendix 14c (ii) (14.1)
Metabolic: BMI (SMD)	JENSEN2008	K = 1; N = 20	0.51 [−0.38, 1.40]	N/A	Very low[1,2,3]	Appendix 14c (ii) (14.2)
Neurological: SAS	JENSEN2008	K = 1; N = 20	−0.43 [−1.32, 0.46]	N/A	Very low[1,2,3]	Appendix 14c (ii) (14.3)
Neurological: akathisia (RR)	JENSEN2008	K = 1; N = 20	2.00 [0.21, 18.69]	N/A	Very low[1,2,3]	Appendix 14c (ii) (14.4)
Leaving the study early for any reason (RR)	JENSEN2008	K = 1; N = 20	1.00 [0.34, 2.93]	N/A	Very low[1,2,3]	Appendix 14c (ii) (14.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, open-label trial, study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 78: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with olanzapine versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	SIKICH2004	K = 1; N = 31	−0.68 [−1.41, 0.05]	N/A	Very low[1,2,3]	Appendix 14c (ii) (15.1)
Positive symptoms (SMD)	SIKICH2004	K = 1; N = 31	−0.58 [−1.30, 0.14]	N/A	Very low[1,2,3]	Appendix 14c (ii) (15.2)
Negative symptoms (SMD)	SIKICH2004	K = 1; N = 31	0.00 [−0.70, 0.70]	N/A	Very low[1,2,3]	Appendix 14c (ii) (15.3)
Global state (severity) (SMD)	SIKICH2004	K = 1; N = 31	−0.70 [−1.43, 0.03]	N/A	Very low[1,2,3]	Appendix 14c (ii) (15.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found, study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 79: Summary of findings table for side effect outcomes reported at treatment endpoint associated with olanzapine versus haloperidol in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	SIKICH2004	K = 1; N = 31	–0.08 [–0.79, 0.62]	N/A	Very low[1,2,3]	Appendix 14c (ii) (16.1)
Metabolic: BMI (SMD)	SIKICH2004	K = 1; N = 31	–0.21 [–0.92, 0.50]	N/A	Very low[1,2,3]	Appendix 14c (ii) (16.2)
Cardio: QT interval (SMD)	SIKICH2004	K = 1; N = 31	0.00 [–0.70, 0.70]	N/A	Very low[1,2,3]	Appendix 14c (ii) (16.3)
Neurological: SAS (SMD)	SIKICH2004	K = 1; N = 31	–0.73 [–1.46, –0.00]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (16.4)
Leaving the study early for any reason (RR)	SIKICH2004	K = 1; N = 31	0.27 [0.07, 1.09]	N/A	Very low[1,2,3]	Appendix 14c (ii) (16.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours olanzapine.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding procedures, trial registration could not be found, study reports LOCF analysis but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.3.6 Clinical evidence for antipsychotic medications administered at different doses

Studies considered

Five RCTs (N = 861) providing relevant clinical evidence for antipsychotic medication administered at different doses for the treatment of the acute episode were identified (AstraZenecaD1441C00112, FINDLING2008A, HAAS2009, HAAS2009B, SINGH2011) (see Table 80 for a summary of study characteristics). All studies were conducted in children and young people experiencing an acute episode of psychosis and schizophrenia aged 18 years and younger and reported at least one outcome in sufficient detail to allow for extraction and analysis.

There was a total of seven comparisons: quetiapine 400.0 mg per day versus quetiapine 800.0 mg per day (AstraZenecaD1441C00112); aripiprazole 10.0 mg per day versus aripiprazole 30.0 mg per day (FINDLING2008A); risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day (HAAS2009B); risperidone 0.15 to 0.6 mg per day versus risperidone 1.5 to 6.0 mg per day (HAAS2009); paliperidone 1.5 mg per day versus paliperidone 3 to 6 mg per day (SINGH2011); paliperidone 1.5 mg per day versus paliperidone 6 to 12 mg per day (SINGH2011); and paliperidone 3 to 6 mg per day versus paliperidone 6 to 12 mg per day (SINGH2011).

Clinical evidence for quetiapine 400 mg per day versus quetiapine 800 mg per day for treatment of the acute episode

One trial (AstraZenecaD1441C00112) (N = 147) assessing quetiapine at different doses (400.0 mg per day versus 800.0 mg per day) in children and young people with schizophrenia with a mean age of 15.4 years (range 13 to 17) was identified.

Efficacy

No significant differences in efficacy outcomes were found at treatment endpoint between the two different doses of quetiapine administered. Evidence from each reported outcome and overall quality of evidence are presented in Table 81; the full evidence profiles can be found in Appendix 17c.

Side effects

No significant differences in side effects were found at treatment endpoint between the two different doses of quetiapine administered. Evidence from each reported outcome and overall quality of evidence are presented in Table 82; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for aripiprazole 10 mg per day versus aripiprazole 30 mg per day for treatment of the acute episode

One trial (FINDLING2008A) (N = 202) assessed aripiprazole at different doses (10 mg per day versus 30 mg per day) in children and young people with schizophrenia with a mean age of 15.5 years (range not reported).

Table 80: Study information table for trials comparing an antipsychotic medication administered at different doses in the treatment of an acute episode in children and young people with psychosis and schizophrenia

Medication dose (mg per day)	Quetiapine 400 mg per day versus 800 mg per day	Aripiprazole 10 mg per day versus 30 mg per day	Risperidone 1 to 3 mg per day versus 4 to 6 mg per day	Risperidone 0.15 to 0.6 mg per day versus 1.5 to 6 mg per day	Paliperidone 1.5 mg per day versus 3 to 6 mg per day versus 6 to 12 mg per day
Total no. of studies (N)	K = 1 (N = 147)	K = 1 (N = 202)	K = 1 (N = 106)	K = 1 (N = 257)	K = 1 (N = 149)
Study ID	AstraZeneca D1441C00112	FINDLING2008A	HAAS2009B	HAAS2009	SINGH2011
Diagnosis	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia
Prior antipsychotic use (% naïve prior to intervention)	Not reported	51.7	Not reported	Not reported	36% atypical, 60% typical
Mean age (range)	15.4 (13.0 to 17.0)	15.5 (not reported)	15.6 (13.0 to 17.0)	15.6 (13.0 to 17.0)	15.4 (not reported)
Sex (% male)	59	57	64	56	59
Ethnicity (% white)	61	37	53	85	68
Treatment length (weeks)	6	6	6	8	6
Length of follow-up (weeks)	6	6	6	8	6
Setting	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient	Inpatient and outpatient
Country	43 international sites, including the US and Asia	US, Europe, South America, Asia, the Caribbean, South Africa	India, Russia, Ukraine, US	Belgium, Bulgaria, Czech Republic, Estonia, Germany, Poland, Romania, US	Russia, India, Ukraine, US, Romania
Funding	AstraZeneca	Otsuka Pharmaceuticals	Johnson & Johnson	Johnson & Johnson	Johnson & Johnson

Table 81: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with quetiapine 400 mg per day versus quetiapine 800 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	AstraZenecaD1441C00112	K = 1; N = 109	0.07 [−0.31, 0.44]	N/A	Very low[1,2]	Appendix 14c (ii) (17.1)
Positive symptoms (SMD)	AstraZenecaD1441C00112	K = 1; N = 109	0.16 [−0.22, 0.53]	N/A	Very low[1,2]	Appendix 14c (ii) (17.2)
Negative symptoms (SMD)	AstraZenecaD1441C00112	K = 1; N = 109	−0.03 [−0.40, 0.35]	N/A	Very low[1,2]	Appendix 14c (ii) (17.3)
Global state (severity) (SMD)	AstraZenecaD1441C00112	K = 1; N = 110	0.14 [−0.23, 0.51]	N/A	Very low[1,2]	Appendix 14c (ii) (17.4)
Depression (SMD)	AstraZenecaD1441C00112	K = 1; N = 109	0.09 [−0.29, 0.46]	N/A	Very low[1,2]	Appendix 14c (ii) (17.5)
Psychosocial functioning (SMD)	AstraZenecaD1441C00112	K = 1; N = 128	0.15 [−0.19, 0.50]	N/A	Very low[1,2]	Appendix 14c (ii) (17.6)
Response (RR)	AstraZenecaD1441C00112	K = 1; N = 110	1.06 [0.78, 1.46]	N/A	Very low[1,2]	Appendix 14c (ii) (17.7)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, unclear rater blinding; study reports LOCF analysis, but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 82: Summary of findings table for side effect outcomes reported at treatment endpoint associated with quetiapine 400 mg per day versus quetiapine 800 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	AstraZenecaD1441C00112	K = 1; N = 105	−0.05 [−0.37, 0.28]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.1)
Metabolic: fasting serum glucose level mg per dl (SMD)	AstraZenecaD1441C00112	K = 1; N = 138	0.12 [−0.21, 0.46]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.3)
Metabolic: fasting total cholesterol mg per dl	AstraZenecaD1441C00112	K = 1; N = 121	0.01 [−0.34, 0.37]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.4)
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	AstraZenecaD1441C00112	K = 1; N = 125	0.04 [−0.31, 0.39]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.5)

Continued

Table 82: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: fasting low-density lipoprotein cholesterol mg per dl (SMD)	AstraZenecaD1441C00112	K = 1; N = 122	0.17 [−0.18, 0.53]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.6)
Metabolic: fasting triglycerides	AstraZenecaD1441C00112	K = 1; N = 122	−0.10 [−0.46, 0.25]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.7)
Cardio: QT interval (SMD)	AstraZenecaD1441C00112	K = 1; N = 128	0.29 [−0.06, 0.64]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.8)
Cardio: QT interval (RR) (prolonged QT interval)	AstraZenecaD1441C00112	K = 1; N = 147	1.01 [0.06, 15.90]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.9)
Cardio: systolic BP (SMD)	AstraZenecaD1441C00112	K = 1; N = 147	0.26 [−0.07, 0.58]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.10)
Cardio: diastolic BP (SMD)	AstraZenecaD1441C00112	K = 1; N = 147	0.10 [−0.22, 0.43]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.11)

Cardio: tachycardia (RR)	AstraZenecaD1441C00112	K = 1; N = 147	0.68 [0.20, 2.30]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.12)
Cardio: standing pulse (SMD)	AstraZenecaD1441C00112	K = 1; N = 147	0.27 [−0.06, 0.59]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.13)
Hormonal: prolactin (SMD)	AstraZenecaD1441C00112	K = 1; N = 123	−0.12 [−0.48, 0.23]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.14)
Hormonal: insulin (SMD)	AstraZenecaD1441C00112	K = 1; N = 121	0.17 [−0.19, 0.52]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.16)
Neurological: akathisia (RR)	AstraZenecaD1441C00112	K = 1; N = 147	1.01 [0.21, 4.86]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.19)
Neurological: extrapyramidal disorder (RR)	AstraZenecaD1441C00112	K = 1; N = 148	1.03 [0.07, 16.12]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.20)
Leaving the study early for any reason (RR)	AstraZenecaD1441C00112	K = 1; N = 147	1.33 [0.70, 2.53]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.28)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, unclear rater blinding, study reports LOCF analysis, but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of reporting bias.

Table 83: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with aripiprazole 10 mg per day versus aripiprazole 30 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophreni

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	FINDLING2008A	K = 1; N = 198	0.13 [−0.15, 0.41]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.1)
Global state (severity) (SMD)	FINDLING2008A	K = 1; N = 196	0.10 [−0.18, 0.38]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.4)
Quality of life (SMD)	FINDLING2008A	K = 1; N = 196	0.63 [0.42, 0.84]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.8)
Psychosocial functioning (SMD)	FINDLING2008A	K = 1; N = 198	0.01 [−0.27, 0.29]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.6)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours aripiprazole 30 mg per day.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design, study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Efficacy
The only significant difference at treatment endpoint between the two doses of aripiprazole administered was on quality of life, favouring 30 mg per day over 10 mg per day (SMD = 0.63; 95% CI, 0.42 to 0.84). Evidence from each reported outcome and overall quality of evidence are presented in Table 83; the full evidence profiles can be found in Appendix 17c.

Side effects
A significant difference between the two doses of aripiprazole administered was found for parkinsonism, with a greater number of participants treated with 30 mg per day experiencing parkinsonism compared with those treated with 10 mg per day (SMD = 0.48; 95% CI, 0.28 to 0.84). No other significant differences between doses for side effect outcomes were found. Evidence from each reported outcome and overall quality of evidence are presented in Table 84; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day for treatment of the acute episode.
One trial (HAAS2009) (N = 106) assessing risperidone at different doses (1 to 3 mg per day versus 4 to 6 mg per day) in children and young people with psychosis and schizophrenia with a mean age of 15.6 years (range 13 to 17) was identified.

Efficacy
No significant differences in efficacy outcomes were found at treatment endpoint between the two different doses of risperidone administered. Evidence from each reported outcome and overall quality of evidence are presented in Table 85; the full evidence profiles can be found in Appendix 17c.

Side effects
Small, significant differences, favouring risperidone 1 to 3 mg per day over risperidone 4 to 6 mg per day were found for weight (SMD = – 0.44; 95% CI, –0.69 to –0.19), prolactin level (SMD = – 0.41; 95% CI, –0.79 to –0.02) and SAS scores (SMD = –0.39; 95% CI, –0.78 to –0.01). No other significant effects were found for side effect outcomes reported at treatment endpoint. Evidence from each reported outcome and overall quality of evidence are presented in Table 86 (on page 295); the full evidence profiles can be found in Appendix 17c.

Clinical evidence for risperidone 0.15 to 0.6 mg per day versus risperidone 1.5 to 6.0 mg per day for treatment of the acute episode
One trial (HAAS2009) (N = 257) assessing risperidone at 0.15 to 0.6 mg per day versus 1.5 to 6.0 mg per day in children and young people with schizophrenia with a mean age of 15.6 years (range 13 to 17) was identified.

Efficacy
Small significant differences, favouring risperidone 1.5 to 6.0 mg per day over risperidone 0.15 to 0.6 mg per day were found on all efficacy outcomes measured at treatment endpoint, including total symptoms (SMD = 0.34; 95% CI, 0.09 to 0.59), positive

Table 84: Summary of findings table for side effect outcomes reported at treatment endpoint associated with aripiprazole 10 mg per day versus aripiprazole 30 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	FINDLING2008A	K = 1; N = 196	−0.09 [−0.37, 0.19]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.1)
Metabolic: BMI (SMD)	FINDLING2008A	K = 1; N = 196	0.00 [−0.28, 0.28]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	FINDLING2008A	K = 1; N = 117	0.26 [−0.10, 0.63]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.3)
Metabolic: fasting total cholesterol mg per dl (SMD)	FINDLING2008A	K = 1; N = 193	−0.09 [−0.38, 0.19]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.4)
Metabolic: fasting high-density lipoprotein cholesterol mg per dl (SMD)	FINDLING2008A	K = 1; N = 107	0.09 [−0.29, 0.48]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.5)
Metabolic: fasting triglycerides	FINDLING2008A	K = 1; N = 87	−0.08 [−0.50, 0.35]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.7)

Cardio: QT interval (SMD)	FINDLING2008A	K = 1; N = 196	0.28 [–0.00, 0.56]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.8)
Hormonal: prolactin	FINDLING2008A	K = 1; N = 190	0.13 [–0.16, 0.41]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.14)
Neurological: parkinsonism (RR)	FINDLING2008A	K = 1; N = 200	0.48 [0.28, 0.84]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.23)
Neurological: akathisia (RR)	FINDLING2008A	K = 1; N = 200	0.50 [0.20, 1.28]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.19)
Neurological: dystonia (RR)	FINDLING2008A	K = 1; N = 200	2.00 [0.37, 10.67]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.22)
Mortality (RR)	FINDLING2008A	K = 1; N = 200	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.27)
Leaving the study early for any reason (RR)	FINDLING2008A	K = 1; N = 202	0.91 [0.49, 1.68]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.28)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours aripiprazole 10 mg per day.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design; study reports LOCF analysis, but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 85: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Positive symptoms (SMD)	HAAS2009B	K = 1; N = 104	0.03 [–0.35, 0.42]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.2)
Negative symptoms (SMD)	HAAS2009B	K = 1; N = 104	–0.09 [–0.47, 0.30]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.3)
Psychosocial functioning (SMD)	HAAS2009B	K = 1; N = 99	–0.12 [–0.51, 0.28]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.6)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design, study reports LOCF but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

symptoms (SMD = 0.42; 95% CI, 0.17 to 0.67), negative symptoms (SMD = 0.42; 95% CI, 0.17 to 0.67) and global state (SMD = 0.41; 95% CI, 0.16 to 0.66). Evidence from each reported outcome and overall quality of evidence are presented in Table 87; the full evidence profiles can be found in Appendix 17c.

Side effects

Small significant differences were found at treatment endpoint, favouring risperidone 0.15 to 0.6 mg per day over risperidone 1.5 to 6.0 mg per day on elevated prolactin level (RR = 0.74; 95% CI, 0.58 to 0.96), number of participants experiencing EPS (RR = 0.30; 95% CI, 0.17 to 0.53), dystonia (RR = 0.33; 95% CI, 0.15 to 0.71) and tremor (RR = 0.29; 95% CI, 0.10 to 0.87). Evidence from each reported outcome and overall quality of evidence are presented in Table 88; the full evidence profiles can be found in Appendix 17c.

Clinical evidence for paliperidone 1.5 mg per day versus paliperidone 3 to 6 mg per day versus paliperidone 6 to 12 mg per day for treatment of the acute episode

One trial (SINGH2011) (N = 149) assessing paliperidone at three different doses (1.5 mg per day versus 3 to 6 mg per day versus 6 to 12 mg per day) in children and young people with schizophrenia was identified. The mean age of the sample was 15.4 years (range not reported).

Table 86: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone 1 to 3 mg per day versus risperidone 4 to 6 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	HAAS2009B	K = 1; N = 157	−0.44 [−0.69, −0.19]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.1)
Cardio: tachycardia (RR)	HAAS2009B	K = 1; N = 106	1.39 [0.24, 7.99]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.12)
Hormonal: prolactin (SMD)	HAAS2009B	K = 1; N = 106	−0.41 [−0.79, −0.02]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.14)
Neurological: AIMS (SMD)	HAAS2009B	K = 1; N = 109	0.23 [−0.15, 0.61]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.17)
Neurological: SAS (SMD)	HAAS2009B	K = 1; N = 106	−0.39 [−0.78, −0.01]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.18)
Neurological: dystonia (RR)	HAAS2009B	K = 1; N = 257	0.33 [0.15, 0.71]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.22)
Neurological: extrapyramidal disorder (RR)	HAAS2009B	K = 1; N = 106	0.58 [0.20, 1.66]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.20)

Continued

Table 86: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Neurological: EPS (RR)	HAAS2009B	K = 1; N = 106	0.83 [0.50, 1.39]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.21)
Mortality (RR)	HAAS2009B	K = 1; N = 106	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.27)
Leaving the study early for any reason (RR)	HAAS2009B	K = 1; N = 106	1.32 [0.55, 3.22]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.28)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 1 to 3 mg per day.
[1]Serious risk of bias (including unclear allocation concealment, unclear rater blinding in the double-blind design, study reports LOCF but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 87: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with risperidone 0.15 to 0.6 mg per day versus risperidone 1.5 to 6.0 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Studies/ number of participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	HAAS2009	K = 1; N = 256	0.34 [0.09, 0.59]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.1)
Positive symptoms (SMD)	HAAS2009	K = 1; N = 256	0.42 [0.17, 0.67]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.2)
Negative symptoms (SMD)	HAAS2009	K = 1; N = 256	0.42 [0.17, 0.67]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.3)
Global state (severity) (SMD)	HAAS2009	K = 1; N = 256	0.41 [0.16, 0.66]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours 1.5 to 6.0 mg per day.
[1]Serious risk of bias (including unclear allocation concealment, unclear whether rater blinding in the double-blind design, study reports LOCF but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 88: Summary of findings table for side effect outcomes reported at treatment endpoint associated with risperidone 0.15 to 0.6 mg per day versus risperidone 1.5 to 6.0 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Hormonal: prolactin level (RR)	HAAS2009	K = 1; N = 257	0.74 [0.58, 0.96]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.15)
Neurological: EPS (RR)	HAAS2009	K = 1; N = 157	0.30 [0.17, 0.53]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.21)
Neurological: symptoms of parkinsonism (RR)	HAAS2009	K = 1; N = 157	0.09 [0.00, 1.54]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.24)
Neurological: tremor (RR)	HAAS2009	K = 1; N = 157	0.29 [0.10, 0.87]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.26)
Neurological: dystonia (RR)	HAAS2009	K = 1; N = 157	0.33 [0.15, 0.71]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.22)
Neurological: dyskinesia (RR)	HAAS2009	K = 1; N = 157	0.27 [0.06, 1.28]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.25)
Leaving the study early for any reason (RR)	HAAS2009	K = 1; N = 157	1.35 [0.95, 1.93]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.28)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 0.15 to 0.6 mg per day.
[1]Serious risk of bias (including unclear allocation concealment, unclear whether rater blinding in the double-blind design, study reports LOCF but high dropout).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Efficacy

Small, significant differences were found at treatment endpoint favouring paliperidone 3 to 6 mg per day versus 1.5 mg per day on total symptoms (SMD = 0.48; 95% CI, 0.09 to 0.88), positive symptoms (SMD = 0.48; 95% CI, 0.08 and 0.87) and psychosocial functioning (SMD = 0.76; 95% CI, 0.36 to 1.16), but no other differences between the three different doses of paliperidone were found. Evidence from each reported outcome and overall quality of evidence are presented in Table 89; the full evidence profiles can be found in Appendix 17c.

Side effects

Small to moderate, significant differences were found at treatment endpoint for weight, favouring paliperidone 1.5 mg per day over 3 to 6 mg per day (SMD = −0.43; 95% CI, −0.83 to −0.04) and 1.5 mg per day over 6 to 12 mg per day (SMD = −0.59; 95% CI, −0.99 to −0.19); and for prolactin level favouring 1.5 mg per day over 3 to 6 mg per day (SMD = −0.62; 95% CI, −1.03 to −0.20) and 1.5 mg per day over 6 to 12 mg per day (SMD = −0.53; 95% CI, −0.94 to −0.11). Evidence from each reported outcome and overall quality of evidence are presented in Table 90; the full evidence profiles can be found in Appendix 17c.

7.3.7 Clinical evidence summary for treatment of the acute episode – evidence for children and young people

In 13 RCTs, with a total of 1,524 participants experiencing an acute episode of psychosis and schizophrenia, the evidence suggests there are small differences in efficacy favouring antipsychotic medication over placebo, including symptoms, global state and psychosocial functioning. No evidence was found for differences in efficacy between antipsychotics and only minimal differences in efficacy between different doses of the same antipsychotic. Placebo was consistently favoured over an antipsychotic on weight gain and BMI, with olanzapine resulting in the greatest weight gain and BMI increase. Significant differences favouring placebo compared with an antipsychotic were also observed on: other metabolic parameters such as fasting serum glucose level, cholesterol and triglycerides; cardiac function, such as blood pressure and QT interval; hormone level (prolactin); and EPS, such as parkinsonism. Of the few differences that existed between different doses of antipsychotic medication regarding side effects, all favoured a 'lower dose' over a 'higher dose'. However, the results of included trials need to be considered in the context of the quality of the evidence. All evidence for antipsychotics for treatment of the acute episode in children and young people with psychosis and schizophrenia was rated as low to very low due to very small sample sizes, a high risk of publication bias and low internal validity of included trials. Therefore no robust conclusions can be drawn regarding antipsychotic medication in the treatment of the acute episode in children and young people with psychosis and schizophrenia. Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?') as well as the paucity and low quality of the evidence identified in children and young people, the GDG

Table 89: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with paliperidone 1.5 mg per day versus paliperidone 3 to 6 mg per day versus paliperidone 6 to 12 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Dose comparison	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	0.48 [0.09, 0.88]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.1)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	−0.23 [−0.63, 0.17]	N/A	Very low[1,2,3]	Appendix 14c (ii) (20.1)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	0.25 [−0.15, 0.64]	N/A	Very low[1,2,3]	Appendix 14c (ii) (19.1)
Positive symptoms (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	0.48 [0.08, 0.87]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.2)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	−0.19 [−0.59, 0.22]	N/A	Very low[1,2,3]	Appendix 14c (ii) (20.2)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	0.31 [−0.08, 0.71]	N/A	Very low[1,2,3]	Appendix 14c (ii) (19.2)
Negative symptoms (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	0.31 [−0.08, 0.71]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.3)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	−0.27 [−0.67, 0.13]	N/A	Very low[1,2,3]	Appendix 14c (ii) (20.3)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	0.00 [−0.39, 0.39]	N/A	Very low[1,2,3]	Appendix 14c (ii) (19.3)

Depression (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	0.18 [−0.21, 0.57]	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.5)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	−0.03 [−0.43, 0.37]	N/A	Very low[1,2,3]	Appendix 14c (ii) (20.4)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	0.15 [−0.25, 0.54]	N/A	Very low[1,2,3]	Appendix 14c (ii) (19.4)
Psychosocial functioning (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	0.76 [0.36, 1.16]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (17.6)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	−0.38 [−0.79, 0.02]	N/A	Very low[1,2,3]	Appendix 14c (ii) (20.5)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	0.38 [−0.01, 0.78]	N/A	Very low[1,2,3]	Appendix 14c (ii) (19.5)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 3–6 mg per day.
[1]Serious risk of bias (study reports LOCF but high dropout, each treatment group exposed to treatment for different lengths of time).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 90: Summary of findings table for side effect outcomes reported at treatment endpoint associated with paliperidone 1.5 mg per day versus paliperidone 3 to 6 mg per day versus paliperidone 6 to 12 mg per day in the treatment of the acute episode in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Dose comparison	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	−0.43 [−0.83, −0.04]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.1)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	−0.14 [−0.54, 0.26]	N/A	Very low[1,2,3]	Appendix 14c (ii) (22.1)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	−0.59 [−0.99, −0.19]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (21.1)
Cardio: QT interval (RR)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.9)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (22.2)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14c (ii) (21.2)

Cardio: tachycardia (RR)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 102	0.13 [0.01, 2.40]	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.12)
		3–6 mg per day versus 6–12 mg per day	K = 1; N = 95	0.73 [0.17, 3.11]	N/A	Very low[1,2,3]	Appendix 14c (ii) (22.3)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 101	0.10 [0.01, 1.76]	N/A	Very low[1,2,3]	Appendix 14c (ii) (21.3)
Hormonal: prolactin (SMD)	SINGH2011	1.5 mg per day versus 3–6 mg per day	K = 1; N = 93	–0.62 [–1.03, –0.20]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (18.14)
		3.6 mg per day versus 6–12 mg per day	K = 1; N = 84	–0.03 [–0.46, 0.39]	N/A	Very low[1,2,3]	Appendix 14c (ii) (22.4)
		1.5 mg per day versus 6–12 mg per day	K = 1; N = 93	–0.53 [–0.94, –0.11]*	N/A	Very low[1,2,3]	Appendix 14c (ii) (21.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
* Favours 1.5 mg per day.
[1]Serious risk of bias study (reports LOCF but high dropout, each treatment group exposed to treatment for different lengths of time).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 7.3.8).

7.3.8 Clinical evidence summary for treatment of the acute episode – evidence for adults for treatment of the acute episode

The review of treatment of the acute episode in the adult *Schizophrenia* guideline (NCCMH, 2010) contained 72 RCTs involving 16,556 participants with an acute exacerbation or recurrence of schizophrenia. There was little evidence of clinically significant differences in efficacy between the oral antipsychotic drugs examined (see Section 6.3 of *Schizophrenia*). Metabolic and neurological side effects were consistent with those reported in the SPC for each drug.

7.4 ANTIPSYCHOTICS IN CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS AND SCHIZOPHRENIA WHOSE ILLNESS HAS NOT RESPONDED ADEQUATELY TO PHARMACOLOGICAL TREATMENT

7.4.1 Introduction

High-dosage antipsychotic medication is commonly used for people whose schizophrenia has not responded adequately to treatment, although there is little evidence to suggest any significant benefit with such a strategy (Royal College of Psychiatrists, 2006). Clinicians may also try switching to another antipsychotic, although similarly the research evidence on the possible value of such a strategy is not consistent or promising (Kinon *et al.*, 1993; Lindenmayer *et al.*, 2002; Shalev *et al.*, 1993). An alternative approach has been to try to potentiate antipsychotics by combining them either with each other or with other classes of drugs. Possible adjuncts to antipsychotic treatment include mood stabilisers and anticonvulsants, such as lithium, carbamazepine, sodium valproate, lamotrigine, antidepressants and benzodiazepines (Barnes *et al.*, 2003; Chong & Remington, 2000; Durson & Deakin, 2001). However, the use of such adjunctive treatments to augment the action of antipsychotics is beyond the scope of this guideline.

In adult populations, J. M. Kane and colleagues (1988, 2001) have established the efficacy of clozapine over FGAs in strictly-defined treatment-resistant schizophrenia, and subsequent meta-analyses have confirmed the superiority of clozapine in terms of reducing symptoms and the risk of relapse (Chakos *et al.*, 2001; Wahlbeck *et al.*, 1999). However, Chakos and colleagues (2001) concluded from their meta-analysis that the evidence for clozapine when compared with the SGAs tested was inconclusive. Even with optimum clozapine treatment, the evidence suggests that only 30 to

60% of people with treatment-resistant schizophrenia show a satisfactory response (Iqbal *et al.*, 2003). As clozapine is associated with severe and potentially life-threatening side effects, particularly the risk of agranulocytosis, the SPC states that the drug should only be considered where there has been a lack of satisfactory clinical improvement despite adequate trials, in dosage and duration, of at least two different antipsychotic agents including an SGA.

In adults, it has been demonstrated that monitoring plasma–clozapine concentration may be helpful in establishing the optimum dose of clozapine in terms of risk–benefit ratio, and also in assessing adherence (Gaertner *et al.*, 2001; Llorca *et al.*, 2002; Rostami-Hodjegan *et al.*, 2004), particularly for people showing a poor therapeutic response or experiencing significant side effects despite appropriate dosage. Studies have shown that an adequate trial will involve titrating the dosage to achieve a target plasma level, usually considered to be above 350 mg per litre, although response may be seen at lower levels (Dettling *et al.*, 2000; Rostami-Hodjegan *et al.*, 2004). If the response to clozapine monotherapy is poor, augmentation strategies may be considered (see NCCMH, 2010, for a review of the evidence in adults). A number of patient-related factors have been reported to increase the variability of plasma–clozapine concentrations, with gender, age and smoking behaviour being the most important (Rostami-Hodjegan *et al.*, 2004). Smoking is thought to increase the metabolism of clozapine by inducing the cytochrome P450 1A2 (CYP1A2) and other hepatic enzymes (Flanagan, 2006; Ozdemir *et al.*, 2002). The metabolism of clozapine is mainly dependent on CYP1A2. This has several clinical implications. First, there is some evidence that smokers are prescribed higher doses by clinicians to compensate for higher clozapine clearance (Tang *et al.*, 2007). Second, plasma concentrations of clozapine and its active metabolite, norclozapine, vary considerably at a given dosage, and this variation may be greater in heavy smokers receiving lower doses of clozapine, increasing the risk of subtherapeutic concentrations (Diaz *et al.*, 2005). Third, prompt adjustment of clozapine dosage in patients who stop smoking during treatment is important to avoid the substantially elevated clozapine concentrations and increased risk of toxicity that would otherwise be expected (Flanagan, 2006; McCarthy, 1994; Zullino *et al.*, 2002).

7.4.2 Clinical review protocol for children and young people with psychosis and schizophrenia whose illness has not responded adequately to pharmacological treatment

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 91. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

Table 91: Clinical review protocol for the review of antipsychotics in the treatment of children and young people with psychosis and schizophrenia whose illness has not responded adequately to pharmacological treatment

Review questions	**RQ B2:** Does the efficacy profile of continuous antipsychotic drug treatment, compared with alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children/young people and adults with psychosis and schizophrenia? **RQ B3:** Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared with adults with psychosis and schizophrenia (in particular, metabolic, neurological and cognitive impairments)? **RQ B7:** For children and young people whose illness has not responded adequately to pharmacological treatment, what is the next most effective treatment strategy and when do you decide to change treatment? Does this differ from adults with schizophrenia? **RQ B8:** Does the most appropriate treatment strategy in people where antipsychotic medication is effective but not tolerated, differ between children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?
Objectives	To provide evidence-based recommendations regarding the pharmacological (antipsychotic) treatment and management of children and young people with psychosis and schizophrenia whose illness has not responded adequately to pharmacological treatment, including a review of the adult *Schizophrenia* guideline (NICE, 2009a; NCCMH, 2010) for its relevance to children and young people.
Population	**Inclusion:** Children and young people (aged 18 years and younger) with psychosis and schizophrenia, who have not responded adequately to pharmacological treatment. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	All antipsychotic medication licensed in the UK for the treatment of children and young people with psychosis and schizophrenia, including considerations related to the age of participants (for example, dose modifications). Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia).

Continued

Table 91: (*Continued*)

	• Amisulpride • Aripiprazole • Benperidol • Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol • Levomepromazine • Olanzapine • Pericyazine • Pimozide • Prochlorperazine • Promazine hydrochloride • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate
Comparison	Alternative management strategies: • Placebo • Psychological intervention • Any of the above interventions offered as an alternative management strategy
Critical outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes, cardiotoxicity) • Remission
Electronic databases	**RQ B2, RQ B7, RQ B8:** Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: AEI, AMED ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, ERIC, HTA, IBSS, Sociological Abstracts, SSA, SSCI Grey literature databases: HMIC, PsycBOOKS, PsycEXTRA

Continued

Table 91: (*Continued*)

	RQ B3: Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: CDSR, CENTRAL, DARE
Date searched	Systematic reviews: 1995 to May 2012 RCTs: inception of databases to May 2012
Study design	Systematic review, RCT
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and at or under 18 years. The review will seek to identify whether modifications in treatment and management of children aged at or under 13 years and younger need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

7.4.3 Studies considered[98]

Three RCTs (N = 86) providing relevant clinical evidence met the eligibility criteria for the review of antipsychotic medication in children and young people with psychosis and schizophrenia whose illness has not responded adequately to pharmacological treatment (KUMRA1996 [Kumra *et al.*, 1996], KUMRA2008A [Kumra

[98]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).

et al., 2008a], SHAW2006 [Shaw *et al*., 2006]). All included RCTs were published in peer-reviewed journals between 1996 and 2008 and reported at least one outcome in sufficient detail to allow for extraction and analysis. Included studies investigated antipsychotic medication use in children and young people aged 18 years and younger. In addition, 582 studies were considered irrelevant to the pharmacological treatment and management of psychosis and schizophrenia in children and young people and excluded from the review. All included RCTs compared clozapine with another antipsychotic medication: haloperidol (KUMRA1996) or olanzapine (KUMRA2008A, SHAW2006). A summary of study characteristics is presented in Table 92. Further information about both included and excluded studies can be found in Appendix 13c.

7.4.4 Clinical evidence for clozapine versus another antipsychotic in children and young people with psychosis and schizophrenia whose illness has not responded adequately to treatment

Data from three RCTs (N = 86) was pooled in an analysis of clozapine versus another antipsychotic (KUMRA1996, KUMRA2008A, SHAW2006) in participants diagnosed with either schizophrenia or a schizophrenic disorder, with a median age of 14.1 years. 'Inadequate response' to treatment was defined by only two studies (KUMRA2008A and SHAW2006) as the persistence of symptoms following adequate dosing of at least two antipsychotics, measured using either the BPRS (KUMRA2008A) or a subjective assessment (SHAW2006). Both of these trials excluded participants who had previously inadequately responded to olanzapine or haloperidol.

Efficacy

KUMRA1996 and KUMRA2008A reported mean endpoint scores and SHAW2006 reported mean change scores. Sensitivity analyses were conducted on outcomes measured using mean endpoint and mean change scores, with more than two included studies. A significant, moderate difference was found at treatment endpoint between participants treated with clozapine and participants treated with another antipsychotic (olanzapine or haloperidol) on total symptoms (SMD = 0.50; 95% CI, 0.06 to 0.94), positive symptoms (SMD = 0.71; 95% CI; 95% CI, 0.27 to 1.16) and negative symptoms (SMD = 0.53; 95% CI, 0.10 to 0.97). However when mean change scores were removed (SHAW2006) in sensitivity analyses only the significant effect observed for positive symptoms remained significant (SMD = 0.73; 95% CI, 0.07 to 1.38). A small significant difference was found for global state, with clozapine favoured over another antipsychotic (SMD = 0.51; 95% CI, 0.01 to 1.01), however no significant difference was found for psychosocial functioning. Evidence from each reported outcome and overall quality of evidence are presented in Table 93; the full evidence profiles can be found in Appendix 17c.

Table 92: Study information table for trials comparing clozapine with another antipsychotic in children and young people with psychosis and schizophrenia whose illness has not responded adequately to treatment

	Trials comparing clozapine with another antipsychotic	
	Olanzapine	**Haloperidol**
Total no. of studies (N)	K = 2 (n = 65)	K = 1 (N = 21)
Study ID	(1) KUMRA2008A (2) SHAW2006	KUMRA1996
Diagnosis	(1) Schizophrenic disorder (2) Schizophrenia	Schizophrenia
Definition of inadequate response	(1) Documented treatment failure of at least two prior adequate antipsychotic trials (not including clozapine or olanzapine) and a baseline BPRS total score of at least 35 and a score of at least 'moderate' on one or more psychotic item(s) on the BPRS. (2) Failure to respond to two antipsychotics (typical or atypical, not including clozapine or olanzapine) used at adequate doses (>100 mg chlorpromazine equivalents) and for adequate duration (>4 weeks unless stopped owing to intolerable adverse effects). Failure was defined as insufficient response with persistence of symptoms significantly impairing the child/young person's functioning according to child, parent, medical and school reports or intolerable adverse effects.	Not reported
Mean age (range)	(1) 15.6 (not reported) (2) 12.3 (7.0 to 16.0)	14.1 (not reported)
Sex (% male)	(1) 54 (2) 60	52
Ethnicity (% white)	(1) 21 (2) 56	Not reported

Continued

Table 92: (*Continued*)

	Trials comparing clozapine with another antipsychotic	
	Olanzapine	**Haloperidol**
Mean (range) medication dose (mg per day)	(1) Clozapine: 403.1 (25.0 to 900.0); olanzapine: 26.2 (5.0 to 30.0) (2) Clozapine: 327.0 (12.5 to 900.0); olanzapine: 18.1 (5.0 to 20.0)	Clozapine 176.0 (25.0 to 125.0); haloperidol: 16.0 (7.0 to 27.0)
Treatment length (weeks)	(1) 12 (2) 8	6
Length of follow-up (weeks)	(1) 12 (2) 8	104
Setting	(1) Inpatient and outpatient (2) Inpatient	Participants were identified though national recruitment via professional and patient advocacy organisations
Country	(1)–(2) US	US
Funding	(1)–(2) Not reported	Not reported

Note. [1]Extractable outcomes.

Side effects

A moderate significant difference was found favouring olanzapine over clozapine for fasting serum glucose level (SMD = −0.79; 95% CI, −1.45 to −0.12). A significant difference favouring clozapine over haloperidol was found at treatment endpoint for the number of people experiencing tachycardia (RR = 4.80; 95% CI, 1.30 to 17.66), but no difference was found between haloperidol and clozapine on this outcome (RR = 0.18; 95% CI, 0.01 to 3.41). No other significant differences were found between clozapine and another antipsychotic on side effect outcomes reported. Evidence from each reported outcome and overall quality of evidence are presented in Table 94; the full evidence profiles can be found in Appendix 17c.

Table 93: Summary of findings table for efficacy outcomes reported at treatment endpoint associated with clozapine versus another antipsychotic in children and young people

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	KUMRA1996 KUMRA2008A SHAW2006	K = 3; N = 85	0.50 [0.06, 0.94]*	(P = 0.54); I^2 = 0%	Very low[1,2,3]	Appendix 14c (iii) (1.1)
Sensitivity analysis: total symptoms (SMD)	KUMRA1996 KUMRA2008A	K = 2; N = 60	0.41 [–0.11, 0.92]	(P = 0.37); I^2 = 0%	Very low[1,2,3]	Appendix 14c (iii) (1.2)
Positive symptoms (SMD)	KUMRA1996 KUMRA2008 SHAW2006	K = 3; N = 85	0.71 [0.27, 1.16]*	(P = 0.49); I^2 = 0%	Very low[1,2,3]	Appendix 14c (iii) (1.3)
Sensitivity analysis: positive symptoms (SMD)	KUMRA1996 KUMRA2008A	K = 2; N = 60	0.73 [0.07, 1.38]*	(P = 0.23); I^2 = 29%	Very low[1,2,3]	Appendix 14c (iii) (1.4)
Negative symptoms (SMD)	KUMRA1996 KUMRA2008A SHAW2006	K = 3; N = 85	0.53 [0.10, 0.97]*	(P = 0.43); I^2 = 0%	Very low[1,2,3]	Appendix 14c (iii) (1.5)
Sensitivity analysis: negative symptoms (SMD)	KUMRA1996 KUMRA2008A	K = 2; N = 60	0.49 [–0.15, 1.14]	(P = 0.23); I^2 = 30%	Very low[1,2,3]	Appendix 14c (iii) (1.6)
Global state (SMD)	KUMRA2008A SHAW2006	K = 2; N = 64	0.51 [0.01, 1.01]*	(P = 0.95); I^2 = 0%	Very low[1,2,3]	Appendix 14c (iii) (1.7)
Psychosocial functioning (SMD)	KUMRA1996 KUMRA2008A	K = 2; N = 60	0.80 [–0.43, 2.03]	(P = 0.04); I^2 = 77%	Very low[1,2,3,4]	Appendix 14c (iii) (1.8)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours clozapine.
[1]Downgraded due to risk of bias (including unclear allocation concealment, blinding of raters unclear, ITT method of analysis unclear or available case analysis used, high dropout, eligibility criteria states that patients must be not be treatment refractory to study medication, trial registration could not be found).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]$I^2 \geq 50\%$, $p < .05$.

Table 94: Summary of findings table for side effect outcomes reported at treatment endpoint associated with clozapine versus another antipsychotic in children and young people

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight kg (SMD)	SHAW2006	K = 1; N = 25	−0.04 [−0.82, 0.75]	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.1)
Metabolic: BMI (SMD)	KUMRA2008A SHAW2006	K = 2; N = 63	0.03 [−0.47, 0.52]	(P = 0.70); I^2 = 0%	Very low[1,2,3]	Appendix 14c (iii) (2.2)
Metabolic: fasting serum glucose level mg per dl (SMD)	KUMRA2008A	K = 1; N = 38	−0.79 [−1.45, −0.12]*	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.3)
Metabolic: fasting total cholesterol mg per dl (SMD)	KUMRA2008A	K = 1; N = 38	0.31 [−0.34, 0.95]	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.4)
Metabolic: fasting triglycerides mg per dl (SMD)	KUMRA2008A	K = 1; N = 38	−0.28 [−0.92, 0.37]	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.5)
Cardio: tachycardia (RR)	KUMRA1996	K = 1; N = 21	0.18 [0.01, 3.41]	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.6)
	SHAW2006	K = 1; N = 22	4.80 [1.30, 17.66]**	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.6)

Continued

Table 94: (*Continued*)

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Neurological: AIMS (SMD)	KUMRA1996	K = 1; N = 21	0.02 [–0.83, 0.88]	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.7)
Neurological: SAS (SMD)	KUMRA1996	K = 1; N = 21	0.66 [–0.23, 1.54]	N/A	Very low[1,2,3]	Appendix 14c (iii) (2.8)
Leaving the study early for any reason (RR)	KUMRA1996 KUMRA2008A SHAW2006	K = 3; N = 85	1.15 [0.43, 3.03]	(P = 0.35); I^2 = 6%	Very low[1,2,3]	Appendix 14c (iii) (2.9)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours olanzapine.
**Favours clozapine.
[1]Downgraded due to risk of bias (including unclear allocation concealment, blinding of raters unclear, ITT method of analysis unclear or available case analysis used, high dropout, eligibility criteria states that patients must be not be treatment refractory to study medication, trial registration could not be found).
[2]Serious risk of reporting bias.
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.4.5 Clinical evidence summary – evidence for children and young people with psychosis and schizophrenia whose illness has not responded adequately to treatment

Three RCTs, with a total of 86 participants whose illness had not responded adequately to treatment, were identified. This provided extremely limited, underpowered data. The evidence suggests that clozapine results in moderately better symptom and global state outcomes compared with another antipsychotic (olanzapine or haloperidol). Only one moderate differential effect in side effects was found for fasting serum glucose level, favouring olanzapine over clozapine. However, the paucity of data and very low quality of the evidence mean it is difficult to draw robust conclusions regarding relative efficacy and safety of antipsychotics in the treatment children and young people whose illness has not adequately responded to treatment. Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence identified in children and young people, the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 7.4.6).

7.4.6 Clinical evidence summary – evidence for adults with schizophrenia whose illness has not responded adequately to treatment

The review of treatment for people whose illness had not responded adequately to treatment in the adult *Schizophrenia* guideline (NCCMH, 2010) contained 18 RCTs including 2,554 participants. Clozapine had the most consistent evidence for efficacy over the FGAs included in the trials reviewed (see Section 6.5 of *Schizophrenia*). Further evidence is required to establish equivalence between clozapine and any other SGA, and to determine whether there are differences between any of the other antipsychotic drugs. Side effects were consistent with those reported in the SPC for each drug. In 10 RCTs including 1,200 participants with persistent negative symptoms, there was no evidence of clinically significant differences in efficacy between any of the antipsychotic drugs examined. Careful clinical assessment to determine whether such persistent features are primary or secondary is warranted, and may identify relevant treatment targets, such as drug-induced parkinsonism, depressive features or certain positive symptoms. In six RCTs including 252 participants with schizophrenia whose illness had not responded adequately to clozapine treatment, there was some evidence that clozapine augmentation with a second antipsychotic might improve both total and negative symptoms if administered for an adequate duration.

7.5 SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION OCCURRING AT OR OVER 12 WEEKS

7.5.1 Introduction

The RCT is widely recognised as the 'gold standard' for evaluating treatment efficacy, but some methodological issues may compromise the generalisability of the findings

to the ordinary treatment setting. An additional issue pertains to the paucity of trials assessing long-term side effects associated with antipsychotic medication in children and young people. The review of RCTs (see Sections 7.2, 7.3 and 7.4) identified only three trials reporting side effect data of 12 weeks or more with a total of 95 participants aged 18 years and younger (ARANGO2009, JENSEN2008, MOZES2006). Detailed review of these studies, including information regarding study characteristics and analyses, has been provided in Sections 7.2 and 7.3 of this chapter. In brief, all RCTs were head-to-head trials of antipsychotics, including two comparisons: risperidone versus olanzapine (MOZES2006) and olanzapine versus quetiapine (JENSEN 2008; ARANGO2009). Trials followed up participants over 12 (MOZES2006, JENSEN2008) or 26 weeks (ARANGO2009) and no significant differences were found between any of the treatment groups across the trials.

Given the paucity of RCTs investigating antipsychotic medication in children and young people and the importance of assessing long-term side effect data in this population, the GDG decided to conduct an additional search for observational study data associated with side effects occurring at 12 weeks or more.

7.5.2 Clinical review protocol – observational study data of side effects occurring at 12 weeks or more

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 95. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

7.5.3 Studies considered[99]

Seven observational studies, with a total of 470 children and young people aged 18 years and younger with psychosis and schizophrenia, were identified that reported side effect outcome data at 12 weeks or more for four antipsychotics: quetiapine (K = 3; N = 246: AZD1441C00150 [AstraZeneca D1441C00150, unpublished], CASTRO-FORNIELES2008 [Castro-Fornieles *et al.*, 2008], SCHIMMELMANN2007 [Schimmelmann *et al.,* 2007]); risperidone (K = 2; N = 57: CASTRO-FORNIELES2008, CROCQ2007 [Crocq *et al.*, 2007]); olanzapine (K = 5; N = 155: CASTRO-FORNIELES2008, CROCQ2007, DITTMANN2008 [Dittmann *et al.*, 2008], ROSS2003 [Ross *et al.*, 2003]); and clozapine (K = 1; N = 12: KUMRA1998 [Kumra *et al.*, 1998]). Data could be extracted and analysed for two studies (CASTRO-FORNIELES2008, CROCQ2007), while the remaining five studies are reported narratively. In addition, 303 studies were excluded from the analysis.

[99]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 95: Clinical review protocol for long-term side effects of antipsychotics occurring at 12 weeks or more

Review questions	**RQ B3:** Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared with adults with psychosis and schizophrenia (in particular, metabolic, neurological and cognitive impairments)?
Objectives	To provide evidence-based recommendations regarding the long-term (12 weeks or more) pharmacological (antipsychotic) treatment and management of the acute episode in children and young people with psychosis and schizophrenia, including a review of the adult *Schizophrenia* guideline (NICE, 2009a; NCCMH, 2010) for its relevance to children and young people.
Population	**Inclusion:** Children and young people (aged 18 years and younger) with psychosis and schizophrenia. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	All antipsychotic medication licensed in the UK for the treatment of children and young people with psychosis and schizophrenia, including considerations related to the age of participants (for example, dose modifications). Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia). • Amisulpride • Aripiprazole • Benperidol • Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol • Levomepromazine • Olanzapine • Pericyazine • Pimozide

Continued

Table 95: (*Continued*)

	• Prochlorperazine • Promazine hydrochloride • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate
Comparison	Alternative management strategies: • Placebo • Psychological intervention • Any of the above interventions offered as an alternative management strategy
Critical outcomes	• Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes, cardiotoxicity)
Electronic databases	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO
Date searched	Inception of databases to May 2012
Study design	Observational studies of 12 weeks or more
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating long-term (12 weeks or more) harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and at or under 18 years. The review will seek to identify whether modifications in treatment and management of children aged at or under 13 years and younger need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available.

Continued

Table 95: (*Continued*)

	• Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

All included participants had psychosis and schizophrenia. The AZD1441C00150 trial included 54% with bipolar disorder; however the data reviewed here pertain to the participants with schizophrenia only. Where reported, the majority of participants were antipsychotic naïve (apart from participants in the DITTMANN2008 trial in which 38% were antipsychotic naïve). The median of the mean ages is 15.2 years. Dose ranges for each drug did not differ significantly between studies. Treatment length ranged from 6 weeks (KUMRA1998) to 52 weeks (ROSS2003). Two studies followed participants post-treatment: at 52 weeks (CASTRO-FORNIELES2008) and 104 to 208 weeks (KUMRA1998). A summary of study characteristics is presented in Table 96; further information about both included and excluded studies can be found in Appendix 13c.

7.5.4 Clinical evidence for metabolic side effects

Weight and BMI

Five included studies with a total of 283 participants assessed weight and BMI in participants treated with olanzapine, quetiapine or risperidone (CASTRO-FORNIELES2008; SCHIMMELMANN2007; CROCQ2007; DITTMANN2008; ROSS2003). Data could be extracted and analysed for two studies (CASTRO-FORNIELES2008, CROCQ2007). At 12 weeks or more, large, significant effects were found on weight and BMI, favouring both quetiapine (weight: SMD = −0.96; 95% CI, −1.73 to −0.18) and risperidone (weight: SMD = 1.75; 95% CI, 0.30 to 3.21; BMI: SMD = 2.17; 95% CI, 1.27 to 3.08) over olanzapine (standard oral tablet). Similarly, at 12 weeks, olanzapine (orally disintegrating tablet) resulted in significantly greater weight and BMI increases than risperidone (weight: SMD = 1.02; 95% CI; 95% CI, 0.36 to 1.69; BMI: SMD = 0.93; 95% CI, 0.27 to 1.59). Olanzapine administered as an orally disintegrating tablet resulted in significant less weight gain (SMD = −1.62; 95% CI, −2.54 to −0.69) and BMI increase (SMD = −1.06; 95% CI, −1.91 to −0.21) compared with a standard oral tablet. No significant between-group differences in weight change were found for quetiapine- and risperidone-treated participants. Evidence from each reported outcome and overall quality of evidence are presented in Table 97.

Table 96: Study information table for observational studies investigating side effects of antipsychotic medication in children and young people with psychosis and schizophrenia

	Quetiapine	Risperidone	Olanzapine	Clozapine
Total no. of studies (N)	K = 3 N = 246	K = 2 N = 57	K = 5 N = 155	K = 1 N = 12
Study ID	(1) AZD1441C00150[1,2] (2) CASTRO-FORNIELES2008[1,3] (3) SCHIMMELMANN2007[1]	(1) CASTRO-FORNIELES 2008[1,3] (2) CROCQ2007[1]	(1) CASTRO-FORNIELES 2008[1,3] (2) CROCQ2007[1] (3) DITTMANN2008[1,4] (4) ROSS2003[1]	KUMRA1998[1,5]
Design	(1) Open-label phase IIIb (2) Naturalistic, longitudinal (3) Prospective, longitudinal	(1) Naturalistic, longitudinal (2) Open-label, non-randomised, observational	(1) Naturalistic longitudinal (2) Open-label, non-randomised, observational (3) Open-label, prospective (4) Prospective, open-label, naturalistic trial	Open, controlled continuation of a 6-week double-blind RCT
Diagnosis	(1)[4] Schizophrenia: 46.1%; bipolar: 53.9% (2) Schizophrenia type disorder: 39.1%; psychotic disorder not otherwise specified (NOS): 38.2%; depressive disorder with psychotic symptoms: 11.8%; bipolar disorder, manic episode with psychotic symptoms: 10.9% (3) 76.8% schizophrenia; 12.5% schizophreniform; 10.7% schizoaffective	(1) Schizophrenia type disorder: 39.1%; psychotic disorder NOS: 38.2%; depressive disorder with psychotic symptoms: 11.8%; bipolar disorder, manic episode with psychotic symptoms: 10.9% (2) Schizophreniform disorder	(1) Schizophrenia type disorder: 39.1%; psychotic disorder NOS: 38.2%; depressive disorder with psychotic symptoms: 11.8%; bipolar disorder, manic episode with psychotic symptoms: 10.9% (2) Schizophreniform disorder (3) Psychosis (86% first episode psychosis)[6] (4) Schizophrenia and schizoaffective	Schizophrenia (inadequate response)

Prior antipsychotic use (% naïve prior to intervention)	(1) Not reported (2) 51 (3) 77	(1) 51 (2) 75	(1) 51 (2) 75 (3) 38 (4) 58	0
Mean age (range)	(1) 14.4 (not reported) (2) 15.5 (9.0 to 17.0) (3) 15.9 (12.0 to 17.9)	(1) 15.5 (range 9.0 to 17.0) (2) 15.2 (not reported)	(1) 15.5 (9.0 to 17.0) (2) 15.2 (not reported) (3) 15.5 (12.0 to 19.0) (4) 10.5 (6.0 to 15.0)	14.2 (6.0 to 18.0)
Sex (% male)	(1) 60 (2) 67 (3) 68	(1) 67 (2) 58	(1) 67 (2) 58 (3) 71 (4) 74	56
Ethnicity (% white)	(1) 71 (2) 86 (3) 84	(1) 86 (2) 100	(1) 86 (2) 100 (3) 95 (4) 84	44
Mean (range) dose (mg per day)	(1) 400.0–800.0 (2) 405.1 (not reported) (3) 594.9 (50.0 to 800.0)	(1) 3.3 (not reported) (2) 2.8 (not reported)	(1) 11.6 (not reported) (2) Standard oral tablets: 16.6 (not reported); orally disintegrating tablets: 18.0 (not reported) (3) 14.0 (10.0 to 20.0) (4) 7.7 (2.5 to 17.5)	176.0 (25.0 to 525.0)[6]
Treatment length (weeks)	(1) 26 (2) 26 (3) 12	(1) 26 (2)12	(1) 26 (2) 12 (3) 24 (4) 52	Unclear

Continued

Table 96: (*Continued*)

	Quetiapine	Risperidone	Olanzapine	Clozapine
Follow-up (weeks)	(1) 26 (2) 52 (3) 12	(1) 52 (2) 12	(1) 52 (2) 12 (3) 24 (4) 52	104 to 208
Setting	(1) Not reported (2) Inpatient and outpatient psychiatric units (3) 98% hospitalised	(1) Inpatient and outpatient psychiatric units (2) Inpatient hospital	(1) Inpatient and outpatient psychiatric units (2) Inpatient hospital (3) Inpatients during phase I (6 weeks); outpatients during phase II (18 weeks) (4) Not reported	Not reported (recruited via professional and patient advocacy organisations)
Country	(1) US (2) Spain (3) Germany	(1) Spain (2) France	(1) Spain (2) France (3) Germany (4) US	US
Funding	(1) AstraZeneca (2) Non-industry funded (3) AstraZeneca	(1)–(2) Not reported	(1)–(2) Not reported (3) Lilly Deutschland (4) Veterans' Administration Research Services, Public Health Service, Eli Lilly	Not reported

Note. [1] Data are reported for the population characteristics of each study, not the population characteristics of each treatment group.
[2]This trial also included people with bipolar disorder with no psychotic symptoms; therefore only data pertaining to participants with schizophrenia were extracted and reviewed.
[3]Data for the three most used antipsychotics during the first 6 months of follow-up were extracted and reviewed.
[4]Error in reporting of the number of participants with specific diagnoses.
[5]An extension trial of clozapine, olanzapine, haloperidol and benzatropine. Reporting of the number of participants in each treatment group is unclear for all treatments except clozapine and therefore only data pertaining to clozapine have been reviewed.
[6]Reported for the 6th week of treatment.

Table 97: Summary of findings table for extractable metabolic side effect outcomes in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Comparison	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: weight change kg (SMD)	CASTRO-FORNIELES 2008[1]	Quetiapine versus risperidone	K = 1; N = 46	−0.02 [−0.64, 0.60]	N/A	Very low[3,4,5]	Appendix 14c (iv) (1.1)
	CASTRO-FORNIELES 2008[1]	Quetiapine versus olanzapine	K = 1; N = 29	−0.96 [−1.73, −0.18]*	N/A	Very low[3,4,5]	Appendix 14c (iv) (1.2)
	CASTRO-FORNIELES 2008[1] CROCQ2007[2]	Olanzapine (standard oral tablet) versus risperidone	K = 2; N = 81	1.75 [0.30, 3.21]**	N/A	Very low[3,4,5]	Appendix 14c (iv) (1.3)
	CROCQ2007[2]	Olanzapine (orally disintegrating tablet) versus risperidone	K = 1; N = 42	1.02 [0.36, 1.69]**	N/A	Very low[3,4,5]	Appendix 14c (iv) (1.4)
	CROCQ2007[2]	Olanzapine (standard oral tablet) versus olanzapine (orally disintegrating tablet)	K = 1; N = 26	−1.62 [−2.54, −0.69]***	N/A	Very low[3,4,5]	Appendix 14c (iv) (1.5)

Continued

Table 97: (*Continued*)

Outcome or subgroup	Study ID	Comparison	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Metabolic: BMI change (SMD)	CROCQ2007[2]	Olanzapine (standard oral tablet) versus risperidone	K = 1; N = 36	2.17 [1.27, 3.08]**	N/A	Very low[3,4,5]	Appendix 14c (iv) (2.1)
	CROCQ2007[2]	Olanzapine (orally disintegrating tablet) versus risperidone	K = 1; N = 42	0.93 [0.27, 1.59]**	N/A	Very low[3,4,5]	Appendix 14c (iv) (2.2)
	CROCQ2007[2]	Olanzapine (standard oral tablet) versus olanzapine (orally disintegrating tablet)	K = 1; N = 26	−1.06 [−1.91, −0.21]***	N/A	Very low[3,4,5]	Appendix 14c (iv) (2.3)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours quetiapine.
**Favours risperidone.
***Favours olanzapine (orally disintegrating tablet).
[1]26 weeks' treatment.
[2]12 weeks' treatment.
[3]Serious risk of bias (including: observational study).
[4]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5]Serious risk of reporting bias.

Table 98 provides a narrative summary of reported results for all included studies measuring weight and BMI at 12, 26 and 52 weeks. Weight gain has been observed in patients treated with olanzapine, risperidone and quetiapine at 12 and 26 weeks, and for participants treated with olanzapine at 52 weeks. In olanzapine-treated participants this increase was significantly greater than in patients treated with risperidone or quetiapine. Similarly significant BMI increases were observed in participants treated with olanzapine and quetiapine at 12 weeks, and olanzapine treated-participants at 26 weeks. Tests of significance between treatments on BMI increase were not reported.

Fasting serum glucose level

One study included 161 participants in an analysis of fasting serum glucose level associated with treatment with quetiapine at 26 weeks (AZD1441C00150). Fasting serum glucose level increased, however the significance of this increase is not reported. Table 99 provides a summary of reported results.

Total cholesterol level

Two studies with a total of 217 participants assessed total cholesterol level in those treated with quetiapine for 12 or 26 weeks (SCHIMMELMANN2007, AZD1441C00150, respectively). Studies reported inconsistent findings: SCHIMMELMANN2007 reported a non-significant increase in patients treated with quetiapine at 12 weeks and AZD1441C00150 reported a decrease (significance not reported) at 26 weeks. Table 100 provides a summary of reported results.

Metabolic: high-density lipoprotein cholesterol

One study included 161 participants in an analysis of high-density lipoprotein cholesterol level associated with treatment with quetiapine at 26 weeks (AZD1441C00150). High-density lipoprotein cholesterol level decreased, however the significance of this decrease is not reported. Table 101 provides a summary of reported results.

Metabolic: low-density lipoprotein cholesterol

One study included 161 participants in an analysis of low-density lipoprotein cholesterol level associated with treatment with quetiapine at 26 weeks (AZD1441C00150). Low-density lipoprotein cholesterol level decreased, however the significance of this decrease is not reported. Table 102 provides a summary of reported results.

Metabolic: triglycerides

One included study with a total of 161 participants assessed triglycerides in participants treated with quetiapine treated at 26 weeks (AZD1441C00150). Triglycerides decreased, however the significance of this decrease is not reported. Table 103 provides a summary of reported results.

Table 98: Summary of results for effect of antipsychotic medication on weight (kg) and BMI (kg per m²)

K = 5; N = 283			
	Study ID	**Intervention**	**Results**
12 weeks	CROCQ2007	Olanzapine	Mean (SD) weight (kg) and BMI (kg per m²) increased for all treatment groups at 12 weeks: *Weight* / *BMI* *Olanzapine standard oral tablet (n = 10)*: 8.9 (5.1)[3] / 1.9 (0.6)[3] *Olanzapine orally disintegrating tablet (n = 16)*: 3.0 (2.1)[1] / 1.1 (0.8)[2] *Risperidone (n = 26)*: 1.0 (1.8)[3] / 0.4 (0.7)[3]
	ROSS2003	Olanzapine	Mean weight (kg) increases were significant ($p < 0.001$) at each timepoint from baseline to 12 weeks (measure of variance not reported): 3 weeks = 1.6; 6 weeks = 3.8; 13 weeks = 4.2
	SCHIMMELMANN2007	Quetiapine	Mean (SD) weight (kg) and BMI (kg/m²) increases from baseline were significant ($p < 0.001$) at 12 weeks: *Baseline* / *12 weeks* *Weight(kg)*: 61.1 (11.6) / 66.9 (11.0) *BMI (kg/m²)*: 20.7 (3.3) / 22.8 (3.1)
26 weeks	ROSS2003	Olanzapine	Mean weight (kg) increase was significantly ($p < 0.001$) different at 26 weeks compared with baseline (measure of variance not reported): 26 weeks = 9.7. BMI significantly increased ($p = 0.001$) at each timepoint (3, 6, 13 and 26 weeks) from baseline; but did not significantly change from 6 months to 1 year (mean changes not reported).

26 weeks	CASTRO-FORNIELES2008	Risperidone Olanzapine Quetiapine	Mean (SD) weight (kg) increased in all treatment groups by 26 weeks. Patients treated with olanzapine gained significantly more weight than those treated with risperidone or quetiapine ($p = 0.02$ and $p = 0.04$ respectively): Risperidone (n = 31): 6.1 (4.8) Quetiapine (n = 15): 6.0 (5.5) Olanzapine (n = 14): 11.7 (6.1)
	DITTMANN2008	Olanzapine	The % of patients with reported treatment-emergent adverse effects who gained weight at 26 weeks was 30.2%. Of those patients with possible olanzapine-related treatment-emergent adverse effects (as judged by a clinician) 65.5% gained weight at 26 weeks.
52 weeks	ROSS2003	Olanzapine	Mean weight (kg) increase was significantly ($p < 0.001$) different at 52 weeks compared with baseline (measure of variance not reported): 52 weeks = 12.8.

Note. Significance (p) of difference between olanzapine orally disintegrating tablet and risperidone and between olanzapine orally disintegrating tablet and olanzapine standard oral tablet, respectively:
[1]$p = 0.002$; $p < 0.001$.
[2]$p = 0.003$; $p = 0.001$.
[3]Significance in differences unclear/not reported.

Table 99: Summary of results for effect of antipsychotic medication on fasting serum glucose level (mg per dl)

K = 1; N = 161			
	Study ID	**Intervention**	**Results**
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was 5.2931 (25.1642) (p value not reported).

Table 100: Summary of results for effect of antipsychotic medication on total cholesterol level (mg per dl)

K = 2; N = 217			
	Study ID	**Intervention**	**Results**
12 weeks	SCHIMMELMANN2007	Quetiapine	A non-significant increase in total mean (SD) cholesterol was observed: 159.7 (34) at baseline to 172.3 (29.8) at 12 weeks.
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was −0.1750 (23.5883) (p value not reported).

Table 101: Summary of results for effect of antipsychotic medication on high-density lipoprotein cholesterol level (mg per dl)

K = 1; N = 161			
	Study ID	**Intervention**	**Results**
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was −0.5940 (8.6012) (p value not reported).

Table 102: Summary of results for effect of antipsychotic medication on low-density lipoprotein cholesterol level (mg per dl)

K = 1; N = 161			
	Study ID	**Intervention**	**Results**
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was −0.1750 (23.5883) (p value not reported).

Table 103: Summary of results for effect of antipsychotic medication on triglycerides (mg per dl)

K = 1; N = 161			
	Study ID	**Intervention**	**Results**
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was −0.1148 (68.0005) (p value not reported).

7.5.5 Clinical evidence for neurological side effects

EPS scales

Four studies with a total of 310 participants used a standard scale (AIMS, SAS, BARS or the UKU Neurologic subscale) to assess EPS (AZD1441C00150, CASTRO-FORNIELES2008, ROSS2003, SCHIMMELMANN2007). Data could be extracted and analysed for one study (CASTRO-FORNIELES2008). At 26 weeks no significant between-group differences in neurological side effects were found. Evidence from each reported outcome and overall quality of evidence are presented in Table 104.

Table 105 provides a narrative summary of reported results for all included studies measuring neurological side effects at 12, 26 and 52 weeks. The majority of participants treated with olanzapine showed no differences at 26 or 52 weeks on the AIMS (ROSS2003). Minimal changes were observed in a study of quetiapine: 8.6% of participants showed an improvement and 5.1% worsened (significance not reported) (AZD1441C00150). No significant differences were observed in participants treated with quetiapine at 12 weeks, or olanzapine at 52 weeks on the SAS (SCHIMMELMANN2007 and ROSS2003, respectively). At 26 weeks the majority of participants treated with quetiapine in the AZD1441C00150 trial showed no change in scores (significance not reported); an improvement was observed in 15.5% participants and a worsening in 8.6% (AZD1441C00150). A significant decrease (improvement) was observed in quetiapine-treated participants at 12 weeks on the BARS (p = 0.001) (SCHIMMELMANN2007) and an improvement in BARS scores was observed in 6.9% of patients and worsening in 2.3% (significance not reported) at 26 weeks (AZD1441C00150). The majority of participants treated with olanzapine showed no change in BARS scores at 52 weeks (ROSS2003). One study used the UKU and reported that only the scores on the Neurological Side Effects Subscale were significantly different between risperidone- and olanzapine-treated participants, with risperidone favoured over olanzapine (p = 0.022) at 26 weeks.

Tardive dyskinesia

One study (N = 12) assessed the risk of tardive dyskinesia at 104 to 204 weeks in children and young people treated with clozapine. Mild tardive dyskinesia was observed in one participant. Table 106 provides a summary of reported results.

Table 104: Summary of findings table for extractable neurological side effect outcomes in children and young people with psychosis and schizophrenia

Outcome or subgroup	Study ID	Comparison	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Neurological: UKU (SMD)	CASTRO-FORNIELES2008[1]	Quetiapine versus risperidone	K = 1; N = 46	–0.28 [–0.90, 0.34]	N/A	Very low[2,3,4]	Appendix 14c (iv) (3.1)
	CASTRO-FORNIELES2008[1]	Quetiapine versus olanzapine	K = 1; N = 29	0.11 [–0.62, 0.84]	N/A	Very low[2,3,4]	Appendix 14c (iv) (3.2)
	CASTRO-FORNIELES2008[1]	Olanzapine (standard oral tablet) versus risperidone	K = 1; N = 45	–0.39 [–1.03, 0.25]	N/A	Very low[2,3,4]	Appendix 14c (iv) (3.3)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]26 weeks' treatment.
[2]Serious risk of bias (including: observational studies).
[3]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4]Serious risk of reporting bias.

Table 105: Summary of results for effect of antipsychotic medication on EPS scales

K = 2; N = 310			
	Study ID	**Intervention**	**Results**
12 weeks	SCHIMMELMANN 2007	Quetiapine	AIMS: measure not used. SAS: a non-significant decrease in mean (SD) scores was observed: 2.4 (4.4) at baseline to 1.4 (2.6) at 12 weeks. BARS: a significant decrease in mean (SD) scores was observed: 1.1 (1.7) at baseline to 0.5 (1.4) at 12 weeks p = 0.001). UKU: measure not used.
26 weeks	AZD1441C00150	Quetiapine	AIMS: 86.3% of participants showed no change; 8.6% showed an improvement (defined as ≤ –1 point change in AIMS–7 total score); and 5.1% worsened (defined as ≥1 point change in AIMS–7 total score) (p value not reported). SAS: 75% of participants showed no change; 15.5% showed an improvement (defined as ≤ –1 point change in SAS total score); and 8.6% worsened (defined as ≥1 point change in SAS total score) (p value not reported). BARS: 90.8% of participants showed no change; 6.9% showed an improvement (defined as ≤ –1 point change in BARS global score); and 2.3% worsened (defined as ≥1 point change in BARS global score) (p value not reported). UKU: measure not used.
	CASTRO-FORNIELES2008	Risperidone Olanzapine Quetiapine	AIMS: measure not used. SAS: measure not used. BARS: measure not used. UKU: The only UKU subscale with significant differences between drugs was the Neurological Side Effects Subscale, on which risperidone scored significantly higher than olanzapine (p = 0.022). Mean (SD) total UKU scores at 6 months: Risperidone (n = 31) 9.6 (6.1) Quetiapine (n = 15) 7.9 (5.4) Olanzapine (n = 14) 7.3 (5.0)
52 weeks	ROSS2003	Olanzapine	AIMS: scores all remained at or close to the minimum values, with no significant differences over the year. SAS: scores all remained at or close to the minimum values, with no significant differences over the year. BARS: scores all remained at or close to the minimum values, with no significant differences over the year. UKU: measure not used.

Table 106: Summary of results for effect of antipsychotic medication on tardive dyskinesia

K = 1; N = 12			
	Study ID	**Intervention**	**Results**
104–208 weeks	KUMRA1998	Clozapine	Of 12 participants who continued to be treated with clozapine at 104 to 208 weeks, one patient at 104 weeks showed evidence of mild tardive dyskinesia.

7.5.6 Clinical evidence for hormonal side effects

Prolactin level (mg per dl)

Three included studies with a total of 313 participants assessed prolactin level in those treated with quetiapine or olanzapine for 12 weeks (SCHIMMELMANN2007) or 26 weeks (AZD1441C00150, DITTMANN2008). A non-significant decrease was observed at 12 weeks in participants treated with quetiapine in SCHIMMELMANN2007; however in AZD1441C00150 an increase was observed at 26 weeks (significance not reported). In DITTMANN2008, 22.9% of participants with possible olanzapine-related emergent adverse effects had increased prolactin levels at 26 weeks. Table 107 provides a summary of reported results.

Thyroid stimulating hormone

Two included studies with a total of 213 participants assessed thyroid stimulating hormone in participants treated with quetiapine for 12 weeks (SCHIMMELMANN2007) or 26 weeks (AZD1441C00150). Quetiapine significantly increased thyroid stimulating hormone at 12 weeks ($p = 0.014$) (SCHIMMELMANN2007) and at 26 weeks (significance not reported) (AZD1441C00150). Table 108 provides a summary of reported results.

7.5.7 Clinical evidence for cardiac side effects

Blood pressure

Two included studies with a total of 231 participants assessed systolic and diastolic blood pressure in participants treated with quetiapine for 12 weeks (SCHIMMELMANN2007) or 26 weeks (AZD1441C00150). Quetiapine increased systolic blood pressure at 12 weeks ($p = ns$) and at 26 weeks (significance not reported). No change in diastolic blood pressure was observed in quetiapine-treated patients at 12 weeks, however an increase was observed at 26 weeks (significance not reported). Table 109 provides a summary of reported results.

Table 107: Summary of results for effect of antipsychotic medication on prolactin level (mg per dl)

K = 3; N = 313			
	Study ID	**Intervention**	**Results**
12 weeks	SCHIMMELMANN2007	Quetiapine	A non-significant decrease in mean (SD) prolactin level was observed: 15.9 (23.3) at baseline to 14.5 (17.9) at 12 weeks.
24–26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was 0.4516 (13.8392) (p value not reported).
	DITTMANN2008	Olanzapine	The % of participants with reported treatment-emergent adverse effects with increased prolactin level at 26 weeks was 25%. Of those with possible olanzapine-related treatment-emergent adverse effects (as judged by a clinician) 22.9% had increased prolactin at 26 weeks.

Table 108: Summary of results for effect of antipsychotic medication on thyroid stimulating hormone (mg per dl)

K = 2; N = 213			
	Study ID	**Intervention**	**Results**
12 weeks	SCHIMMELMANN 2007	Quetiapine	A significant increase in mean (SD) thyroid stimulating hormone was observed: 1.8 (0.7) at baseline to 2.4 (1.5) at 12 weeks (p = 0.014).
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change at 26 weeks from baseline was 0.3223 (1.2095) (p value not reported).

Table 109: Summary of results for effect of antipsychotic medication on blood pressure (mm Hg)

K = 2; N = 231			
	Study ID	**Intervention**	**Results**
12 weeks	SCHIMMELMANN 2007	Quetiapine	A non-significant increase in mean (range) systolic BP was observed: 113 (90–148) at baseline to 117 (90–135) at 12 weeks. No change in mean (range) diastolic BP was observed: 72 (47–100) at baseline to 72 (60–85) at 12 weeks.
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change in suspine systolic BP at 26 weeks from baseline was 0.3 (10.40). Mean (SD) change in standing systolic BP was 1.3 (9.11) (p value not reported). Mean (SD) change in suspine diastolic BP at 26 weeks from baseline was 0.7 (8.96). Mean (SD) change in standing diastolic BP was 1.3 (9.11) (p value not reported).

QTc interval

One study included 118 participants in an analysis of QTc interval in participants treated with quetiapine for 26 weeks (AZD1441C00150). Direction of mean change in QTc interval depended on the clinical correction used. Table 110 provides a summary of reported results.

Table 110: Summary of results for effect of antipsychotic medication on blood pressure (mm Hg)

K = 1; N = 118			
	Study ID	**Intervention**	**Results**
26 weeks	AZD1441C00150	Quetiapine	Mean (SD) change in Fridericia's corrected QTc interval (msec): −0.03 (16.09) and in Bazett's corrected QTc interval (msec): 0.12 (22.69).

7.5.8 Leaving the study early for any reason

The percentage of participants leaving the study early for any reason was reported by four studies (AZD1441C00150, DITTMANN2008, KUMRA1998, ROSS2003) and ranged between 26% at 52 weeks for olanzapine-treated participants and 62% at 24 weeks, also for olanzapine-treated participants (see Table 111).

7.5.9 Clinical evidence summary – evidence for side effects of antipsychotic medication at 12 weeks or more in children and young people

In three RCTs of 95 participants and seven observational studies of 470 participants, the range of side effects of antipsychotic medication at 12 weeks or more on children and young people with psychosis and schizophrenia included metabolic, neurological, hormonal and cardiac function changes. The most consistently reported side effect was weight gain and BMI increase. Several studies have shown this is particularly pronounced in olanzapine-treated patients. Increases to weight and BMI were observed at 12, 26 and 52 weeks. Dropout rates across observational studies were insufficiently reported. Very few studies, all of which were very low quality, mean that it is difficult to draw robust conclusions regarding the long-term harm caused by antipsychotic medication in this age group. Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence identified in children and young people, the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 7.5.10).

7.5.10 Clinical evidence summary – evidence for side effects of antipsychotic medication in adults

The review in the adult *Schizophrenia* guideline (NCCMH, 2010), which pooled data from 138 evaluations of one antipsychotic versus another antipsychotic, did not reveal metabolic and neurological side effects that were inconsistent with those reported in the SPC for each drug (see Section 6.7 of *Schizophrenia*). Because most trials were of relatively short duration and not designed to prospectively examine side effects, these trials provide little insight into the longer-term adverse effects of treatment or whether there are clinically significant differences between antipsychotic drugs.

7.6 HEALTH ECONOMIC EVIDENCE

The systematic search of the economic literature undertaken for this guideline did not identify any eligible studies on pharmacological interventions. The adult *Schizophrenia* guideline (NCCMH, 2010) developed a decision-analytic model to assess the relative cost effectiveness of pharmacological interventions. The model

Table 111: Dropout rates (%): leaving the study early for any reason

Study IDs	Treatment					
	Follow-up (weeks)	Olanzapine	Quetiapine	Risperidone	Clozapine	Haloperidol
AZD1441C00150	26	N/A	38	N/A	N/A	N/A
CASTRO-FORNIELES2008	52	Not reported	Not reported	Not reported	N/A	N/A
CROCQ2007	12	Not reported	N/A	Not reported	N/A	N/A
DITTMANN2008	24	62	N/A	N/A	N/A	N/A
KUMRA1998	108–204	Not reported	N/A	N/A	Not reported	Not reported
ROSS2003	52	26	N/A	N/A	N/A	N/A
SCHIMMELMANN2007	12	N/A	48	N/A	N/A	N/A

particularly focused on antipsychotic medication preventing relapse in people with schizophrenia who were in remission. The model assessed olanzapine, amisulpride, zotepine, aripiprazole, paliperidone, risperidone and haloperidol for the time periods of 10 years and lifetime. The Markov model considered events such as relapse, discontinuation of treatment because of intolerable side effects and switching to another antipsychotic drug, discontinuation of treatment because of other reasons and moving to no treatment, development of side effects such as acute EPS, weight gain, diabetes and glucose intolerance, complications related to diabetes and death.

The model used clinical data from systematic reviews, which also included mixed treatment analysis. The relapse data on zotepine, paliperidone and aripiprazole came from single placebo-controlled trials. The number of QALYs gained was the final outcome measure used in the model. Resource use data were acquired from published resources, supplemented with the expert opinion of the GDG where required, and the analysis was from the perspective of the public and social sector. National UK costs were used in 2007 prices.

The results were presented as estimated ICERs of individual antipsychotic drugs. The deterministic analysis results showed that zotepine dominated all treatments in the 10 years and lifetime horizons. Olanzapine ranked second in terms of cost effectiveness in both time periods of the model. However, if the NHS threshold of £20,000/QALY were increased to £30,000/QALY, paliperidone was the second best cost-effective option over the lifetime period. The results were most sensitive to the probability of relapse.

The probabilistic analysis was carried out to take into account uncertainty associated with the input parameters and the non-linearity characterising the economic model. The cost-effectiveness acceptability curve presented the results of probabilistic analysis with zotepine having highest probability of cost effectiveness. The probability was rather low in the range of 27 to 30%. The probability of cost effectiveness for other antipsychotics ranged from 5% (haloperidol) to 16% (paliperidone). The low level of probabilities indicates substantial uncertainty associated with the economic model, therefore, no one antipsychotic was clearly cost effective when compared with other antipsychotics included in the model.

The economic considerations from *Schizophrenia* (NCCMH, 2010) should be interpreted with caution for children and young people with psychosis and schizophrenia. The pathways of treatment for this population can differ in terms of resource use and cost; for instance the duration of stay in hospital might be longer for children and young people due to the relative lack of alternative intensive or assertive community provision, compared with adults. Nevertheless, the economic considerations from *Schizophrenia* provide useful insights for the treatment of psychosis and schizophrenia in children and young people.

7.7 FROM EVIDENCE TO RECOMMENDATIONS

Symptom reduction is one of the primary efficacy outcomes of interest for antipsychotic medication targeting psychosis and schizophrenia. As symptoms are almost

always accompanied by considerable distress, and because the onset of psychosis and schizophrenia during childhood disrupts social and cognitive development, psychosocial functioning, depression, anxiety and quality of life are also important outcomes to measure when assessing the relative effectiveness of any antipsychotic medication in children and young people.

The evidence for the efficacy of antipsychotic medication in children and young people is comparable to the data obtained in adults and suggests minimal differences between antipsychotic medications for the treatment of first episode psychosis and no differences in efficacy between antipsychotic medications in subsequent acute episodes. Similarly, only small differential effects were found between antipsychotic medication and placebo in participants treated for an acute episode; and in studies investigating the relative efficacy of different doses of antipsychotic medication, there was little evidence to suggest that larger doses resulted in consistently better efficacy outcomes. Where differences between doses were identified, higher doses were favoured over lower doses; however these effects tended to be small in magnitude. Taken together, these data raise at least the possibility that antipsychotics may be less effective in children and young people than in adults.

Evidence drawn from the adult *Schizophrenia* guideline (NCCMH, 2010) demonstrated that clozapine had the most robust evidence for efficacy for people whose illness had not responded adequately to treatment, however for children and young people, the evidence base was extremely small and the data underpowered. Even so, clozapine demonstrated moderately better symptom and global state outcomes over an active comparator. In adults there is evidence for possible benefit of adding a second antipsychotic to clozapine if clozapine alone is ineffective; no such trials have been undertaken in young people. Although clozapine is not licensed in children and young people, few drugs are. Given the relatively small evidence base, which is of low quality, evidence in adults with schizophrenia is the closest proxy for evidence in children and young people with the condition.

Adverse effects (including EPS) and negative effects on metabolic parameters, cardiac function and hormone level were clearly evident across RCTs and observational studies, emphasising the need to routinely monitor side effects associated with antipsychotic medication. However, the paucity of studies and low quality of the evidence results in piecemeal data for any individual antipsychotic.

The most consistent result pertains to weight gain observed in all antipsychotics. Olanzapine resulted in significantly greater weight gain and BMI increase compared with placebo or an active comparator, with moderate to large differential effects observed in participants with first episode psychosis. The differential effect associated with olanzapine was not observed in the head-to-head trials of subsequent acute episodes or in cases of inadequate response; however these trials were small in number and tended to be underpowered.

Minimal differences between different doses of antipsychotic medication as initial treatment, or as treatment for subsequent acute episodes, were observed. Where differences did exist, effect sizes were small to moderate in magnitude; lower doses were favoured over higher doses, indicating the importance of starting on a low dose of medication. This was also specified in the adult *Schizophrenia*

guideline. The significant side effects associated with antipsychotic medication observed in short-term trials (4 to 12 weeks) suggest the need to begin monitoring side effects immediately upon administration; and data from the few longer-term RCTs and observational studies suggest that the side effects observed need to be routinely monitored thereafter as long as the child or young person is taking the medication. Weight gain in particular can increase rapidly within the first month, indicating the need for very close monitoring during this period. The GDG was concerned that the evidence perhaps signalled that side effects such as weight gain and diabetes might be more likely and/or more substantial in children and young people than in adults.

The systematic search of the economic literature undertaken did not identify any eligible studies on pharmacological interventions in children and young people with psychosis and schizophrenia. The GDG therefore considered the decision-analytic model developed for the adult *Schizophrenia* guideline, which assessed the relative cost effectiveness of pharmacological interventions for schizophrenia in adults. The deterministic analysis presented estimated ICERs of individual antipsychotic medication and showed that zotepine dominated all treatments for both time periods of the model (10 years and lifetime). Olanzapine ranked second in terms of cost-effectiveness in both time periods using the NHS threshold of £20,000/QALY; and paliperidone ranked second when the threshold was increased to £30,000/QALY. However, the probabilistic analysis indicated that no antipsychotic was clearly cost effective compared with the other alternatives included in the model. The GDG agreed that any economic considerations for children and young people with psychosis and schizophrenia that used data from the adult *Schizophrenia* guideline should be interpreted carefully due to differences in pathways of treatment. However, it was also agreed that these data may also provide useful insights for children and young people with psychosis and schizophrenia, most notably in the finding that relapse is the major driver of cost in schizophrenia, dwarfing the costs of even the most expensive medication.

Although antipsychotic medication is an important component of treatment and management of psychosis and schizophrenia in children and young people, its evidence base is limited. Moreover, design problems in the individual trials continue to make interpretation of the clinical evidence difficult. Such problems include using available case analysis, unclear reporting or high risk of bias for sequence generation, allocation concealment and blinding procedures, and differences between treatment arms in terms of medication dose.

The GDG considered all the clinical and economic evidence summarised in this section to formulate recommendations. Due to the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence, particularly in cases of inadequate response, the GDG also made judgements by drawing on the existing evidence in adults, and, via the process of informal consensus (detailed in Chapter 3), of its applicability to children and young people. Within this context, it was understood that many of the antipsychotic drugs, in common with most medications used for treating children and young people, have not

been granted a marketing authorisation (product licence) for use in this population and prescribers should be aware of the altered professional responsibility inherent in their use (Paediatric Formulary Committee, 2011; Royal College of Paediatrics and Child Health, 2010).

Overall, the evidence in children and young people with psychosis and schizophrenia, as well as evidence from the adult *Schizophrenia* guideline, does not allow for any general recommendation for one antipsychotic to be preferred over another on clinical or economic grounds. However, there is evidence from *Schizophrenia* that supports the specific recommendation of clozapine for people whose illness does not respond adequately to other antipsychotic medications (the GDG made a further recommendation for research into the clinical effectiveness of clozapine in children and young people who have symptoms of schizophrenia that are not responsive to combined psychological and pharmacological intervention, see Section 7.9). In addition, evidence from the adult *Schizophrenia* guideline suggests that choosing the most appropriate drug and formulation for an individual may be more important than the drug group (FGAs versus SGAs) and the GDG for this guideline agreed that treatment with an antipsychotic in a child or young person with psychosis and schizophrenia should be considered an explicit individual therapeutic trial.

In summary, the GDG decided to recommend antipsychotic medication in combination with psychological interventions for children and young people with psychosis and schizophrenia, for both symptom reduction and relapse prevention. However, the evidence base for this has been predominantly drawn from RCTs conducted in adult populations. The much larger dataset in adults includes high-quality evidence supporting the use of oral antipsychotics to improve symptoms and improve relapse rates, family intervention to reduce relapse rates, and CBT to decrease rehospitalisation and duration of rehospitalisation as well as symptoms. Although the evidence presented in this guideline for children and young people is, in some of these areas, equivocal, the adult evidence is strong enough to maintain the use of a combination of oral antipsychotics, family intervention and CBT as the central treatments in most settings for the first episode and subsequent acute episodes (see recommendation 7.8.1.1 and 7.8.4.1). The GDG wished to emphasise that antipsychotic medication should not be initiated in primary care unless it was done in consultation with a consultant psychiatrist with training in child and adolescent mental health (7.8.1.2).

The GDG highlighted the following key points to be considered before initiating antipsychotic medication. First, the GDG agreed that clinicians should be guided to prescribe in an effective way, displaying caution and sensibility. Therefore, careful explanation, taking account of the age and stage of development of the child or young person, regarding the rationale for antipsychotic medications, their modes of action and possible benefits and side effects, is required (see recommendation 7.8.2.1 and 7.8.7.1). The GDG considered this an important precursor in allowing the child or young person and, where appropriate their parent or carer, to make decisions in

collaboration with the prescriber about antipsychotic medication based on the information provided, including evaluation of side effects and benefits in relation to the child or young person's own individual preferences.

Second, medication should always be started at a low dose, if possible, and following a full discussion of the possible side effects. Starting at a lower dose allows for monitoring of the early emergence of side effects and in this age group the evidence suggests lower doses may be sufficient in terms of efficacy. Doses can be titrated upwards, within the range specified by the *BNF for Children (*BNFC; Paediatric Formulary Committee, 2011) on the understanding that many antipsychotic drugs have not been licensed for use in children and young people and, therefore, the BNF for adults may need to be considered.

In addition, the GDG was particularly concerned that professionals should undertake baseline physical investigations of weight and height, pulse and blood pressure, fasting blood glucose, HbA_1c, blood lipid profile and prolactin levels, and any movement disorder (see recommendation 7.8.3.1). The GDG emphasised that these should continue to be monitored regularly and systematically throughout treatment, as well as efficacy, adherence and physical health (see recommendation 7.8.3.4).

The GDG considered the growing evidence for harmful effects of antipsychotic medications, especially in the young, and took the view that antipsychotics should be reviewed on an annual basis looking at the overall benefits and the incidence and experience of side effects (see recommendation 7.8.3.11), and made a further recommendation for research into the most effective management strategy for preventing the development of excessive weight gain and metabolic syndrome associated with the use of antipsychotic medication in children and young people (see Section 7.9).

In the development of recommendations for the pharmacological treatment and management of psychosis and schizophrenia in children and young people, the GDG also considered the underlying evidence and recommendations in the adult *Schizophrenia* guideline (NCCMH, 2010; NICE, 2009a) and adapted them (see Table 112) based on the methodological principles outlined in Chapter 3. Where recommendations required adaptation, the rationale is provided in the third column. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendations in the *Schizophrenia* guideline (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 7.8 in this guideline.

In adapting recommendations regarding rapid tranquillisation, the GDG was concerned about its use in children and young people and wished to make clear in a new recommendation that healthcare professionals should be trained and competent in undertaking this procedure in children and young people (see recommendation 7.8.5.1).

Table 112: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for pharmacological treatment and management

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.2.4.2 Before starting antipsychotic medication, offer the person with schizophrenia an electrocardiogram (ECG) if: • specified in the SPC a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure) • there is personal history of cardiovascular disease, or • the service user is being admitted as an inpatient.	Before starting antipsychotic medication, offer the child or young person an electrocardiogram (ECG) if: • specified in the SPC for adults and/or children • a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure) • there is a personal history of cardiovascular disease • there is a family history of cardiovascular disease such as premature sudden cardiac death or prolonged QT interval, or • the child or young person is being admitted as an inpatient. (7.8.3.2)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it based on GDG expert opinion to specify that a family history of cardiovascular disease should prompt use of an ECG.
1.2.4.3 Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following: • Record the indications and expected benefits and risks of oral antipsychotic	Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial. Include the following: • From a discussion with the child or young person and their parent or carer,	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it based on GDG expert opinion to take account of special considerations

medication, and the expected time for a change in symptoms and appearance of side effects. • At the start of treatment give a dose at the lower end of the licensed range and slowly titrate upwards within the dose range given in the *British National Formulary* (BNF) or SPC. • Justify and record reasons for dosages outside the range given in the BNF or SPC. • Monitor and record the following regularly and systematically throughout treatment, but especially during titration: – efficacy, including changes in symptoms and behaviour – side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia, for example the overlap between akathisia and agitation or anxiety – adherence – physical health. • Record the rationale for continuing, changing or stopping medication, and the effects of such changes.	record the side effects the child or young person is most and least willing to tolerate. • Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects. • At the start of treatment give a dose below the lower end of the licensed range for adults if the drug is not licensed for children and young people and at the lower end of the licensed range if the drug is licensed for children and young people; slowly titrate upwards within the dose range given in the *British National Formulary* (BNF), the *British National Formulary for Children* (BNFC) or the SPC. • Justify and record reasons for dosages above the range given in the BNF, BNFC or SPC. • Record the rationale for continuing, changing or stopping medication, and the effects of such changes. • Carry out a trial of the medication at optimum dosage for 4–6 weeks. (7.8.3.3)	when prescribing antipsychotic medication in children and young people. A new recommendation was developed for monitoring side effects (see 7.8.3.4). Three specific changes were made in the adaptation of this recommendation. The first bullet point was added because the GDG were concerned about the increased risk, including side effects, associated with the use of antipsychotic medication in children and young people. Although a separate recommendation was developed to ensure the adequate monitoring of side effects, the GDG felt that it was also necessary to alert professionals to the need for regular monitoring in this recommendation. The fourth bullet point was added in line with recommendations from the BNFC. The fourth bullet point of recommendation 1.2.4.3 from *Schizophrenia* on side effects was excluded as the GDG felt that it was more relevant to adults than children and because a separate recommendation had been developed on this issue for children and young people.

Continued

Table 112: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
• Carry out a trial of the medication at optimum dosage for 4–6 weeks.		
1.2.4.4 Discuss any non-prescribed therapies the service user wishes to use (including complementary therapies) with the service user, and carer if appropriate. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological treatments.	Discuss any non-prescribed therapies that children or young people, or their parents or carers, wish to use (including complementary therapies) with them. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological interventions. (7.8.3.5)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.2.4.5 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the service user, and carer if appropriate. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological treatments.	Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the child or young person, and their parents or carers where this has been agreed. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological interventions and the potential of illicit drugs to exacerbate psychotic symptoms. (7.8.3.6)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it because of the GDG's concerns for the potential of illicit drugs to exacerbate psychotic symptoms in children and young people.

1.2.4.6 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 1.2.4.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects each week or as appropriate. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF or SPC.	'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 7.8.3.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects at least weekly. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF, BNFC or SPC. (7.8.3.7)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required other than to limit the review to at least weekly.
1.2.4.7 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').	Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation'). (7.8.3.8)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.2.4.8 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).	Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). (7.8.3.9)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.2.4.9 If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.	If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary. (7.8.3.10)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Continued

Table 112: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.3.2.1 For people with an acute exacerbation or recurrence of schizophrenia, offer oral antipsychotic medication. The choice of drug should be influenced by the same criteria recommended for starting treatment (see Section 1.2.4). Take into account the clinical response and side effects of the service user's current and previous medication.	For children or young people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 7.8.2.1–7.8.3.11). Take into account the clinical response to and side effects associated with current and previous medication, and monitor as described in recommendation 7.8.3.4. (7.8.4.2)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.3.1 Occasionally people with schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. The management of immediate risk should follow the relevant NICE guidelines (see recommendations 1.3.3.2 and 1.3.3.5).	Occasionally children and young people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. Be particularly cautious when considering high-potency antipsychotic medication (such as haloperidol) in children and young	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it based on GDG expert opinion to account for special considerations regarding the use of rapid tranquillisation in children and young people.

	people, especially those who have not taken antipsychotic medication before, because of the increased risk of acute dystonic reactions in that age group. (7.8.5.2)	
1.3.3.3 After rapid tranquillisation, offer the person with schizophrenia the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes.	After rapid tranquillisation, offer the child or young person the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes. (7.8.5.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.5.3 Inform the service user that there is a high risk of relapse if they stop medication in the next 1–2 years.	Inform the child or young person and their parents or carers that there is a high risk of relapse if medication is stopped in the 1–2 years following an acute episode. (7.8.6.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.3.5.4 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse.	If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. (7.8.6.2)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Continued

Table 112: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.3.5.5 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.	After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years. (7.8.6.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.4.4.1 The choice of drug should be influenced by the same criteria recommended for starting treatment (see Section 1.2.4).	**Promoting recovery and providing possible future care in secondary care** The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 7.8.2.1–7.8.3.11). (7.8.7.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.4.4.2 Do not use targeted, intermittent dosage maintenance strategies* routinely. However, consider them for people with schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity. *Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.	Do not use targeted, intermittent dosage maintenance strategies* routinely. However, consider them for children and young people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity. (7.8.7.2) *Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

1.4.6.1 For people with schizophrenia whose illness has not responded adequately to pharmacological or psychological treatment: • review the diagnosis • establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration • review engagement with and use of psychological treatments and ensure that these have been offered according to this guideline. If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for people in close contact with their families • consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.	For children and young people with psychosis and schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions: • review the diagnosis • establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration • review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families • consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. (7.8.8.1)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.
1.4.6.2 Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second-generation antipsychotic.	Offer clozapine to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs each used for 6–8 weeks. (7.8.8.2)	The GDG considered this recommendation to be relevant to the care of children and young people with schizophrenia, and adapted it because the status of ‘atypical’ (as opposed to ‘typical’) and of ‘second-generation’ (as opposed to ‘first generation’) antipsychotics has been questioned. The GDG took the view

Continued

Table 112: (*Continued*)

Original recommendation from *Schizophrenia* (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
		that given the questionable status and the lack of evidence about these classes in the context of inadequate response to treatment, it would be preferable to not specify what class of antipsychotic should be included in the definition of inadequate response. The last sentence is therefore omitted. In addition, the GDG judged that specifying duration for treatment resistance is important because clozapine is often only used after protracted periods of ineffective treatment in children and young people.
1.4.6.3 For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, healthcare professionals should consider recommendation 1.4.6.1 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine.	For children and young people whose illness has not responded adequately to clozapine at an optimised dose, consider a multidisciplinary review, and recommendation 7.8.8.1 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine. (7.8.8.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, with no significant adaptation required.

Finally, a recommendation from NICE technology appraisal guidance 213 *Aripiprazole for the Treatment of Schizophrenia in People Aged 15 to 17 Years* was incorporated (NICE, 2011b), as set out in the scope (see Appendix 1) (see recommendations 7.8.4.3).

7.8 RECOMMENDATIONS

7.8.1 Treatment options for first episode psychosis

7.8.1.1 For children and young people with first episode psychosis offer

- oral antipsychotic medication[100] (see recommendations 7.8.2.1–7.8.3.11) in conjunction with
- psychological interventions (family intervention with individual CBT, delivered as set out in recommendations 6.6.9.3, 6.5.13.3 and 6.8.3.1–6.8.3.5)[101].

7.8.1.2 Antipsychotic medication in children and young people with a first presentation of sustained psychotic symptoms should not be started in primary care unless it is done in consultation with a consultant psychiatrist with training in child and adolescent mental health.

7.8.2 Choice of antipsychotic medication

7.8.2.1 The choice of antipsychotic medication[102] should be made by the parents or carers of younger children, or jointly with the young person and their parents or carers, and healthcare professionals. Provide age-appropriate information and discuss the likely benefits and possible side effects of each drug including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences).

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[100] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[101] This recommendation also appears in Chapter 6 where psychological interventions are reviewed.

[102] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

7.8.3 How to use oral antipsychotic medication

7.8.3.1 Before starting antipsychotic medication[103], undertake and record the following baseline investigations[104]:

- weight and height (both plotted on a growth chart)
- waist and hip circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA_1c), blood lipid profile and prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity.

7.8.3.2 Before starting antipsychotic medication, offer the child or young person an electrocardiogram (ECG) if:

- specified in the SPC for adults and/or children
- a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
- there is a personal history of cardiovascular disease
- there is a family history of cardiovascular disease such as premature sudden cardiac death or prolonged QT interval, or
- the child or young person is being admitted as an inpatient.[105]

7.8.3.3 Treatment with antipsychotic medication[106] should be considered an explicit individual therapeutic trial. Include the following:

- From a discussion with the child or young person and their parent or carer, record the side effects the child or young person is most and least willing to tolerate.
- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose below the lower end of the licensed range for adults if the drug is not licensed for children and young people and at the lower end of the licensed range if the drug is licensed for children and young people; slowly titrate upwards within the dose range

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[103]At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[104]See Table 125 (on page 387) for baseline investigations and monitoring for children and young people who are prescribed antipsychotic medication (read in conjunction with the BNF, BNFC and SPC).

[105]Adapted from *Schizophrenia* (NICE, 2009a).

[106]At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

given in the *British National Formulary* (BNF), the *British National Formulary for Children* (BNFC) or the SPC.

- Justify and record reasons for dosages above the range given in the BNF, BNFC or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks.[107]

7.8.3.4 Monitor and record the following regularly and systematically throughout treatment, but especially during titration[108]:

- efficacy, including changes in symptoms and behaviour
- side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety)
- the emergence of movement disorders
- weight, weekly for the first 6 weeks, then at 12 weeks and then every 6 months (plotted on a growth chart)
- height every 6 months (plotted on a growth chart)
- waist and hip circumference every 6 months (plotted on a percentile chart)
- pulse and blood pressure (plotted on a percentile chart) at 12 weeks and then every 6 months
- fasting blood glucose, HbA_1c, blood lipid and prolactin levels at 12 weeks and then every 6 months
- adherence
- physical health.

The secondary care team should maintain responsibility for monitoring physical health and the effects of taking antipsychotic medication in children and young people for at least the first 12 months or until their condition has stabilised. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements.

7.8.3.5 Discuss any non-prescribed therapies that children or young people, or their parents or carers, wish to use (including complementary therapies) with them. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological interventions.[109]

7.8.3.6 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the child or young person, and their parents or carers where this has been agreed. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological interventions and the potential of illicit drugs to exacerbate psychotic symptoms.[110]

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[107]Adapted from *Schizophrenia* (NICE, 2009a).

[108]See Table 125 (on page 387) for baseline investigations and monitoring for children and young people who are prescribed antipsychotic medication (read in conjunction with the BNF, BNFC and SPC).

[109]Adapted from *Schizophrenia* (NICE, 2009a).

[110]Adapted from *Schizophrenia* (NICE, 2009a).

7.8.3.7 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 7.8.3.3. Review clinical indications, frequency of administration, therapeutic benefits and side effects at least weekly. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF, BNFC or SPC.[111]

7.8.3.8 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').[112]

7.8.3.9 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).[113]

7.8.3.10 If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.[114]

7.8.3.11 Review antipsychotic medication annually, including observed benefits and any side effects.

7.8.4 Subsequent acute episodes of psychosis or schizophrenia

7.8.4.1 For children and young people with an acute exacerbation or recurrence of psychosis or schizophrenia offer:

- oral antipsychotic medication[115] in conjunction with
- psychological interventions (family intervention with individual CBT).[116]

7.8.4.2 For children or young people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication.[117] The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 7.8.2.1–7.8.3.11). Take into account the clinical response to and side effects associated with current and previous medication, and monitor as described in recommendation 7.8.3.4.[118]

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[111]Adapted from *Schizophrenia* (NICE, 2009a).

[112] Adapted from *Schizophrenia* (NICE, 2009a).

[113] Adapted from *Schizophrenia* (NICE, 2009a).

[114]Adapted from *Schizophrenia* (NICE, 2009a).

[115]At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[116]This recommendation also appears in Chapter 6 where the psychological interventions are reviewed.

[117] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[118]Adapted from *Schizophrenia* (NICE, 2009a).

7.8.4.3 Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone. [This recommendation is from *Aripiprazole for the Treatment of Schizophrenia in People Aged 15 to 17 Years* (NICE technology appraisal guidance 213).[119]]

7.8.5 Rapid tranquillisation and restraint

7.8.5.1 Healthcare professionals undertaking rapid tranquillisation and/or restraint in children and young people with psychosis or schizophrenia should be trained and competent in undertaking these procedures in children and young people.

7.8.5.2 Occasionally children and young people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. Be particularly cautious when considering high-potency antipsychotic medication (such as haloperidol) in children and young people, especially those who have not taken antipsychotic medication before, because of the increased risk of acute dystonic reactions in that age group.[120]

7.8.5.3 After rapid tranquillisation, offer the child or young person the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes.[121]

7.8.6 Early post-acute period

7.8.6.1 Inform the child or young person and their parents or carers that there is a high risk of relapse if medication is stopped in the 1–2 years following an acute episode.[122]

7.8.6.2 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse.[123]

7.8.6.3 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.[124]

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[119]NICE, 2011b.
[120]Adapted from *Schizophrenia* (NICE, 2009a).
[121]Adapted from *Schizophrenia* (NICE, 2009a).
[122]Adapted from *Schizophrenia* (NICE, 2009a).
[123]Adapted from *Schizophrenia* (NICE, 2009a).
[124]Adapted from *Schizophrenia* (NICE, 2009a).

7.8.7 Promoting recovery and providing possible future care in secondary care

7.8.7.1 The choice of drug[125] should be influenced by the same criteria recommended for starting treatment (see recommendations 7.8.2.1–7.8.3.11).[126]

7.8.7.2 Do not use targeted, intermittent dosage maintenance strategies[127] routinely. However, consider them for children and young people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity.[128]

7.8.8 Interventions for children and young people whose illness has not responded adequately to treatment

7.8.8.1 For children and young people with psychosis or schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions:

- review the diagnosis
- establish that there has been adherence to antipsychotic medication[129], prescribed at an adequate dose and for the correct duration
- review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families
- consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.[130,131]

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[125]At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[126]Adapted from *Schizophrenia* (NICE, 2009a).

[127]Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.

[128]Adapted from *Schizophrenia* (NICE, 2009a).

[129] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[130]Adapted from *Schizophrenia* (NICE, 2009a).

[131]This recommendation also appears in Chapter 6 where psychological interventions are reviewed.

7.8.8.2 Offer clozapine[132] to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs each used for 6–8 weeks.[133]

7.8.8.3 For children and young people whose illness has not responded adequately to clozapine[134] at an optimised dose, consider a multidisciplinary review, and recommendation 7.8.8.1 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine.[135]

7.9 RESEARCH RECOMMENDATIONS

- What is the clinical effectiveness of clozapine for children and young people with schizophrenia with symptoms unresponsive to antipsychotic medication and psychological treatment combined? (See Appendix 12 for further details.)
- What is the most effective management strategy for preventing the development of excessive weight gain and metabolic syndrome associated with the use of antipsychotic medication in children and young people? (See Appendix 12 for further details.)

[132]At the time of publication, clozapine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[133]Adapted from *Schizophrenia* (NICE, 2009a).

[134]At the time of publication, clozapine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[135]Adapted from *Schizophrenia* (NICE, 2009a).

8 COGNITION, EMPLOYMENT AND EDUCATION

8.1 INTRODUCTION

Education, training and employment are essential components of every child and young person's transition into adulthood, increasing self-esteem, facilitating social inclusion and providing opportunities to engage in meaningful and rewarding activities in a structured way. However, the symptoms of psychosis and schizophrenia, as well as treatment with antipsychotic medication, can interfere with a child or young person's ability to continue attending and engaging with these activities, and, in the longer term, their cognitive function. Some interventions that have attempted to improve cognitive function, such as CRT, have been used to enhance engagement with, and performance in, education and work.

The *Back on Track* (NIACE, 2010) project emphasised the importance of mental health and education services working together to help children and young people with their educational attainment, achievement and performance in school or college. However, health, education and social services are separate public services that frequently operate independently and do not 'join up' to provide early intervention and collaborative care for children and young people with psychosis and schizophrenia. Nevertheless, once a person has an established psychosis, including schizophrenia, they are often not in education or work for some time (NIACE, 2010) unless special efforts to prevent this are put in place at the start. Children and young people with psychosis and schizophrenia find it difficult to get back into education and work once they have been out of it for some time and this can result in high levels of unemployment. Vocational rehabilitation programmes have been developed, such as prevocational training or supported employment, aimed to encourage, support and prepare young people for re-entry into education or employment. Due to limited evidence good practice has developed from consensus opinion (Bertolote & McGorry, 2008; Killackey *et al*., 2010).

This chapter reviews the evidence for CRT and vocational rehabilitation as psychosocial interventions to enhance engagement with, and performance in, education, training or employment.

8.2 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 113. A full review protocol can be found in Appendix 7 and further information about the search strategy can be found in Appendix 8.

Table 113: Clinical review protocol for the review of cognition, employment and education in children and young people with psychosis and schizophrenia

Review question	**RQ C1a**: For children and young people with psychosis and schizophrenia, are there any psychological or psychosocial interventions (CRT) that enhance cognition and/or improve engagement with education/occupational activities?
Objectives	To provide evidence-based recommendations regarding interventions that may enhance cognition or improve engagement with education or occupational activities for children and young people and particularly those from black and minority ethnic groups.
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	• CRT • Psychoeducation • Social skills training
Comparison	Alternative management strategies: • Treatment as usual • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Engagement with education/occupational activities. • Educational attainment • Engagement with mental health services • Cognition (including social cognition)
Secondary outcomes	• Symptoms • Psychosocial functioning
Electronic databases	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases and grey literature (see Appendix 8)

Continued

Table 113: (*Continued*)

Date searched	Systematic reviews: 1995 to May 2012 RCT: inception of databases to May 2012
Study design	RCT, systematic review
Review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and at or under 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25 years, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

8.3 STUDIES CONSIDERED[136]

Two studies (N = 58) providing relevant clinical evidence in children and young people under the age of 18 years and meeting the eligibility criteria for this review were identified (UELAND2004 [Ueland & Rund, 2004], URBEN2012 [Urben

[136] 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).

et al., 2012]). URBEN2012 included children and young people aged 18 years or younger with either a psychotic disorder or at high risk of developing psychosis. In addition, three studies were identified that contained a sample in which some children and young people were over 18, but where the mean age of the total sample was 25 years or under (EACK2009 [Eack *et al.*, 2009], KILLACKEY2008 [Killackey *et al.*, 2008], WYKES2007 [Wykes *et al.*, 2007]). In all other respects, these studies met the eligibility criteria for this review and so were included and data extrapolated. Therefore a total of five RCTs (N = 197) were included in this review. All RCTs were published in peer-reviewed journals between 2004 and 2012. Three studies reported outcomes in sufficient detail to allow for extraction and analysis (EACK2009, KILLACKEY2008, UELAND2004) and additional unpublished data were obtained for a further study (URBEN2012). No RCTs investigating educational or service-level interventions were identified. Further information about included studies can be found in Appendix 13d.

8.4 COGNITIVE REMEDIATION THERAPY

8.4.1 Introduction

Definition

Cognitive remediation therapy (CRT) was defined as:

- an identified procedure that is specifically focused on basic cognitive processes, such as attention, working memory and executive functioning, or
- having the specific intention of bringing about an improvement in social cognition, and
- having the specific intention of bringing about an improvement in the level of performance on that specified cognitive function or other functions, including daily living, educational, social or vocational skills.

8.4.2 Studies considered

Studies considered relevant to the review of CRT included one RCT of cognitive enhancement therapy (CRT [computer-based neurocognitive training] and group-based social cognition therapy) versus psychoeducation (EACK2009); one RCT of CRT (focused computer-based) versus psychoeducation (UELAND2004); one RCT of CRT versus treatment as usual in the UK (WYKES2007); and one RCT of CRT (focused computer assisted) versus computer games (URBEN2012) (see Table 114 for a summary of the study characteristics). EACK2009 described its experimental and control interventions as 'cognitive enhancement therapy' and 'enrichment supportive therapy' but the GDG judged the procedures and intentions of these treatments to be sufficiently similar to CRT to include this study in the analysis of CRT versus psychoeducation. URBEN2012 included a mixed sample of 21 participants with psychotic disorders and 11 participants at high risk of psychosis.

Table 114: Study information table for trials of CRT

	Cognitive enhancement therapy (CRT and group group-based social cognition therapy) versus psychoeducation	**CRT versus psychoeducation**	**CRT versus treatment as usual**	**CRT versus computer games**
Total no. of studies (N)	1 (N = 58)	1 (N = 26)	1 (N = 40)	1 (N = 32)
Study ID	EACK2009*	UELAND2004*	WYKES2007	URBEN2012*
Diagnosis	Schizophrenic disorder (stable)	Psychosis mixed (including bipolar disorder)	Schizophrenic disorder	Psychosis (n = 21) or at high risk of psychosis (n = 11)
Mean age	25.9	15.3	18.2	15.5
Sex (% male)	69	54	65	64
Ethnicity (% white)	69	Not reported	Not reported	Not reported
Treatment length (weeks)	104	26	14	8
Length of follow-up (weeks)	N/A	52	26	26
Setting	Outpatient	Inpatient	Inpatient	Day care unit
Country	US	Norway	UK	Switzerland

Note. *Extractable outcomes

8.4.3 Cognitive enhancement therapy versus psychoeducation

One study (EACK2009) reported outcomes for cognitive enhancement therapy versus psychoeducation at 104 weeks post-treatment. The sample included young people with a mean age of 25.9 years; the treatment consisted of computer-based CRT and also contained a large social cognition component (45 sessions of social-cognitive group sessions) and lasted for 2 years. Moderate to large differential effects favouring cognitive enhancement therapy were found for total psychotic symptoms (SMD = −0.72; 95% CI, −1.25 to −0.19), negative symptoms (SMD = − 0.96; 95% CI, −1.51 to −0.41), psychosocial functioning (SMD = −0.86; 95% CI, −1.41, to −0.32) and social cognition (SMD = −1.20; 95% CI, −1.76 to −0.64). Furthermore, at 2 years post-treatment significantly more participants receiving cognitive enhancement therapy (13 out of 31) than enrichment supportive therapy (four out of 27) were actively engaged in paid, competitive employment (assuming dropouts did not gain employment, RR = 2.83; 95% CI, 1.05 to 7.65; see Appendix 14d [3.6]). No significant effect was found for leaving the study early for any reason. Evidence from each reported outcome and overall quality of evidence are presented in Table 115; the full evidence profiles can be found in Appendix 17d.

8.4.4 CRT versus psychoeducation

One study (UELAND2004) reported outcomes for CRT versus psychoeducation in children and young people 18 years or younger at 26 and 52 weeks. No significant effects were found for psychotic symptoms and psychosocial functioning at 6 months post-treatment (see Table 116) or 1 year's follow-up (see Table 117). Data pertaining to participant discontinuation were not reported. The full evidence profiles can be found in Appendix 17d.

8.4.5 CRT versus treatment as usual

One study compared CRT with treatment as usual in the UK in children and young people aged 25 years or younger (WYKES2007). Efficacy data could not be extracted for this study. However, the authors reported that there were no between group differences on cognitive outcomes. Similarly, there was no evidence for an effect of CRT on psychotic symptoms, quality of life or social functioning; however, this intervention was not designed to directly target these outcomes. At 14 weeks post-treatment, dropout was similar between groups (RR = 1.03; 95% CI, 0.75 to 1.40) and this remained at 26 weeks' follow-up (RR = 0.97; 95% CI, 0.69 to 1.35). Evidence from each reported outcome and overall quality of evidence are presented in Table 118 and Table 119; the full evidence profiles can be found in Appendix 17d.

Table 115: Summary of findings table for outcomes reported for cognitive enhancement therapy (CRT and group-based social cognition therapy) versus psychoeducation at 104 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	EACK2009	K = 1, N = 58	−0.72 [−1.25, −0.19]*	N/A	Low[1, 2]	Appendix 14d (3.2)
Negative symptoms (SMD)	EACK2009	K = 1, N = 58	−0.96 [−1.51, −0.41]*	N/A	Low[1, 2]	Appendix 14d (3.3)
Anxiety/depression (SMD)	EACK2009	K = 1, N = 58	−0.41 [−0.93, 0.11]	N/A	Low[1, 2]	Appendix 14d (3.1)
Psychosocial functioning(SMD)	EACK2009	K = 1, N = 58	−0.86 [−1.41, −0.32]*	N/A	Low[1, 2]	Appendix 14d (3.4)
Social cognition (SMD)	EACK2009	K = 1, N = 58	−1.20 [−1.76, −0.64]*	N/A	Low[1, 2]	Appendix 14d (3.5)
Sensitivity analysis: employment (assuming dropouts did not gain employment; RR)	EACK2009	K = 1, N = 58	2.83 [1.05, 7.65]*	N/A	Low[1, 2]	Appendix 14d (3.6)
Leaving study early for any reason (RR)	EACK2009	K = 1, N = 58	1.22 [0.44, 3.40]	N/A	Low[1, 2]	Appendix 14d (3.7)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours CRT.
[1]Serious risk of bias (including unclear allocation concealment, unblind raters).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 116: Summary of findings table for outcomes reported for CRT versus psychoeducation at 26 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	UELAND2004	K = 1, N = 25	−0.19 [−0.98, 0.60]	N/A	Low[1,2]	Appendix 14d (1.1)
Positive symptoms (SMD)	UELAND2004	K = 1, N = 25	−0.33 [−1.13, 0.47]	N/A	Low[1,2]	Appendix 14d (1.2)
Negative symptoms (SMD)	UELAND2004	K = 1, N = 25	−0.17 [−0.96, 0.62]	N/A	Low[1,2]	Appendix 14d (1.3)
Psychosocial functioning (SMD)	UELAND2004	K = 1, N = 26	−0.46 [−1.24, 0.32]	N/A	Low[1,2]	Appendix 14d (1.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, unblind raters, trial registration not found, available case analysis used and dropout not reported by group).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 117: Summary of findings table for outcomes reported for CRT versus psychoeducation at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	UELAND2004	K = 1, N = 24	−0.40 [−1.22, 0.42]	N/A	Low[1, 2]	Appendix 14d (2.1)
Positive symptoms (SMD)	UELAND2004	K = 1, N = 24	−0.35 [−1.17, 0.47]	N/A	Low[1, 2]	Appendix 14d (2.2)
Negative symptoms (SMD)	UELAND2004	K = 1, N = 24	−0.66 [−1.50, 0.17]	N/A	Low[1, 2]	Appendix 14d (2.3)
Psychosocial functioning(SMD)	UELAND2004	K = 1, N = 25	−0.15 [−0.94, 0.64]	N/A	Low[1, 2]	Appendix 14d (2.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, unblind raters, trial registration not found, available case analysis used and dropout not reported by group).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 118: Summary of findings table for outcomes reported for CRT versus treatment as usual at 14 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Leaving study early for any reason (RR)	WYKES2007	K = 1, N = 40	1.03 [0.75, 1.40]	N/A	Low[1, 2]	Appendix 14d (4.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, unable to find trial registration, LOCF reported but high dropout).
[2] OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 119: Summary of findings table for outcomes reported for CRT versus treatment as usual at 26 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Leaving study early for any reason (RR)	WYKES2007	K = 1, N = 40	0.97 [0.69, 1.35]	N/A	Low[1, 2]	Appendix 14d (5.1)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation, unable to find trial registration, LOCF reported but high dropout).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

8.4.6 CRT versus computer games

One study compared a programme of computer-assisted CRT (involving training in attention, concentration, memory, conceptualisation, and visuospatial and visuomotor skills) with computer games (requiring the use of attention and visuomotor skills) in children and young people aged 18 years or younger with psychotic disorders or at high risk of developing psychosis (URBEN2012).

At 8 weeks post-treatment CRT was found to be no more effective at improving psychotic symptoms, global state or social functioning than computer games. Furthermore, at 26 weeks' follow-up there were no significant between group differences in global state or dropout (RR = 1.17; 95% CI, 0.41 to 3.35). Of the 22 participants for whom follow-up data were available, 16 had a psychotic disorder and six were at risk of developing psychosis. No data pertaining to transition to psychosis were reported. Evidence from each reported outcome and overall quality of evidence are presented in Table 120 and Table 121. The full evidence profiles can be found in Appendix 17d.

8.4.7 Clinical evidence summary – evidence for children and young people

In four RCTs, with a total of 156 participants with psychosis and schizophrenia the evidence for CRT was limited. One small RCT of 'cognitive enhancement therapy', which consisted of computer-based CRT and group-based social cognition therapy, found moderate effects favouring cognitive enhancement therapy over psychoeducation on symptoms, psychosocial functioning and social cognition. In addition, participants in the cognitive enhancement therapy group were almost three times more likely to be actively engaged in competitive employment than those in the psychoeducation group (EACK2009). However, the results of a second small study of CRT as a supplement to psychoeducation in children and young people aged 18 years or younger suggested that in this age group the remediation programme does not add any benefit over and above the psychoeducational approach. Similarly, CRT was not found to be more beneficial than playing computer games for children and young people aged 18 years or younger with psychosis or at high risk of developing it. Overall, the paucity and low quality of evidence means it is difficult to draw robust conclusions about the efficacy of CRT in this population.

Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence identified in children and young people, the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 8.4.8).

8.4.8 Clinical evidence summary – evidence for adults

In the six RCTs (out of 17 included in the meta-analysis in the adult *Schizophrenia* guideline [NCCMH, 2010]) that reported cognitive outcomes at follow-up, there was limited evidence that CRT produced sustained benefits in terms of cognition (see

Table 120: Summary of findings table for outcomes reported for CRT versus computer games at 8 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Total symptoms (SMD)	URBEN2012	K = 1, N = 28	0.26 [−0.49, 1.00]	N/A	Very low[1, 2, 3]	Appendix 14d (6.1)
Positive symptoms (SMD)	URBEN2012	K = 1, N = 28	0.35 [−0.39, 1.10]	N/A	Very low[1, 2, 3]	Appendix 14d (6.2)
Negative symptoms (SMD)	URBEN2012	K = 1, N = 28	0.29 [−0.46, 1.04]	N/A	Very low[1, 2, 3]	Appendix 14d (6.3)
General symptoms (SMD)	URBEN2012	K = 1, N = 28	0.23 [−0.52, 0.97]	N/A	Very low[1, 2, 3]	Appendix 14d (6.4)
Global state (severity) (SMD)	URBEN2012	K = 1, N = 28	0.21 [−0.53, 0.96]	N/A	Very low[1, 2, 3]	Appendix 14d (6.5)
Social functioning	URBEN2012	K = 1, N = 28	0.31 [−0.44, 1.06]	N/A	Very low[1, 2, 3]	Appendix 14d (6.6)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment unblind raters, trial registration not found, available case analysis used).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (as sample contains participants at serious risk of psychosis).

Table 121: Summary of findings table for outcomes reported for CRT versus computer games at 26 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Global state (SMD)	URBEN 2012	K = 1, N = 22	0.60 [–0.27, 1.46]	N/A	Very low[1, 2, 3]	Appendix 14d (7.1)
Leaving study early for any reason (RR)	URBEN 2012	K = 1, N = 32	1.17 [0.41, 3.35]	N/A	Very low[1, 2, 3]	Appendix 14d (7.2)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment unblind raters, trial registration not found, available case analysis used).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3]Serious risk of indirectness (as sample contains participants at serious risk of psychosis).

Section 8.5 of *Schizophrenia*). However, these effects were driven primarily by two studies (Hogarty *et al*, 2004; Penadés *et al*., 2006); therefore, sensitivity analyses were used to explore how robust the findings were. Removal of these studies led to the loss of effects for all but one cognitive domain (reasoning and problem solving).

There was limited evidence suggesting that CRT might improve social functioning when compared with standard care. However, this effect was driven by a range of studies conducted by Velligan and colleagues (Velligan *et al*., 2000, 2002, 2008a and 2008b), in which the intervention was more comprehensive than typical CRT programmes in the UK, and included the use of individually tailored environmental supports to ameliorate areas in addition to basic cognitive functions. The UK-based studies, although well-conducted, did not report evidence of improvement in social or vocational functioning or symptoms at either end of treatment or follow-up. Overall, there was no consistent evidence that CRT alone is effective in improving the critical outcomes, including relapse rates, rehospitalisation, mental state and quality of life. Furthermore, where effects of treatment were found, the evidence is difficult to interpret as many studies report non-significant findings without providing appropriate data for the meta-analysis. Therefore the magnitude of the effect is likely to be overestimated for all outcomes.

8.5 VOCATIONAL REHABILITATION

8.5.1 Introduction

Definitions

For this review, the GDG used the following definitions:

- Prevocational training is defined as any approach to vocational rehabilitation in which participants are expected to undergo a period of preparation before being

encouraged to seek competitive employment. This preparation phase could involve either work in a sheltered environment (such as a workshop or work unit) or some form of pre-employment training or transitional employment. This included both traditional (sheltered workshop) and 'clubhouse' approaches.

- Supported employment is any approach to vocational rehabilitation that attempts to place service users in competitive employment immediately. It was acceptable for supported employment to begin with a short period of preparation, but this had to be of less than 1 month's duration and not involve work placement in a sheltered setting, training or transitional employment.
- Modifications of vocational rehabilitation programmes are defined as either prevocational training or supported employment that has been enhanced by some technique to increase participants' motivation. Typical techniques consist of payment for participation in the programme or some form of psychological intervention.
- Standard care is defined as the usual psychiatric care for participants in the trial without any specific vocational component. In all trials where an intervention was compared with standard care, unless otherwise stated, participants would have received the intervention in addition to standard care. Thus, for example, in a trial comparing prevocational training and standard community care, participants in the prevocational training group would also have been in receipt of standard community services, such as outpatient appointments.

8.5.2 Studies considered

One study (N = 41) compared individual placement and support (IPS) plus treatment as usual in a specialised centre, EPPIC, in Australia with EPPIC treatment as usual (KILLACKEY2008). IPS was defined by the authors as a highly defined form of supported employment. However, treatment as usual was also very comprehensive and included individual case management and medical review, referral to external vocational agencies, as well as involvement with the group programme at EPPIC, which might have involved participation in the vocationally oriented groups within the group programme (see Table 122 for a summary of the study characteristics).

8.5.3 Individual placement and support versus EPPIC treatment as usual

At 26 weeks post-treatment significantly more participants in the IPS group (13 out of 20) compared with the EPPIC treatment as usual group (two out of 21) had found a job, enrolled in a course or done both (RR = 6.83; 95% CI, 1.76 to 26.51; see Appendix 14d [8.1]). Furthermore, of the fifteen individuals who gained employment those in the IPS group worked significantly more weeks (SMD = −0.49; 95% CI, −1.99 to 1.02) but not significantly more hours per week (SMD = −0.71; 95% CI, −2.22 to 0.81). Finally, one participant in the IPS group compared with five

Table 122: Study information table for trials comparing individual placement and support with EPPIC treatment as usual

	IPS versus EPPIC treatment as usual
Total no. of studies (N)	1 (N = 41)
Study ID	KILLACKEY2008*
Diagnosis	First episode schizophrenic disorder
Mean age	21.4
Sex (% male)	81
Ethnicity (% white)	Not reported
Treatment length (weeks)	26
Length of follow-up (weeks)	N/A
Setting	Specialist centre
Country	Australia
Note. *Extractable outcomes	

participants in the EPPIC treatment as usual group dropped out; however, this difference was not statistically significant (RR = 0.21; 95% CI, 0.03 to 1.64; see Appendix 14d [8.5]). Evidence from each reported outcome and overall quality of evidence are presented in Table 123. The full evidence profiles can be found in Appendix 17d.

8.5.4 Clinical evidence summary – evidence for children and young people

No RCTs in children and young people aged 18 years or younger were identified. There is limited evidence from one RCT (N = 41) in Australia that a highly defined form of supported employment is superior to a very comprehensive treatment as usual, in helping children and young people aged 25 years or younger either gain employment or enrol on a course. Overall, the paucity and low quality of evidence means it is difficult to draw robust conclusions about the efficacy of vocational interventions in this population.

Given the starting point for this guideline ('Are there grounds for believing that treatment in children and young people should be any different from adults?'), as well as the paucity and low quality of the evidence identified in children and young people, the GDG decided to also draw on the existing evidence in adults, a summary of which can be found below (see Section 8.5.5).

Table 123: Summary of findings table for outcomes reported for IPS versus EPPIC treatment as usual at 26 weeks post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero-geneity	Quality of evidence (GRADE)[a]	Forest plot
Sensitivity analysis: employed/ enrolled on a course (assuming dropouts did not gain employment; RR)	KILLACKEY 2008	K = 1, N = 41	6.83 [1.76, 26.51]*	N/A	Low[1, 2]	Appendix 14d (8.1)
Number of weeks worked (SMD)	KILLACKEY 2008	K = 1, N = 15	– 0.49 [–1.99, 1.02]	N/A	Low[1, 2]	Appendix 14d (8.2)
Number of hours worked per week (SMD)	KILLACKEY 2008	K = 1, N = 15	– 0.71 [–2.22, 0.81]	N/A	Low[1, 2]	Appendix 14d (8.3)
Leaving the study early for any reason (RR)	KILLACKEY 2008	K = 1, N = 41	0.21 [0.03, 1.64]*	N/A	Low[1, 2]	Appendix 14d (8.4)

Note. [a]The GRADE approach was used to grade the quality of evidence for each outcome, see Section 3.5.5 for further detail.
*Favours IPS.
[1]Serious risk of bias (including inadequate allocation concealment, unclear rater blinding, more people in the treatment as usual group were in marital or marital-like relationships tending to bias the study against finding success for the vocational intervention because people in marital relationships tend to function better socially and in employment).
[2]OIS (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

8.5.5 Clinical evidence summary – evidence for adults

In the adult *Schizophrenia* guideline (NCCMH, 2010) a Cochrane review (Crowther *et al*., 2001) of 18 RCTs was updated with two RCTs (Mueser *et al*., 2004, Lehman *et al*., 2002[137]). There was evidence from studies in the US to suggest that supported employment is superior to prevocational training programmes in helping people with serious mental health problems gain competitive employment (see Section 9.6 of *Schizophrenia*).

8.6 EDUCATION

8.6.1 Introduction

'Enjoying and achieving', 'making a positive contribution' and 'economic wellbeing' are three of the five aims set by the *Every Child Matters* agenda (Boateng, Chief Secretary to the Treasury, 2003). Regardless of medical needs, all children of compulsory school age should receive appropriate education (Department for Education and Skills, 2001a). Children with early onset psychosis may be considered to have special educational needs and require individual educational planning[138]. Request for an assessment of special educational needs may take up to 26 weeks once an educational authority has agreed to the assessment (Department for Children, Schools & Families, 2009). In the initial stage of illness there may not be enough information about any change in the child's educational performance for the educational authority to make a decision to assess a child. However, diagnosis and liaison with the child's school and education authority should occur to ensure a plan is put in place to meet their needs. Baseline assessments can be useful so that the child or young person's educational progress can be tracked and evidenced to enable appropriate planning.

8.6.2 Studies considered

No RCTs investigating educational interventions were identified. Therefore recommendations were developed through GDG consensus.

8.7 FROM EVIDENCE TO RECOMMENDATIONS

Due to the paucity and low quality of the evidence for CRT as an intervention for enhancing cognition in children and young people with psychosis and schizophrenia, it is difficult to draw any conclusions and therefore make any recommendations for CRT.

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[137] Unpublished data only.

[138]Codes of practice for special educational needs differ in England and Wales. For England, refer to: *Special Educational Needs: Code of Practice (*Department for Education and Skills, 2001b). For Wales, refer to: *Special Educational Needs: Code of Practice for Wales* (Welsh Assembly Government, 2004b).

There is some low quality evidence that supported employment has a beneficial effect in helping young people aged under 25 years to gain employment or to enrol on a course; but this evidence alone is insufficient to make a recommendation. However, evidence from the adult *Schizophrenia* guideline (NCCMH, 2010) suggests that supported employment in the US is clearly superior to prevocational training programmes; and on the balance of this evidence the GDG decided to adapt the recommendations in *Schizophrenia* (NICE, 2009a) regarding supported employment and the related good practice points (see Table 124) for use in this guideline based on the methodological principles outlined in Chapter 3. Where recommendations required adaptation, the rationale is provided in the third column. Where the only adaptation was to change 'service users' to 'children and young people with psychosis or schizophrenia' or 'families and carers' to 'parents and carers' this is noted in the third column as 'no significant adaptation required'. In column 1 the numbers refer to the recommendation numbers in the *Schizophrenia* guideline (NICE, 2009a). In column 2 the numbers in brackets following the recommendation refer to Section 8.8 in this guideline.

The GDG also consulted a special adviser to provide input on education, employment and occupational activities in children and young people with psychosis and schizophrenia based on their expert knowledge in this area. Due to the lack of evidence, recommendations were developed by consensus. It was agreed that children and young people should be maintained within education and additional educational support should be provided if their performance has been affected. During first episode psychosis and where children and young people are unable to attend school or college, alternative educational input, commensurate with their capacity to engage with educational activity, should be sought (see recommendation 8.8.2.1).

Additionally, liaison between mental health services, the school and parents or carers is required to assess the child or young person's special educational needs (see recommendations 8.8.1.1, 8.8.3.1 and 8.8.3.2). If it is agreed that this is needed, the health and social care professionals should explain to the parents or carers how to apply for this assessment and support the parents or carers and child or young person through this process.

8.8 RECOMMENDATIONS

8.8.1 General principles of care

8.8.1.1 Help the child or young person to continue their education. Contact the school or college, subject to consent, to ask for additional educational support if their performance has been affected by their condition.

8.8.2 Assessment and care planning in secondary care

8.8.2.1 For children and young people with first episode psychosis who are unable to attend mainstream school or college, facilitate alternative educational input

Table 124: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for education and employment programmes

Original recommendation from Schizophrenia (NICE, 2009a)	Recommendation following adaptation for this guideline	Reasons for adaptation
1.4.7.1 Supported employment programmes should be provided for those people with schizophrenia who wish to return to work or gain employment. However, they should not be the only work-related activity offered when individuals are unable to work or are unsuccessful in their attempts to find employment.	Provide supported employment programmes for those young people with psychosis or schizophrenia above compulsory school age who wish to return to work or find employment. Consider other work-related activities and programmes when individuals are unable to work or are unsuccessful in their attempts to find employment. (8.8.3.3)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis and schizophrenia, and adapted it to conform with changes to NICE style for recommendations.
1.4.7.2 Mental health services should work in partnership with local stakeholders, including those representing BME [black and minority ethnic] groups, to enable people with mental health problems, including schizophrenia, to access local employment and educational opportunities. This should be sensitive to the person's needs and skill level and is likely to involve working with agencies such as Jobcentre Plus, disability employment advisers and non-statutory providers.	Mental health services should work in partnership with local stakeholders, including those representing black and minority ethnic groups, to enable young people with psychosis or schizophrenia to access local employment and educational opportunities. This should be sensitive to the young person's needs and skill level and is likely to involve working with agencies such as Jobcentre Plus, disability employment advisers and non-statutory providers. (8.8.3.4)	The GDG considered this recommendation to be relevant to the care of young people with psychosis or schizophrenia, with no significant adaptation required.
1.4.7.3 Routinely record the daytime activities of people with schizophrenia in their care plans, including occupational outcomes.	Routinely record the daytime activities of children and young people with psychosis or schizophrenia in their care plans, including educational and occupational outcomes. (8.8.3.5)	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or schizophrenia, with no significant adaptation required.

in line with their capacity to engage with educational activity and according to their individual needs, with an ultimate goal of returning to mainstream education, training or employment.

8.8.3 Education, employment and occupational activities

8.8.3.1 For children and young people of compulsory school age, liaise with the child or young person's school and educational authority, subject to consent, to ensure that ongoing education is provided.

8.8.3.2 Liaise with the child or young person's school and with their parents or carers, subject to consent, to determine whether a special educational needs assessment is necessary. If it is agreed that this is needed, explain to parents or carers how to apply for an assessment and offer support throughout the process.

8.8.3.3 Provide supported employment programmes for those young people with psychosis or schizophrenia above compulsory school age who wish to return to work or find employment. Consider other work-related activities and programmes when individuals are unable to work or are unsuccessful in their attempts to find employment.[139]

8.8.3.4 Mental health services should work in partnership with local stakeholders, including those representing black and minority ethnic groups, to enable young people with psychosis or schizophrenia to access local employment and educational opportunities. This should be sensitive to the young person's needs and skill level and is likely to involve working with agencies such as Jobcentre Plus, disability employment advisers and non-statutory providers.[140]

8.8.3.5 Routinely record the daytime activities of children and young people with psychosis or schizophrenia in their care plans, including educational and occupational outcomes.[141]

[139] Adapted from *Schizophrenia* (NICE, 2009a).
[140] Adapted from *Schizophrenia* (NICE, 2009a).
[141] Adapted from *Schizophrenia* (NICE, 2009a).

9 SUMMARY OF RECOMMENDATIONS

9.1 GENERAL PRINCIPLES OF CARE

Working safely and effectively with children and young people

9.1.1.1 Health and social care professionals working with children and young people with psychosis or schizophrenia should be trained and competent to work with children and young people with mental health problems of all levels of learning ability, cognitive capacity, emotional maturity and development.

9.1.1.2 Health and social care professionals should ensure that they:

- can assess capacity and competence, including 'Gillick competence', in children and young people of all ages, and
- understand how to apply legislation, including the Children Act (1989; amended 2004)[142], the Mental Health Act (1983; amended 1995 and 2007[143,144]) and the Mental Capacity Act (2005)[145], in the care and treatment of children and young people.

9.1.1.3 Consider children and young people with psychosis or schizophrenia for assessment according to local safeguarding procedures if there are concerns regarding exploitation or self-care, or if they have been in contact with the criminal justice system.[146]

9.1.1.4 Health and social care providers should ensure that children and young people with psychosis or schizophrenia:

- can routinely receive care and treatment from a single multidisciplinary community team
- are not passed from one team to another unnecessarily
- do not undergo multiple assessments unnecessarily.[147]

9.1.1.5 Help the child or young person to continue their education. Contact the school or college, subject to consent, to ask for additional educational support if their performance has been affected by their condition.

Establishing relationships with children and young people and their parents or carers

9.1.1.6 Work in partnership with children and young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity and parents or carers. Offer help, treatment and

[142] HMSO, 2004.
[143] HMSO, 2007.
[144] Including the Code of Practice: Mental Health Act 1983 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_084597)
[145] HMSO, 2005.
[146] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[147] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

care in an atmosphere of hope and optimism. Take time to build trusting, supportive, empathic and non-judgemental relationships as an essential part of care.[148]

9.1.1.7 When working with children and young people with psychosis or schizophrenia:

- aim to foster autonomy, promote active participation in treatment decisions, and support self-management and access to peer support in children and young people of an appropriate developmental level, emotional maturity and cognitive capacity
- maintain continuity of individual therapeutic relationships wherever possible
- offer access to a trained advocate.[149]

9.1.1.8 When working with children and young people with psychosis or schizophrenia and their parents or carers:

- make sure that discussions take place in settings in which confidentiality, privacy and dignity are respected
- be clear with the child or young person and their parents or carers about limits of confidentiality (that is, which health and social care professionals have access to information about their diagnosis and its treatment and in what circumstances this may be shared with others).[150]

9.1.1.9 Discuss with young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity how they want their parents or carers to be involved in their care. Such discussions should take place at intervals to take account of any changes in circumstances, including developmental level, and should not happen only once.[151]

9.1.1.10 Advise parents and carers about their right to a formal carer's assessment of their own physical and mental health needs, and explain how to access this.[152]

Communication and information

9.1.1.11 Health and social care professionals working with children and young people with psychosis or schizophrenia should be trained and skilled in:

- negotiating and working with parents and carers, and
- managing issues relating to information sharing and confidentiality as these apply to children and young people.

9.1.1.12 If a young person is 'Gillick competent' ask them what information can be shared before discussing their condition and treatment with their parents or carers.

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[148] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[149] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[150] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[151] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[152] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

9.1.1.13 When communicating with children and young people with psychosis or schizophrenia and their parents or carers:
- take into account the child or young person's developmental level, emotional maturity and cognitive capacity including any learning disabilities, sight or hearing problems or delays in language development
- use plain language where possible and clearly explain any clinical language
- check that the child or young person and their parents or carers understand what is being said
- use communication aids (such as pictures, symbols, large print, braille, different languages or sign language) if needed.

9.1.1.14 Provide children and young people with psychosis or schizophrenia and their parents or carers, comprehensive written information about:
- the nature of, and interventions for, psychosis and schizophrenia (including biomedical and psychosocial perspectives on causes and treatment) in an appropriate language or format, including any relevant 'Information for the public' booklets
- support groups, such as third sector, including voluntary, organisations.[153]

9.1.1.15 Ensure that you are:
- familiar with local and national sources (organisations and websites) of information and/or support for children and young people with psychosis or schizophrenia and their parents or carers
- able to discuss and advise how to access these resources
- able to discuss and actively support children and young people and their parents or carers to engage with these resources.[154]

9.1.1.16 When communicating with a child or young person with psychosis or schizophrenia, use diverse media, including letters, phone calls, emails or text messages, according to their preference.[155]

9.1.1.17 Copy all written communications with other health or social care professionals to the child or young person and/or their parents or carers at the address of their choice, unless this is declined.[156]

Culture, ethnicity and social inclusion

9.1.1.18 When working with children and young people with psychosis or schizophrenia and their parents or carers:
- take into account that stigma and discrimination are often associated with using mental health services
- be respectful of and sensitive to children and young people's gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability

[153] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[154] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[155] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[156] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

- be aware of possible variations in the presentation of mental health problems in children and young people of different genders, ages, cultural, ethnic, religious or other diverse backgrounds.[157]

9.1.1.19 When working with children and young people and their parents or carers who have difficulties speaking or reading English:

- provide and work proficiently with interpreters if needed
- offer a list of local education providers who can provide English language teaching.

9.1.1.20 Health and social care professionals working with children and young people with psychosis or schizophrenia and their parents or carers should have competence in:

- assessment skills for people from diverse ethnic and cultural backgrounds
- using explanatory models of illness for people from diverse ethnic and cultural backgrounds
- explaining the possible causes of psychosis and schizophrenia and treatment options
- addressing cultural and ethnic differences in treatment expectations and adherence
- addressing cultural and ethnic differences in beliefs regarding biological, social and family influences on the possible causes of mental health problems
- conflict management and conflict resolution.[158]

9.1.1.21 Health and social care professionals inexperienced in working with children and young people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds, and their parents or carers, should seek advice and supervision from healthcare professionals who are experienced in working transculturally.[159]

9.1.1.22 Local mental health services should work with primary care, other secondary care and local third sector, including voluntary, organisations to ensure that:

- all children and young people with psychosis or schizophrenia have equal access to services based on clinical need and irrespective of gender, sexual orientation, socioeconomic status, age, background (including cultural, ethnic and religious background) and any disability
- services are culturally appropriate.[160]

9.1.1.23 Mental health services should work with local voluntary black and minority ethnic groups to jointly ensure that culturally appropriate psychological and psychosocial treatment, consistent with this guideline and delivered by competent practitioners, is provided to children and young people from diverse ethnic and cultural backgrounds.[161]

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[157] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[158] Adapted from *Schizophrenia* (NICE, 2009a).
[159] Adapted from *Schizophrenia* (NICE, 2009a).
[160] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[161] Adapted from *Schizophrenia* (NICE, 2009a).

Transfer and discharge

9.1.1.24 Anticipate that withdrawal and ending of treatments or services, and transition from one service to another, may evoke strong emotions and reactions in children and young people with psychosis or schizophrenia and their parents or carers. Ensure that:

- such changes, especially discharge and transfer from CAMHS to adult services, or to primary care, are discussed and planned carefully beforehand with the child or young person and their parents or carers, and are structured and phased
- the care plan supports effective collaboration with social care and other care providers during endings and transitions, and includes details of how to access services in times of crisis
- when referring a child or young person for an assessment in other services (including for psychological interventions), they are supported during the referral period and arrangements for support are agreed beforehand with them.[162]

9.2 POSSIBLE PSYCHOSIS

Referral from primary care

9.2.1.1 When a child or young person experiences transient or attenuated psychotic symptoms or other experiences suggestive of possible psychosis, refer for assessment without delay to a specialist mental health service such as CAMHS or an early intervention in psychosis service (14 years or over).

Assessment in specialist mental health services

9.2.1.2 Carry out an assessment of the child or young person with possible psychosis, ensuring that:

- assessments in CAMHS include a consultant psychiatrist
- assessments in early intervention in psychosis services are multidisciplinary
- where there is considerable uncertainty about the diagnosis, or concern about underlying neurological illness, there is an assessment by a consultant psychiatrist with training in child and adolescent mental health.

9.2.1.3 If a clear diagnosis of psychosis cannot be made, monitor regularly for further changes in symptoms and functioning for up to 3 years. Determine the frequency and duration of monitoring by:

- the severity and frequency of symptoms
- the level of impairment and/or distress in the child or young person, and
- the degree of family disruption or concern.

[162] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

9.2.1.4 If discharge from the service is requested, offer follow-up appointments and the option to self-refer at a later date. Ask the GP to continue monitoring changes in mental state.

Treatment options for symptoms not sufficient for a diagnosis of psychosis or schizophrenia

9.2.1.5 When transient or attenuated psychotic symptoms or other mental state changes associated with distress, impairment or help-seeking behaviour are not sufficient for a diagnosis of psychosis or schizophrenia:

- consider individual cognitive behavioural therapy (CBT) (delivered as set out in recommendation 9.3.1.28) with or without family intervention (delivered as set out in recommendation 9.3.1.27), and
- offer treatments recommended in NICE guidance for children and young people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse.

9.2.1.6 Do not offer antipsychotic medication:

- for psychotic symptoms or mental state changes that are not sufficient for a diagnosis of psychosis or schizophrenia, or
- with the aim of decreasing the risk of psychosis.

9.3 FIRST EPISODE PSYCHOSIS

Referral from primary care

9.3.1.1 Urgently refer all children and young people with a first presentation of sustained psychotic symptoms (lasting 4 weeks or more) to a specialist mental health service, either CAMHS (up to 17 years) or an early intervention in psychosis service (14 years or over), which includes a consultant psychiatrist with training in child and adolescent mental health.

9.3.1.2 Antipsychotic medication in children and young people with a first presentation of sustained psychotic symptoms should not be started in primary care unless it is done in consultation with a consultant psychiatrist with training in child and adolescent mental health.

Assessment and care planning in secondary care

9.3.1.3 When carrying out an assessment:

- ensure there is enough time for:
  - the child or young person and their parents or carers to describe and discuss their problems
  - summarising the conclusions of the assessment and for discussion, with questions and answers
- explain and give written material in an accessible format about any diagnosis given

- give information about different treatment options, including pharmacological and psychological interventions, and their benefits and side effects, to promote discussion and shared understanding
- offer support after the assessment, particularly if sensitive issues, such as childhood trauma, have been discussed.[163]

9.3.1.4 Ensure that children and young people with first episode psychosis receive a comprehensive multidisciplinary assessment. The assessment should address the following domains:

- psychiatric (mental health problems, risk of harm to self or others, alcohol consumption and prescribed and non-prescribed drug history)
- medical, including medical history and full physical examination to identify physical illness (including organic brain disorders) and prescribed drug treatments that may result in psychosis
- psychological and psychosocial, including social networks, relationships and history of trauma
- developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)
- physical health and wellbeing (including weight and height, and information about smoking, diet and exercise, and sexual health)
- social (accommodation, culture and ethnicity, leisure activities and recreation, carer responsibilities [for example, of parents or siblings])
- educational and occupational (attendance at school or college, educational attainment, employment and functional activity)
- economic (family's economic status).

9.3.1.5 Routinely monitor for other coexisting mental health problems, including depression and anxiety, and substance misuse, particularly in the early phases of treatment.[164]

9.3.1.6 Develop a care plan with the parents or carers of younger children, or jointly with the young person and their parents or carers, as soon as possible, and:

- include activities that promote physical health and social inclusion, especially education, but also employment, volunteering and other occupations such as leisure activities
- provide support to help the child or young person and their parents or carers realise the plan
- give an up-to-date written copy of the care plan to the young person and their parents or carers if the young person agrees to this; give a copy of the care plan to the parents or carers of younger children; agree a suitable time to review it
- send a copy to the primary healthcare professional who made the referral.[165]

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[163] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[164] Adapted from *Schizophrenia* (NICE, 2009a).
[165] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

9.3.1.7 Support children and young people to develop strategies, including risk- and self-management plans, to promote and maintain independence and self-efficacy, wherever possible. Incorporate these strategies into the care plan.[166]

9.3.1.8 If the child or young person is at risk of crisis, develop a crisis plan with the parents or carers of younger children, or jointly with the young person and their parents or carers, and with their care coordinator. The plan should be respected and implemented, incorporated into the care plan and include:

- possible early warning signs of a crisis and coping strategies
- support available to help prevent hospitalisation
- where the child or young person would like to be admitted in the event of hospitalisation
- definitions of the roles of primary and secondary care professionals and the degree to which parents or carers are involved
- information about 24-hour access to services
- the names of key clinical contacts.[167]

9.3.1.9 For children and young people with first episode psychosis who are unable to attend mainstream school or college, facilitate alternative educational input in line with their capacity to engage with educational activity and according to their individual needs, with an ultimate goal of returning to mainstream education, training or employment.

9.3.1.10 If the child or young person and/or their parent or carer is unhappy about the assessment, diagnosis or care plan, give them time to discuss this and offer them the opportunity for a second opinion.[168]

Treatment options for first episode psychosis

9.3.1.11 For children and young people with first episode psychosis offer:

- oral antipsychotic medication[169] (see recommendations 9.3.1.14–9.3.1.25) in conjunction with
- psychological interventions (family intervention with individual CBT, delivered as set out in recommendations 9.3.1.26–9.3.1.32).

9.3.1.12 If the child or young person and their parents or carers wish to try psychological interventions (family intervention with individual CBT) alone without antipsychotic medication, advise that psychological interventions are more effective when delivered in conjunction with antipsychotic medication. If the child or young person and their parents or carers still wish to try psychological interventions alone, then offer family intervention with individual CBT. Agree a time limit (1 month or less) for reviewing treatment

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[166] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

[167] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

[168] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

[169] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

options, including introducing antipsychotic medication. Continue to monitor symptoms, level of distress, impairment and level of functioning, including educational engagement and achievement, regularly.

9.3.1.13 If the child or young person shows symptoms and behaviour sufficient for a diagnosis of an affective psychosis or disorder, including bipolar disorder and unipolar psychotic depression, follow the recommendations in 'Bipolar disorder' (NICE clinical guideline 38)[170] or 'Depression in children and young people' (NICE clinical guideline 28).[171]

Choice of antipsychotic medication

9.3.1.14 The choice of antipsychotic medication[172] should be made by the parents or carers of younger children, or jointly with the young person and their parents or carers, and healthcare professionals. Provide age-appropriate information and discuss the likely benefits and possible side effects of each drug including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences).

How to use oral antipsychotic medication

9.3.1.15 Before starting antipsychotic medication[173], undertake and record the following baseline investigations[174]:

- weight and height (both plotted on a growth chart)
- waist and hip circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA_1c), blood lipid profile and prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity.

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[170] NICE, 2006.

[171] NICE, 2005.

[172] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[173] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[174] See Table 125 for a summary of baseline investigations and monitoring for children and young people who are prescribed antipsychotic medication (read in conjunction with the BNF, BNFC and SPC).

Table 125: Baseline investigations and monitoring for children and young people who are prescribed antipsychotic medication (read in conjunction with the BNF, BNFC and SPC)

	Baseline investigations before starting antipsychotic medication	Monitor weekly for the first 6 weeks	Monitor at 12 weeks	Monitor every 6 months thereafter	Monitor regularly throughout treatment, and especially during titration
Weight[a] (plotted on a growth chart)	Yes	Yes	Yes	Yes	
Height[a] (plotted on a growth chart)	Yes			Yes	
Waist and hip circumference (plotted on a percentile chart)	Yes			Yes	
Pulse	Yes		Yes	Yes	
Blood pressure (plotted on a percentile chart)	Yes		Yes	Yes	
Fasting blood glucose	Yes		Yes	Yes	
HbA_1c (glycosylated haemoglobin)	Yes		Yes	Yes	
Blood lipid profile	Yes		Yes	Yes	
Prolactin level	Yes		Yes	Yes	

Continued

Table 125: (*Continued*)

	Baseline investigations before starting antipsychotic medication	Monitor weekly for the first 6 weeks	Monitor at 12 weeks	Monitor every 6 months thereafter	Monitor regularly throughout treatment, and especially during titration
Movement disorders (extrapyramidal symptoms, akathisia, dystonia and tardive dyskinesia)	Yes				Yes[b]
Nutritional status, diet and level of physical activity	Yes				Yes
The side effects the child or young person is most or least willing to tolerate	Yes				
ECG	Yes[c]				
Efficacy					Yes
Side effects					Yes
Adherence					Yes

Note: [a]Calculate and document BMI (percentile).
[b]Even if no baseline assessment (and at each clinic visit if more frequent).
[c]If specified in the SPC for adults and/or children; a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure); there is personal history of cardiovascular disease; there is a family history of cardiovascular disease such as sudden cardiac death or prolonged QT interval; or the child or young person is being admitted as an inpatient.

9.3.1.16 Before starting antipsychotic medication, offer the child or young person an electrocardiogram (ECG) if:

- specified in the SPC for adults and/or children
- a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure)
- there is a personal history of cardiovascular disease
- there is a family history of cardiovascular disease such as premature sudden cardiac death or prolonged QT interval, or
- the child or young person is being admitted as an inpatient.[175]

9.3.1.17 Treatment with antipsychotic medication[176] should be considered an explicit individual therapeutic trial. Include the following:

- From a discussion with the child or young person and their parent or carer, record the side effects the child or young person is most and least willing to tolerate.
- Record the indications and expected benefits and risks of oral antipsychotic medication, and the expected time for a change in symptoms and appearance of side effects.
- At the start of treatment give a dose below the lower end of the licensed range for adults if the drug is not licensed for children and young people and at the lower end of the licensed range if the drug is licensed for children and young people; slowly titrate upwards within the dose range given in the *British National Formulary* (BNF), the *British National Formulary for Children* (BNFC) or the SPC.
- Justify and record reasons for dosages above the range given in the BNF, BNFC or SPC.
- Record the rationale for continuing, changing or stopping medication, and the effects of such changes.
- Carry out a trial of the medication at optimum dosage for 4–6 weeks.[177]

9.3.1.18 Monitor and record the following regularly and systematically throughout treatment, but especially during titration:

- efficacy, including changes in symptoms and behaviour
- side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety)
- the emergence of movement disorders
- weight, weekly for the first 6 weeks, then at 12 weeks and then every 6 months (plotted on a growth chart)
- height every 6 months (plotted on a growth chart)

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[175] Adapted from *Schizophrenia* (NICE, 2009a).

[176] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[177] Adapted from *Schizophrenia* (NICE, 2009a).

- waist and hip circumference every 6 months (plotted on a percentile chart)
- pulse and blood pressure (plotted on a percentile chart) at 12 weeks and then every 6 months
- fasting blood glucose, HbA_1c, blood lipid and prolactin levels at 12 weeks and then every 6 months
- adherence
- physical health.

The secondary care team should maintain responsibility for monitoring physical health and the effects of antipsychotic medication in children and young people for at least the first 12 months or until their condition has stabilised. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements.

9.3.1.19 Discuss any non-prescribed therapies that children or young people, or their parents or carers, wish to use (including complementary therapies) with them. Discuss the safety and efficacy of the therapies, and possible interference with the therapeutic effects of prescribed medication and psychological interventions.[178]

9.3.1.20 Discuss the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs with the child or young person, and their parents or carers where this has been agreed. Discuss their possible interference with the therapeutic effects of prescribed medication and psychological interventions and the potential of illicit drugs to exacerbate psychotic symptoms.[179]

9.3.1.21 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 9.3.1.17. Review clinical indications, frequency of administration, therapeutic benefits and side effects at least weekly. Check whether 'p.r.n.' prescriptions have led to a dosage above the maximum specified in the BNF, BNFC or SPC.[180]

9.3.1.22 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').[181]

9.3.1.23 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).[182]

9.3.1.24 If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.[183]

9.3.1.25 Review antipsychotic medication annually, including observed benefits and any side effects.

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[178] Adapted from *Schizophrenia* (NICE, 2009a).
[179] Adapted from *Schizophrenia* (NICE, 2009a).
[180] Adapted from *Schizophrenia* (NICE, 2009a).
[181] Adapted from *Schizophrenia* (NICE, 2009a).
[182] Adapted from *Schizophrenia* (NICE, 2009a).
[183] Adapted from *Schizophrenia* (NICE, 2009a).

How to deliver psychological interventions

9.3.1.26 When delivering psychological interventions for children and young people with psychosis or schizophrenia, take into account their developmental level, emotional maturity and cognitive capacity, including any learning disabilities, sight or hearing problems or delays in language development.

9.3.1.27 Family intervention should:

- include the child or young person with psychosis or schizophrenia if practical
- be carried out for between 3 months and 1 year
- include at least 10 planned sessions
- take account of the whole family's preference for either single-family intervention or multi-family group intervention
- take account of the relationship between the parent or carer and the child or young person with psychosis or schizophrenia
- have a specific supportive, educational or treatment function and include negotiated problem solving or crisis management work.[184]

9.3.1.28 CBT should be delivered on a one-to-one basis over at least 16 planned sessions (although longer may be needed) and:

- follow a treatment manual[185] so that:
  - children and young people can establish links between their thoughts, feelings or actions and their current or past symptoms, and/or functioning
  - the re-evaluation of the child or young person's perceptions, beliefs or reasoning relates to the target symptoms
- also include at least one of the following components:
  - normalising, leading to understanding and acceptability of their experience
  - children and young people monitoring their own thoughts, feelings or behaviours with respect to their symptoms or recurrence of symptoms
  - promoting alternative ways of coping with the target symptom
  - reducing distress
  - improving functioning.[186]

Monitoring and reviewing psychological interventions

9.3.1.29 When providing psychological interventions, routinely and systematically monitor a range of outcomes across relevant areas, including the child or young person's satisfaction and, if appropriate, parents' or carers' satisfaction.[187]

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[184] Adapted from *Schizophrenia* (NICE, 2009a).

[185] Treatment manuals that have evidence for their efficacy from clinical trials are preferred. If developed for adults, the approach should be adapted to suit the age and developmental level of the child or young person.

[186] Adapted from *Schizophrenia* (NICE, 2009a).

[187] Adapted from *Schizophrenia* (NICE, 2009a).

9.3.1.30 Healthcare teams working with children and young people with psychosis or schizophrenia should identify a lead healthcare professional within the team whose responsibility is to monitor and review:
- access to and engagement with psychological interventions
- decisions to offer psychological interventions and equality of access across different ethnic groups.[188]

Competencies for delivering psychological interventions

9.3.1.31 Healthcare professionals delivering psychological interventions should:
- have an appropriate level of competence in delivering the intervention to children and young people with psychosis or schizophrenia
- be regularly supervised during psychological therapy by a competent therapist and supervisor.[189]

9.3.1.32 Trusts should provide access to training that equips healthcare professionals with the competencies required to deliver the psychological interventions for children and young people recommended in this guideline.[190]

9.4 SUBSEQUENT ACUTE EPISODES OF PSYCHOSIS OR SCHIZOPHRENIA

9.4.1.1 For children and young people with an acute exacerbation or recurrence of psychosis or schizophrenia offer:
- oral antipsychotic medication[191] in conjunction with
- psychological interventions (family intervention with individual CBT).

Pharmacological interventions

9.4.1.2 For children or young people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication.[192] The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 9.3.1.14–9.3.1.25). Take into account the clinical response to and side

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[188] Adapted from *Schizophrenia* (NICE, 2009a).

[189] Adapted from *Schizophrenia* (NICE, 2009a).

[190] Adapted from *Schizophrenia* (NICE, 2009a).

[191] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[192] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

effects associated with current and previous medication, and monitor as described in recommendation 9.3.1.18.

9.4.1.3 Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone. [This recommendation is from *Aripiprazole for the Treatment of Schizophrenia in People Aged 15 to 17 Years* (NICE technology appraisal guidance 213).[193]]

Psychological and psychosocial interventions

9.4.1.4 Offer family intervention (delivered as set out in recommendation 9.3.1.27) to all families of children and young people with psychosis or schizophrenia, particularly for preventing and reducing relapse. This can be started either during the acute phase or later, including in inpatient settings.[194]

9.4.1.5 Offer CBT (delivered as set out in recommendation 9.3.1.28) to all children and young people with psychosis or schizophrenia, particularly for symptom reduction. This can be started either during the acute phase or later, including in inpatient settings.[195]

9.4.1.6 Consider arts therapies (for example, dance movement, music or art therapy or drama-therapy) for all children and young people with psychosis or schizophrenia, particularly for the alleviation of negative symptoms. This can be started either during the acute phase or later, including in inpatient settings.[196]

9.4.1.7 If arts therapies are considered, they should be provided by Health Professions Council (HPC) registered arts therapists, with experience of working with children and young people with psychosis or schizophrenia. The intervention should be provided in groups unless difficulties with acceptability and access and engagement indicate otherwise. Arts therapies should combine psychotherapeutic techniques with activity aimed at promoting creative expression, which is often unstructured and led by the child or young person. Aims of arts therapies should include:

- enabling children and young people with psychosis or schizophrenia to experience themselves differently and to develop new ways of relating to others
- helping children and young people to express themselves and to organise their experience into a satisfying aesthetic form
- helping children and young people to accept and understand feelings that may have emerged during the creative process (including, in some cases, how they came to have these feelings) at a pace suited to them.[197]

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[193] NICE, 2011b.
[194] Adapted from *Schizophrenia* (NICE, 2009a).
[195] Adapted from *Schizophrenia* (NICE, 2009a).
[196] Adapted from *Schizophrenia* (NICE, 2009a).
[197] Adapted from *Schizophrenia* (NICE, 2009a).

9.4.1.8 Do not routinely offer counselling and supportive psychotherapy (as specific interventions) to children and young people with psychosis or schizophrenia. However, take the child or young person's and their parents' or carers' preferences into account, especially if other more efficacious psychological interventions, such as CBT, family intervention and arts therapies, are not available locally.[198]

9.4.1.9 Do not offer adherence therapy (as a specific intervention) to children and young people with psychosis or schizophrenia.[199]

9.4.1.10 Do not routinely offer social skills training (as a specific intervention) to children and young people with psychosis or schizophrenia.[200]

9.4.1.11 When psychological interventions, including arts therapies, are started in the acute phase (including in inpatient settings), the full course should be continued after discharge without unnecessary interruption.[201]

9.5 REFERRAL IN CRISIS AND CHALLENGING BEHAVIOUR

9.5.1.1 When a child or young person is referred in crisis they should be seen by specialist mental health secondary care services within 4 hours of referral.[202]

9.5.1.2 To avoid admission, aim to:

- explore with the child or young person and their parents or carers what support systems they have, including other family members and friends
- support a child or young person in crisis and their parents or carers in their home environment
- make early plans to help the child or young person maintain their day-to-day activities, including education, work, voluntary work, and other occupations and leisure activities, wherever possible.[203]

9.5.1.3 At the end of a crisis assessment, ensure that the decision to start home treatment depends not on the diagnosis, but on:

- the level of distress
- the severity of the problems
- the vulnerability of the child or young person and issues of safety and support at home
- the child or young person's cooperation with treatment.[204]

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[198] Adapted from *Schizophrenia* (NICE, 2009a).
[199] Adapted from *Schizophrenia* (NICE, 2009a).
[200] Adapted from *Schizophrenia* (NICE, 2009a).
[201] Adapted from *Schizophrenia* (NICE, 2009a).
[202] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[203] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[204] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

9.5.1.4 Consider the support and care needs of parents or carers of children or young people in crisis. Where needs are identified, ensure they are met when it is safe and practicable to do so.[205]

9.5.1.5 Follow the recommendations in *Self-Harm* (NICE clinical guideline 16)[206] when managing acts of self-harm in children and young people with psychosis or schizophrenia who are 8 years or over.[207]

Hospital care

9.5.1.6 If a child or young person needs hospital care, this should be in a setting appropriate to their age and developmental level.

9.5.1.7 Before referral for hospital care, think about the impact on the child or young person and their parents, carers and other family members, especially when the inpatient unit is a long way from where they live. Consider alternative care within the community wherever possible. If hospital admission is unavoidable, provide support for parents or carers when the child or young person is admitted.

9.5.1.8 Give verbal and written information to children and young people with psychosis or schizophrenia admitted to hospital, and their parents or carers, about:

- the hospital and the ward in which the child or young person will stay
- treatments, activities and services available
- expected contact from health and social care professionals
- rules of the ward (including substance misuse policy)
- their rights, responsibilities and freedom to move around the ward and outside
- meal times
- visiting arrangements.

Make sure there is enough time for the child or young person and their parents or carers to ask questions.[208]

9.5.1.9 Undertake shared decision-making routinely with children or young people in hospital who are of an appropriate developmental level, emotional maturity and cognitive capacity, including, whenever possible, those who are subject to the Mental Health Act (1983; amended 1995 and 2007).[209] Include their parents or carers if appropriate.[210]

9.5.1.10 Ensure that children and young people of compulsory school age have access to a full educational programme while in hospital. The programme should meet the National Curriculum, be matched to the child or young person's developmental level and educational attainment, and should take account of their illness and degree of impairment.

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[205] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[206] NICE, 2004a.
[207] Adapted from *Schizophrenia* (NICE, 2009a).
[208] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[209] HMSO, 2007.
[210] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).

9.5.1.11 Ensure that children and young people in hospital continue to have access to a wide range of meaningful and culturally appropriate occupations and activities 7 days per week, and not restricted to 9am to 5pm. These should include creative and leisure activities, exercise, self-care and community access activities (where appropriate). Activities should be facilitated by appropriately trained educational, health or social care professionals.[211]

9.5.1.12 Children and young people receiving community care before hospital admission should be routinely visited while in hospital by the health and social care professionals responsible for their community care.[212]

9.5.1.13 Promote good physical health, including healthy eating, exercise and smoking cessation.

Rapid tranquillisation and restraint

9.5.1.14 Healthcare professionals undertaking rapid tranquillisation and/or restraint in children and young people with psychosis or schizophrenia should be trained and competent in undertaking these procedures in children and young people.

9.5.1.15 Occasionally children and young people with psychosis or schizophrenia pose an immediate risk to themselves or others during an acute episode and may need rapid tranquillisation. Be particularly cautious when considering high-potency antipsychotic medication (such as haloperidol) in children and young people, especially those who have not taken antipsychotic medication before, because of the increased risk of acute dystonic reactions in that age group.[213]

9.5.1.16 After rapid tranquillisation, offer the child or young person the opportunity to discuss their experiences. Provide them with a clear explanation of the decision to use urgent sedation. Record this in their notes.[214]

9.6 EARLY POST-ACUTE PERIOD

9.6.1.1 In the early period of recovery following an acute episode, reflect upon the episode and its impact with the child or young person and their parents or carers, and make plans for recovery and possible future care.

9.6.1.2 Inform the child or young person and their parents or carers that there is a high risk of relapse if medication is stopped in the 1–2 years following an acute episode.[215]

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[211] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[212] Adapted from *Service User Experience in Adult Mental Health* (NICE, 2011a).
[213] Adapted from *Schizophrenia* (NICE, 2009a).
[214] Adapted from *Schizophrenia* (NICE, 2009a).
[215] Adapted from *Schizophrenia* (NICE, 2009a).

9.6.1.3 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse.[216]

9.6.1.4 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.[217]

9.7 PROMOTING RECOVERY AND PROVIDING POSSIBLE FUTURE CARE IN PRIMARY CARE

9.7.1.1 Develop and use practice case registers to monitor the physical and mental health of children and young people with psychosis or schizophrenia in primary care.[218]

9.7.1.2 GPs and other primary healthcare professionals should monitor the physical health of children and young people with psychosis or schizophrenia at least once a year. They should bear in mind that people with schizophrenia are at higher risk of cardiovascular disease than the general population.

9.7.1.3 Identify children and young people with psychosis or schizophrenia who smoke or who have high blood pressure, raised lipid levels or increased waist measurement at the earliest opportunity and monitor for the emergence of cardiovascular disease and diabetes.

9.7.1.4 Treat children and young people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care. Use the appropriate NICE guidance for children and young people where available.[219,220]

9.7.1.5 Healthcare professionals in secondary care should ensure, as part of the care programme approach (CPA) in England and care and treatment plans in Wales, that children and young people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 9.7.1.2–9.7.1.4. Healthcare professionals in secondary care should continue to maintain responsibility for monitoring and managing any side effects of antipsychotic medication.[221]

9.7.1.6 When a child or young person with a diagnosis of psychosis or schizophrenia presents with a suspected relapse (for example, with increased psychotic symptoms or a significant increase in the use of alcohol or other substances) and is still receiving treatment, primary healthcare professionals should refer to the crisis section of the care plan. Consider

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[216] Adapted from *Schizophrenia* (NICE, 2009a).
[217] Adapted from *Schizophrenia* (NICE, 2009a).
[218] Adapted from *Schizophrenia* (NICE, 2009a).
[219] See *Type 1 Diabetes* (NICE clinical guideline 15) (NICE, 2004b).
[220] Adapted from *Schizophrenia* (NICE, 2009a).
[221] Adapted from *Schizophrenia* (NICE, 2009a).

referral to the key clinician or care coordinator identified in the crisis plan.[222]

9.7.1.7 For a child or young person with psychosis or schizophrenia being cared for in primary care, consider referral to secondary care again if there is:

- poor response to treatment
- non-adherence to medication
- intolerable side effects from medication or the child or young person or their parents or carers request a review of side effects
- the child or young person or their parents or carers request psychological interventions not available in primary care
- comorbid substance misuse
- risk to self or others.[223]

9.8 PROMOTING RECOVERY AND PROVIDING POSSIBLE FUTURE CARE IN SECONDARY CARE

9.8.1.1 Children and young people with psychosis or schizophrenia who are being treated in an early intervention in psychosis service should have access to that service for up to 3 years (or until their 18th birthday, whichever is longer) whatever the age of onset of psychosis or schizophrenia.

Psychological interventions

9.8.1.2 Offer family intervention to families of children and young people with psychosis or schizophrenia to promote recovery. Deliver family intervention as described in recommendation 9.3.1.27.[224]

9.8.1.3 Consider family intervention particularly for families of children and young people with psychosis or schizophrenia who have:

- recently relapsed or are at risk of relapse
- persisting symptoms.[225]

9.8.1.4 Offer CBT to assist in promoting recovery in children and young people with persisting positive and negative symptoms and for those in remission. Deliver CBT as described in recommendation 9.3.1.28.[226]

9.8.1.5 Consider arts therapies (see recommendation 9.4.1.7) to assist in promoting recovery, particularly in children and young people with negative symptoms.[227]

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[222] Adapted from *Schizophrenia* (NICE, 2009a).
[223] Adapted from *Schizophrenia* (NICE, 2009a).
[224] Adapted from *Schizophrenia* (NICE, 2009a).
[225] Adapted from *Schizophrenia* (NICE, 2009a).
[226] Adapted from *Schizophrenia* (NICE, 2009a).
[227] Adapted from *Schizophrenia* (NICE, 2009a).

Pharmacological interventions

9.8.1.6 The choice of drug[228] should be influenced by the same criteria recommended for starting treatment (see recommendations 9.3.1.14–9.3.1.25).[229]

9.8.1.7 Do not use targeted, intermittent dosage maintenance strategies[230] routinely. However, consider them for children and young people with psychosis or schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect sensitivity.[231]

Interventions for children and young people whose illness has not responded adequately to treatment

9.8.1.8 For children and young people with psychosis or schizophrenia whose illness has not responded adequately to pharmacological or psychological interventions:

- review the diagnosis
- establish that there has been adherence to antipsychotic medication[232], prescribed at an adequate dose and for the correct duration
- review engagement with and use of psychological interventions and ensure that these have been offered according to this guideline; if family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families
- consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.[233]

9.8.1.9 Offer clozapine[234] to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment despite

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[228] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[229] Adapted from *Schizophrenia* (NICE, 2009a).

[230] Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.

[231] Adapted from *Schizophrenia* (NICE, 2009a).

[232] At the time of publication, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[233] Adapted from *Schizophrenia* (NICE, 2009a).

[234] At the time of publication, clozapine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

the sequential use of adequate doses of at least two different antipsychotic drugs each used for 6–8 weeks.[235]

9.8.1.10 For children and young people whose illness has not responded adequately to clozapine[236] at an optimised dose, consider a multidisciplinary review, and recommendation 9.8.1.8 (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8–10 weeks. Choose a drug that does not compound the common side effects of clozapine.[237]

Education, employment and occupational activities for children and young people with psychosis and schizophrenia

9.8.1.11 For children and young people of compulsory school age, liaise with the child or young person's school and educational authority, subject to consent, to ensure that ongoing education is provided.

9.8.1.12 Liaise with the child or young person's school and with their parents or carers, subject to consent, to determine whether a special educational needs assessment is necessary. If it is agreed that this is needed, explain to parents or carers how to apply for an assessment and offer support throughout the process.

9.8.1.13 Provide supported employment programmes for those young people with psychosis or schizophrenia above compulsory school age who wish to return to work or find employment. Consider other work-related activities and programmes when individuals are unable to work or are unsuccessful in their attempts to find employment.[238]

9.8.1.14 Mental health services should work in partnership with local stakeholders, including those representing black and minority ethnic groups, to enable young people with psychosis or schizophrenia to access local employment and educational opportunities. This should be sensitive to the young person's needs and skill level and is likely to involve working with agencies such as Jobcentre Plus, disability employment advisers and non-statutory providers.[239]

9.8.1.15 Routinely record the daytime activities of children and young people with psychosis or schizophrenia in their care plans, including educational and occupational outcomes.[240]

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[235] Adapted from *Schizophrenia* (NICE, 2009a).

[236] At the time of publication, clozapine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's *Good Practice in Prescribing Medicines – Guidance for Doctors* (2013) (http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp) for further information.

[237] Adapted from *Schizophrenia* (NICE, 2009a).

[238] Adapted from *Schizophrenia* (NICE, 2009a).

[239] Adapted from *Schizophrenia* (NICE, 2009a).

[240] Adapted from *Schizophrenia* (NICE, 2009a).

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APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

1 GUIDELINE TITLE

Psychosis and schizophrenia in children and young people: recognition and management

1.1 SHORT TITLE

Psychosis and schizophrenia in children and young people

2 THE REMIT

The Department of Health has asked NICE: 'to produce a clinical guideline on the recognition and management of schizophrenia presenting before the age of 18 years'.

3 CLINICAL NEED FOR THE GUIDELINE

3.1 EPIDEMIOLOGY

Schizophrenia is a term used to describe a major psychiatric disorder (or cluster of disorders) that alters a person's perception, thoughts, affect and behaviour. The symptoms of schizophrenia are usually divided into positive symptoms (such as hallucinations and delusions) and negative symptoms (such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect). Children and young people who develop schizophrenia each have their own unique combination of symptoms and experiences, the precise pattern of which will be influenced by their circumstances and stage of development.

Psychotic disorders, including schizophrenia, are major mental illnesses. The estimated prevalence across all ages and populations in the UK is 0.7%. Schizophrenia usually starts in late adolescence and early adulthood but can begin in early adolescence, although rarely before the age of 10. In the UK the lifetime prevalence of schizophrenia and schizophrenia-related disorders is approximately 14.5 per 1000 people, although there is considerable variation between estimates.

According to the ONS, the prevalence of all mental health disorders in children aged between 5 and 16 years is 9.6%. In 2002, the ONS reported that the prevalence of

psychotic disorders in children aged between 5 and 18 years was 0.4%. A survey of hospital bed use in England and Wales between 1998 and 2004 suggests that schizophrenia accounts for 24.5% of all adolescent (10 to 18 years) psychiatric admissions (the overall admission rate is 0.46 per 1000 for this age range) with an exponential rise across the adolescent years. The rise in incidence increases most from 15 years onwards.

The prognosis of schizophrenia in adults has generally been seen to be much worse than in fact it is. Long-term follow-up studies in adults suggested that after 5 years of illness one quarter of people recover completely. For most people the condition gradually improves over their lifetime and it deteriorates in only 10% throughout life. Schizophrenia has a worse prognosis with onset in childhood or adolescence than with onset in adult life.

About one fifth of children and young people with schizophrenia have a good outcome with only mild impairment. However, one third has severe impairment that requires intensive social and psychiatric support. A recent Israeli whole-population study found that people younger than 17 years with schizophrenia had a poorer outcome overall with longer length of initial hospital stay, higher incidence of readmission, more days per year in hospital and more admissions to hospital than people aged 18 and older. Schizophrenia is also very frequently associated with significant impairments in many aspects of life – social, educational, vocational and family – and it is associated with increased morbidity and mortality through both suicide and natural deaths.

Recognising schizophrenia in children and young people may be difficult for healthcare professionals who may be unaware of its occurrence in this age group and unfamiliar with the clinical picture of schizophrenia in younger people.

The symptoms and experience of schizophrenia are often distressing and the effects of the illness are pervasive, with a significant number of children and young people continuing to experience long-term disability. Schizophrenia can have a major detrimental effect on children and young people's personal, social, educational and occupational functioning, placing a heavy burden on individuals and their carers, as well as making potentially large demands on the social and healthcare system.

The cumulative cost of the care of people with schizophrenia is high. In 1992/93 the direct cost of health and social care for people with schizophrenia was estimated to be 2.8% of total NHS expenditure, and 5.4% of NHS inpatient costs. Health and social services costs alone amounted to £810 million, of which inpatient care cost more than £652 million. It is likely that the younger onset of schizophrenia will prove to be most costly for the person, their family and society.

3.2 CURRENT PRACTICE

With psychosis, and schizophrenia in particular, onset in childhood and early adolescence represents a major health challenge. There have been some significant improvements in pharmacotherapy, family interventions, psychosocial and psychological treatments, and most recently in the use of arts therapies. Through the National Service Framework for Mental Health, several service innovations originally developed and evaluated in other countries have been implemented in adult services across

England and Wales. These have been reviewed in the NICE guideline for adults with schizophrenia (NICE clinical guideline 82)[241]. However, there is considerable variation in both services and treatments for adults with schizophrenia, and probably more so for children and young people with schizophrenia.

The mainstay of treatment for all people with schizophrenia since the 1950s has been antipsychotic drugs, including chlorpromazine, haloperidol, trifluoperazine, sulpiride, olanzapine, risperidone and aripiprazole. Initial speculation that the newer and more expensive 'atypical antipsychotics' were superior to so-called 'typicals' evaporated. Nevertheless, the most commonly used drugs now are the newer ones (olanzapine and risperidone). There is limited evidence of the efficacy of antipsychotic drugs in children and young people with schizophrenia. There are also concerns that children and young people are more sensitive than adults to the potential adverse effects of antipsychotics, including weight gain, metabolic effects and movement disorders.

Psychological treatments that have been used for children, young people and adults with schizophrenia include family interventions, cognitive behavioural therapy (CBT), cognitive remediation therapy, social skills training, psychoeducation, arts therapies and many others. For adults, the evidence for effectiveness is limited to family interventions, CBT and arts therapies. Provision of these therapies for adults and young people, especially for family interventions, is variable and largely poor despite the growing evidence base.

Services for children and young people with schizophrenia include child and adolescent mental health services (CAMHS), especially Tiers 2 and 3 (community services) and Tier 4 (inpatient services), and early intervention services (EIS).

EIS were introduced for people aged 15 to 35 as part of the National Service Framework for Mental Health. They provide a more intensive therapeutic service than traditional community services for young people and adults. They are designed to intervene early, providing evidence-based treatments (pharmacotherapy, family interventions and CBT), family, social and occupational support, in a 'normalising' environment for the first 3 years after onset of psychosis. For adults, these services reduce relapse rates and symptoms of schizophrenia, improve quality of life and are preferred to community mental health teams. Precisely which aspects of EIS underpin these better outcomes is subject to debate. We do not know if EIS are better than generic CAMHS for children and young people with schizophrenia. The provision of all these services, how they are configured locally (for example, the degree of integration of the two services for people under 18) and how people are transferred from one to another or to adult services are highly variable geographically.

Children, young people and adults with schizophrenia from black and minority ethnic backgrounds tend to present late to services, are more frequently subject to compulsion and have less access to psychological therapies than their white counterparts. Much of the difference in receiving appropriate services at the right time seems to be determined by difficulty in gaining access to services and difficulty in engaging with healthcare professionals in primary and secondary mental healthcare. However, some

[241]NICE, 2009a.

studies that show ethnic variations in the take up of acute services and the need for compulsory admissions also show a broader picture of more similarities than differences.

Services for children and young people with schizophrenia need to be comprehensive and well integrated because schizophrenia affects all aspects of their life and experience. Educational outcomes can be seriously affected by schizophrenia. There is considerable geographical variation in the configuration and integration of CAMHS and EIS mental health services, and in the provision and integration of other services for children and young people with schizophrenia, including education services, social services, employment and rehabilitation support. Provision for the specific needs of 16 and 17 year olds with schizophrenia, in particular, can be fragmented and inadequate. They may not have family support or be in education and yet they do not qualify as an adult. They can experience difficulties in gaining access to appropriate types of accommodation or vocational/occupational support and rehabilitation.

4 THE GUIDELINE

The guideline development process is described in detail on the NICE website (see Section 6, 'Further information'). This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health. The areas that will be addressed by the guideline are described in the following sections.

4.1 POPULATION

4.1.1 Groups that will be covered

a. Children and young people (younger than 18) who have a clinical diagnosis of schizophrenia (including schizoaffective disorder and delusional disorder).
b. Children and young people who are at risk of developing psychosis and those who have early psychosis but do not have a formal diagnosis of schizophrenia.
c. Children and young people with schizophrenia and a mild learning disability.
d. Specific consideration will be given to the needs of children and young people from black and minority ethnic groups.

4.1.2 Groups that will not be covered

a. Adults (aged 18 and older).
b. Children and young people with psychotic disorders other than schizophrenia [but please see 4.1.1 b)].

4.2 HEALTHCARE SETTING

a. Care that is received in primary care, secondary and tertiary CAMHS (Tiers 1 to 4) and EIS from healthcare professionals who have direct contact with,

and make decisions concerning the care of, children and young people with schizophrenia.

b. The transition from CAMHS to adult services, and the treatment and care received during transition.

c. The guideline will also be relevant to the work of, but will not cover the practice of, healthcare professionals and others working in accident and emergency (A&E) departments, paramedic services, services for the homeless, prison medical services, the police and those who work in forensic services and criminal justice. It will also be relevant to professionals who work in schools, colleges and other educational settings, and to those who work with looked after children.

4.3 CLINICAL MANAGEMENT

4.3.1 Key clinical issues that will be covered

a. Recognition of schizophrenia and criteria for diagnosis, including the recognition and management of at risk mental states and early psychosis before a formal diagnosis of schizophrenia has been made.

b. Psychological or psychosocial interventions:
   - CBT
   - cognitive remediation
   - counselling and supportive psychotherapy
   - family interventions (including family therapy)
   - psychodynamic psychotherapy and psychoanalysis
   - psychoeducation
   - social skills training
   - arts therapies.

c. All antipsychotics licensed for the treatment of schizophrenia in the UK, including considerations related to the age of the child or young person, such as modifications to the dose. Note that guideline recommendations will not normally fall outside licensed indications. Exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended (for this guideline a number of drugs will be reviewed that are licensed for adults with schizophrenia but not for children or young people). The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual service users.

d. Starting treatment with antipsychotic medication and/or a psychological or psychosocial intervention.

e. Treatment of an acute psychotic episode with antipsychotic medication and/or a psychological or psychosocial intervention.

f. Promoting recovery after an acute psychotic episode, using antipsychotic medication and/ or a psychological or psychosocial intervention.

g. Assessment and management (for example, routine blood tests and physical monitoring) of known side effects of antipsychotic medication, and of the child or young person's physical health.

h. Treatment options if antipsychotic medication and/or a psychological intervention is ineffective and/or not tolerated.
i. The organisation and integration of services, outlining a care pathway including primary care, CAMHS, EIS, and tertiary CAMHS (inpatient services).
j. Ways to improve access to, and engagement with, mental health services for children and young people and particularly those from black and minority ethnic groups.
k. Recommendations categorised as good practice points in NICE clinical guideline 82[242] will be reviewed for their relevance to children and young people with schizophrenia (including issues around consent and advance directives).

4.3.2 Clinical issues that will not be covered

a. Validity of diagnosis.
b. Primary prevention (although management of at risk mental states and early psychotic symptoms prior to a diagnosis of schizophrenia will be covered; see 4.1.1.b).
c. Management of violence in children and young people with schizophrenia.

4.4 MAIN OUTCOMES

a. Better recognition and earlier treatment.
b. Better treatment and care based on the best evidence available for effectiveness, safety and cost effectiveness.
c. Reduced adverse events resulting from pharmacological treatment, including side effects and discontinuation-related effects.
d. Better mental health and related outcomes.
e. Improvements in the experience of care for children, young people and their families.
f. Better equity in access to and engagement with services for children and young people from black and minority ethnic groups.
g. Better integration of services, treatment and care, with clearer care pathways.
h. Better support and guidance for the child or young person's family.
i. Increased access to education and to better address the educational expectations of the child or young person.
j. Social and educational wellbeing.
k. Improved cognitive functioning (including better access to education).

4.5 ECONOMIC ASPECTS

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate.

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[242]NICE, 2009a.

The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in *The Guidelines Manual* (see Section 6, 'Further information').

4.6 STATUS

4.6.1 Scope
This is the final scope.

4.6.2 Timing
The development of the guideline recommendations will begin in March 2011.

5 RELATED NICE GUIDANCE

5.1 PUBLISHED GUIDANCE

5.1.1 NICE guidance to be incorporated
This guideline will incorporate the following NICE guidance:

- *Aripiprazole for the Treatment of Schizophrenia in People Aged 15 to 17 Years.* NICE technology appraisal guidance 213 (2011).[243] Available from www.nice.org.uk/guidance/TA213

5.1.2 Other related NICE guidance

- *Schizophrenia* (update). NICE clinical guideline 82 (2009).[244] Available from www.nice.org.uk/guidance/CG82

6 FURTHER INFORMATION

Information on the guideline development process is provided in:

- *How NICE Clinical Guidelines Are Developed: an Overview for Stakeholders, the Public and the NHS*
- *The Guidelines Manual*.[245]

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

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[243]NICE, 2011b.
[244]NICE, 2009a.
[245]NICE, 2009b.

APPENDIX 2: DECLARATIONS OF INTERESTS BY GUIDELINE DEVELOPMENT GROUP MEMBERS

With a range of practical experience relevant to psychosis and schizophrenia in children and young people in the GDG, members were appointed because of their understanding and expertise in healthcare for children and young people with psychosis and schizophrenia and support for their parents and carers, including: scientific issues; health research; the delivery and receipt of healthcare, along with the work of the healthcare industry; and the role of professional organisations and organisations for children and young people with psychosis and schizophrenia, and their parents and carers.

To minimise and manage any potential conflicts of interest, and to avoid any public concern that commercial or other financial interests have affected the work of the GDG and influenced guidance, members of the GDG must declare as a matter of public record any interests held by themselves or their families which fall under specified categories (see below). These categories include any relationships they have with the healthcare industries, professional organisations and organisations for children and young people with psychosis and schizophrenia, and their parents and carers.

Individuals invited to join the GDG were asked to declare their interests before being appointed. To allow the management of any potential conflicts of interest that might arise during the development of the guideline, GDG members were also asked to declare their interests at each GDG meeting throughout the guideline development process. The interests of all the members of the GDG are listed below, including interests declared prior to appointment and during the guideline development process.

Categories of interest
Paid employment

Personal pecuniary interest: financial payments or other benefits from either the manufacturer or the owner of the product or service under consideration in this guideline, or the industry or sector from which the product or service comes. This includes holding a directorship, or other paid position; carrying out consultancy or fee paid work; having shareholdings or other beneficial interests; receiving expenses and hospitality over and above what would be reasonably expected to attend meetings and conferences.

Personal family interest: financial payments or other benefits from the healthcare industry that were received by a GDG member's family.

Non-personal pecuniary interest: financial payments or other benefits received by the GDG member's organisation or department, but where the GDG member has not personally received payment, including fellowships and other support provided by the

healthcare industry. This includes a grant or fellowship or other payment to sponsor a post, or contribute to the running costs of the department; commissioning of research or other work; contracts with, or grants from, NICE.

Personal non-pecuniary interest: these include, but are not limited to, clear opinions or public statements the GDG member has made about children and young people with psychosis and schizophrenia, holding office in a professional organisation or advocacy group with a direct interest in psychosis and schizophrenia in children and young people, and other reputational risks relevant to psychosis and schizophrenia in children and young people.

Guideline Development Group - Declarations of interest	
Professor Chris Hollis - Chair, Guideline Development Group	
Employment	Professor of Child and Adolescent Psychiatry, University of Nottingham; Honorary Consultant in Developmental Neuropsychiatry, Nottinghamshire Healthcare NHS Trust.
Personal pecuniary interest	Received £900 fee for an educational event in December 2009 lecturing on social impairments in ADHD at a meeting sponsored by Janssen-Cilag. This payment was non-specific (that is, it does not relate to a product or service under consideration in this guideline).
Personal family interest	None
Non-personal pecuniary interest	Nottingham University Psychiatry department receives grant income to undertake research in schizophrenia (Medical Research Council, Wellcome Trust, NIHR) and evaluation of treatments (Cochrane Collaboration Schizophrenia Centre). Collaboration with Tim Kendall on an NIHR HTA evidence synthesis systematic review on 'Treatment for tics in children with Tourette's syndrome'.
Personal non-pecuniary interest	Published articles and written book chapters on subjects covered by this guidance.

	Is an expert adviser to the Prescribing Observatory for Mental Health (POMH-UK) regarding antipsychotic prescribing in children and young people. Has given expert advice to the European Medicines Agency (EU) on use of aripiprazole for young people with schizophrenia. Was invited by Shire to present the latest ADHD research findings at an educational event in Leicester on 8 October 2010. This invitation was received and accepted prior to the appointment as GDG chair. To the best of his knowledge, Shire does not market any drug for schizophrenia/psychosis. He confirmed that he would not accept any further invitations to speak at educational or promotional events sponsored by pharmaceutical companies during his tenure as GDG chair. Has been commissioned to revise a chapter on 'Schizophrenia and allied disorders' for the sixth edition of Michael Rutter's *Child and Adolescent Psychiatry* for submission in March 2013.
Actions taken	None
Professor Tim Kendall – Facilitator, Guideline Development Group	
Employment	Director, NCCMH, Royal College of Psychiatrists; Medical Director/Consultant Adult Psychiatrist, Sheffield Health and Social Care NHS Foundation Trust; Visiting Professor, University College London.
Personal pecuniary interest	None
Personal family interest	None

Non-personal pecuniary interest	Grant holder for £1.44 million per year (approximately) from NICE for guideline development work. Carried out funded work for NICE International. Undertook research into mental health and the mental health workforce for the Department of Health, Royal College of Psychiatrists and Academy of Medical Royal Colleges. Received funding of £80,000 (approximately) from the Academy of Medical Royal Colleges to carry out a systematic review of the mental health impact of abortion. Was invited to be a member of the Mental Health Services Subgroup of the new established Clinical Advisory Group on Specialised Services. The Clinical Advisory Group has been established to advise ministers on the initial list of services to be commissioned by the NHS Commissioning Board. Collaboration with Chris Hollis on an NIHR HTA evidence synthesis systematic review on 'Treatment for tics in children with Tourette's syndrome'.
Personal non-pecuniary interest	Has published various articles on selective publishing by pharmaceutical companies and on early intervention services for young people and young adults with schizophrenia. Has written an editorial entitled 'Treating negative symptoms of schizophrenia' for the *BMJ* [10 March 2012, volume 344]. Collaborated with David Shiers and others on a study of a health economic model on the key drivers for physical ill health for the London School of Economics and the Institute of Psychiatry.

Action taken	None
Professor Max Birchwood	
Employment	Professor of Youth Mental Health, School of Psychology, University of Birmingham; Clinical Director, YouthSpace Mental Health Programme, Birmingham and Solihull Mental Health NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Rory Byrne	
Employment	Service User Representative; Researcher, Greater Manchester West Mental Health NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Andrew Clark	
Employment	Consultant in Adolescent Psychiatry, Greater Manchester West Mental Health NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	Is Workforce Lead for the Royal College of Psychiatrists with the responsibility for coordinating advice on psychiatric workforce numbers required and communicating this to other bodies (the Department of Health, NHS Employers, and so on).
Personal non-pecuniary interest	Variety of publications related to treatment of young people with psychosis.

Action taken	None
Ms Jaeta Egoh	
Employment	Service User Representative
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Professor Elena Garralda	
Employment	Professor and Honorary Consultant in Child and Adolescent Psychiatry, Imperial College London and Central and North West London Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Laura Graham	
Employment	Carer Representative; Involvement Worker and Young Person's Panel Adviser for Rethink Mental Illness.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Anthony James	
Employment	Consultant Child and Adolescent Psychiatrist and Honorary Senior Lecturer, Oxfordshire and Buckinghamshire Mental Health NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None

Personal non-pecuniary interest	Member of the Schizophrenia International Research Society.
Action taken	None
Mr Tim McDougall	
Employment	Nurse Consultant, Clinical Director (Tier 4 CAMHS) and Lead Nurse (CAMHS), Cheshire and Wirral Partnership NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Professor Anthony Morrison	
Employment	Professor of Clinical Psychology, Greater Manchester West Mental Health NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Co-authoring with David Shiers and others an editorial regarding antipsychotics and patient choice (submitted to *The British Journal of Psychiatry* in March 2012).
Action taken	None
Dr Gillian Rose	
Employment	Consultant Child and Adolescent Psychiatrist, Central and North West London NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Dr David Shiers	
Employment	GP Adviser to the National Audit of Schizophrenia (The Royal College of Psychiatrists) and Rethink Mental Illness Trustee.
Personal pecuniary interest	Received lecture fee of £450 for presenting to a specialist mental health audience in Southampton, organised and paid for by Janssen-Cilag in September 2010. Title of keynote presentation was 'Early intervention in psychosis – looking after the body as well as the mind'. Joint editor of *Promoting Recovery in Early Psychosis* (Wiley-Blackwell, 2010): royalties of £169.14 received for first time on 23 March 2012.
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Co-author of Myles, N., Newall, H. D., Curtis, J., *et al.* (2012) Tobacco use before, at and after first-episode of psychosis: a systematic review and meta-analysis. *Journal of Clinical Psychiatry*, *73*, 468–475. Co-authoring an EIP guideline produced by IRIS Imitative Ltd (a social enterprise). Co-author of Newall, H., Myles, N., Ward, P.B., *et al.* (2012) Efficacy of metformin for prevention of weight gain in psychiatric populations: a review. *International Clinical Psychopharmacology*, *27*, 69–75. Co-authoring with Tony Morrison and others an editorial regarding antipsychotics and patient choice (submitted to *The British Journal of Psychiatry* in March 2012). Collaboration with Tim Kendall and others in a study of a health economic model on the key drivers for physical ill health for the London School of Economics and the Institute of Psychiatry.

Action taken	None
Dr Kirsty Smedley	
Employment	Consultant Clinical Psychologist, The Priory Hospital Cheadle Royal; Honorary Lecturer, Manchester University.
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Darryl Thompson	
Employment	Psychosocial Interventions Development Lead, South West Yorkshire Partnership NHS Foundation Trust.
Personal pecuniary interest	None
Personal family interest	Wife is a self-employed acupuncturist.
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Attended training course on Family Work in Early Psychosis at The Meriden Family Programme, Birmingham, May 2011. Attended Behavioural Family Therapy, Training Trainers Course at The Meriden Family Programme, Birmingham, March 2012.
Action taken	None
Dr David Ward	
Employment	Consultant Adolescent Psychiatrist, Newcastle CAMHS and Early Intervention in Psychosis Service (2010 to 2011).
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

NCCMH staff	
Ms Henna Bhatti	
Employment	Research Assistant, NCCMH (2010 to 2011)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Melissa Chan	
Employment	Systematic Reviewer, NCCMH (2010 to 2011)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mr Nadir Cheema	
Employment	Health Economist, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Marie Halton	
Employment	Research Assistant, NCCMH (2010 to 2011)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Hannah Jackson	
Employment	Research Assistant, NCCMH (2011 to 2012)
Personal pecuniary interest	None

Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Linnéa Larsson	
Employment	Project Manager and Research Assistant, NCCMH (2012 to 2013)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Christina Loucas	
Employment	Research Assistant, NCCMH (2012 to 2013)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Mrs Kate Satrettin	
Employment	Project Manager, NCCMH (2010 to 2012)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Christine Sealey	
Employment	Associate Director, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

Ms Megan Stafford	
Employment	Systematic Reviewer, NCCMH (2011 to 2013)
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms Sarah Stockton	
Employment	Senior Information Scientist, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Clare Taylor	
Employment	Senior Editor, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

APPENDIX 3: SPECIAL ADVISERS TO THE GUIDELINE DEVELOPMENT GROUP

Peter Pratt
Chief Pharmacist, Sheffield Care Trust

Andrew Richards
Educational Psychologist, Exeter University

Janette Steel OBE
Principal, Chelsea Community Hospital School

APPENDIX 4: STAKEHOLDERS WHO SUBMITTED COMMENTS IN RESPONSE TO THE CONSULTATION DRAFT OF THE GUIDELINE

Bristol-Myers Squibb and Otsuka Pharmaceuticals
Central and North West London NHS Foundation Trust
College of Mental Health Pharmacy
Community Links
Department of Health
Eli Lilly and Co Ltd
Greater Manchester West Mental Health Services NHS Foundation Trust
International Society for Psychological and Social Approaches to Psychosis – UK network
Lancashire Care NHS Foundation Trust
Neonatal and Paediatric Pharmacists Group
NHS Sheffield
Nottinghamshire Healthcare NHS Trust
Roche Products Ltd
Royal College of General Practitioners
Royal College of Nursing
Royal College of Psychiatrists
Royal College of Psychiatrists in Wales
South West Yorkshire Partnership NHS Foundation Trust
Thorn Steering Group, Queens University Belfast
University of Glamorgan Faculty of Health Sport and Science
Welsh Government
West London Mental Health NHS Trust
Worcestershire Health and Care NHS Trust

APPENDIX 5: RESEARCHERS CONTACTED TO REQUEST INFORMATION ABOUT UNPUBLISHED DATA OR SOON-TO-BE PUBLISHED STUDIES

Professor Celso Arango
Head of Adolescent Unit, Psychiatry Department, Adolescent Unit, Hospital General Universitario Gregorio Marañón, Spain

Dr Andreas Bechdolf
Associate Professor, Deputy Head Department of Psychiatry, University of Cologne, Germany

Dr Gregor E. Berger
The Scloessli Clinic, Department of Research and Education, Schlösslistrasse, Switzerland

Dr Magali Haas
Johnson and Johnson Pharmaceutical Research and Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium

Professor Henry J. Jackson
Professor and Head of Department of Psychology, University of Melbourne, Australia

Rakesh Kantaria
Medical Affairs Leader, Astra Zeneca, Luton, UK

Dr Eilis Kennedy
Consultant Child Psychiatrist, Child and Family Department, Tavistock Clinic, London, UK

Dr Ludmila Kryzhanovskaya
Lilly Research Laboratories, Indianapolis, USA

Dr Sanjiv Kumra
Associate Professor, Division of Child and Adolescent, Psychiatry, University of Minnesota, Minneapolis, USA

Professor Patrick McGorry
Professor of Youth Mental Health at the University of Melbourne, Clinical Director of Orygen Youth Health and Executive Director of the Orygen Research Centre, Australia

Professor Anthony Morrison
Professor of Clinical Psychology, University of Manchester, Manchester, UK

Dr Judith Rietdijk
Institute of Health and Care Research Amsterdam, Department of Clinical Psychology, Amsterdam, the Netherlands

Dr Philip Shaw
Child Psychiatry Branch, National Institute of Mental Health, Bethesda, USA

Dr Linmarie Sikich
Child and Adolescent Psychiatrist, Department of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, North Carolina, USA

Dr Sébastien Urben
Psychologue, Responsable de Recherche, Service Universitaire de Psychiatrie de l'Enfant et de l'Adolescent (SUPEA), Lausanne, Switzerland

Dr Alison Yung
Associate Professor, Department of Psychiatry, University of Melbourne and ORYGEN Research Centre, Australia

APPENDIX 6: REVIEW QUESTIONS

A. Recognition

Scope Section 4.3.1 (a)

No.	Review questions	Guideline chapter
A1	In children and young people, what are the specific behaviours and symptoms that are associated with an increased risk of developing psychosis and schizophrenia (at risk mental state)? Sub-questions: a) What is the course of these behaviours and symptoms? b) What are the specific behaviours and symptoms that prompt initial recognition of psychosis or prompt diagnosis of schizophrenia?	Chapter 5

B. Treatment

Scope Section 4.3.1 (b) – (h), (k)

No.	Review questions	Guideline chapter
B1	For children and young people who are at risk of developing psychosis and schizophrenia (at risk mental state), does the provision of pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes?	Chapter 5
B2	Does the efficacy profile of continuous antipsychotic drug treatment, compared with alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children/young people and adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 7

No.	Review questions	Guideline chapter
B3	Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared with adults with psychosis and schizophrenia (in particular, metabolic, neurological and cognitive impairments)? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosiss) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 7
B4*	Do clinicians manage and monitor side effects of antipsychotic treatment differently in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 7
B5	For initial treatment in children and young people with psychosis and schizophrenia: a) Should the dose/duration (and, where relevant, frequency) be different compared with adults? b) *Are there any different factors (including patient population, age, and so on) that predict the nature and degree of response to medication, which should be considered in children and young people with psychosis and schizophrenia that it is not necessary to consider in adults with psychosis and schizophrenia?	Chapter 7
B6*	Are the same baseline measurements/ monitoring procedures undertaken before initiating antipsychotic medication used in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 7

No.	Review questions	Guideline chapter
B7	For children and young people whose illness has not responded to pharmacological treatment, what is the next most effective treatment strategy and when do you decide to change treatment? Does this differ from adults with psychosis and schizophrenia?	Chapter 7
B8	Does the most appropriate treatment strategy in people where antipsychotic medication is effective but not tolerated differ between children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 7
B9*	Does the length of antipsychotic medication that is continued for prevention of relapse (maintaining and promoting recovery) differ between children and young people with psychosis and schizophrenia and adults with psychosis and schizophrenia?	Chapter 7
B10*	Does the risk of adverse effects associated with antipsychotic augmentation differ between children/young people and adults with psychosis and schizophrenia that is in remission?	Chapter 7
B11	Do the advantages and disadvantages of psychological or psychosocial interventions, compared with alternative management, differ between children/young people and adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 6
B12	Are the advantages and disadvantages of combining particular psychological/ psychosocial interventions with an antipsychotic, either concurrently or sequentially, different for children and young people with psychosis and schizophrenia	Chapter 6

No.	Review questions	Guideline chapter
	compared with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	
B13	Should the duration (and, where relevant, frequency) of an initial psychological/ psychosocial intervention be different in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 6
B14	Is the most effective format for particular psychological/ psychosocial interventions (for example, group or individual) the same for children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 6
B15*	Do the competencies or training requirements for practitioners to be able to deliver psychological/psychosocial interventions differ for those working with children and young people with psychosis and schizophrenia compared with those working with adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 6

No.	Review questions	Guideline chapter
B16*	Are there any different factors (including patient population, age, and so on) that predict the nature and degree of response to psychological/psychosocial interventions, which should be considered in children and young people with psychosis and schizophrenia that it is not necessary to consider in adults with psychosis and schizophrenia? The following subgroups should be considered: • Initial treatment (first episode psychosis) • Acute treatment (not first episode psychosis) • Treatment resistance • Remission • Maintaining and promoting recovery	Chapter 6
* This review question was posed for GDG consideration and not answered via systematic review.		

C. Service settings and educational needs

Scope Section 4.3.1 (i) and (j)

No.	Review questions	Guideline chapter
C1	For children and young people with psychosis and schizophrenia: a) Are there any psychological or psychosocial interventions (CRT) that enhance cognition and/or improve engagement with education/occupational activities? b) *What are the competencies or training requirements for practitioners to be able to deliver such interventions?	Chapter 8
C2	For children and young people with psychosis and schizophrenia (particularly from black and minority ethnic groups), do specialised intensive services (EIP services; specialist CAMHS) improve access and engagement with mental health services?	Chapter 4
C3*	What is the best way of providing educational opportunities to integrate/coordinate access to education/employment opportunities for children and young people with schizophrenia: school, or a classroom in a CAMHS unit?	Chapter 8
* This review question was posed for GDG consideration and not answered via systematic review.		

Appendix 6

D. Experience of care

No.	Review questions	Guideline chapter
D1	For children and young people with psychosis and schizophrenia, what can be done to improve their experience of care?	Chapter 4

APPENDIX 7: REVIEW PROTOCOLS

Access to and delivery of services

Topic	**Access to and delivery of services**
Scope	4.3.1 (i) and (j)
Review question(s)	**RQ C2**: For children and young people with psychosis and schizophrenia (particularly from black and minority ethnic groups), do specialised intensive services (EIP services; specialist CAMHS) improve access and engagement with mental health services?
Sub-question(s)	None
Chapter	Chapter 4
Sub-section	None
Topic Group	None
Sub-section lead	N/A
Objectives	To provide evidence-based recommendations, via GDG consensus where necessary, regarding ways to improve access to and engagement with mental health services for children and young people with psychosis and schizophrenia, particularly those from black and minority ethnic groups.
Criteria for considering studies for the review	
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. Consideration should be given to the specific needs of children and young people with a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of bipolar disorder.

Intervention	Specialised intensive services (for example, CAMHS, EIP)
Comparison	Alternative management strategies: • Non-specialised services • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Symptoms • Psychosocial functioning
Secondary outcomes	None
Other outcomes	None
Study design	RCTs; systematic reviews
Include unpublished data?	Yes (if criteria met). The GDG will use a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG will not accept evidence submitted as commercial in confidence. However, the GDG recognises 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.
Dosage	N/A
Minimum sample size	>10 per arm. Exclude studies with > 50% attrition from either arm of the trial (unless adequate statistical methodology has been applied to account for missing data)
Study setting	Any
Databases searched	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, ERIC, HTA, IBSS, Sociological Abstracts, SSCI – Web of Science Grey literature databases: HMIC, PsycBOOKS, PsycEXTRA

Database search dates	Systematic reviews: 1995 to May 2012 RCTs: inception of databases to May 2012
General search strategy used	Core/topic specific databases – generic search: [(population terms – version 1) AND (systematic review/ RCT study design filters)] Grey literature databases – generic search: [(Population search terms only – version 1)]
Amendments to filter/ search strategy	None
Searching other resources	• Hand-reference searching of reference lists of included studies. • GDG members will be asked to confirm that the list of included studies includes key papers.
Existing reviews	No
Updated	No
Not updated	N/A
The review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the impact of specialised intensive services on access and engagement with mental health services. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. The main review will focus on children and young people between the ages of 14 and 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made.

Experience of care

Topic	**Experience of care**
Scope	The GDG considered this an important topic to consider post-finalisation of the scope.
Review question(s)	**RQ D1:** For children and young people with psychosis and schizophrenia, what can be done to improve their experience of care?

Sub-question(s)	None
Chapter	Chapter 4
Sub-section	None
Topic Group	Service users, carer representatives and members of the reviewing team
Sub-section lead	N/A
Objectives	To identify the experiences of care (access to services, treatment and management) for children and young people with psychosis and schizophrenia
Criteria for considering studies for the review	
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. Consideration should be given to the specific needs of children and young people with a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of bipolar disorder.
Intervention	Specialised intensive services (CAMHS, EIP)
Comparison	Alternative management strategies: • Non-specialised services • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	Experience of care
Secondary outcomes	None
Other outcomes	None
Study design	Existing NICE guidelines will be reviewed with the aim of incorporating or adapting recommendations pertaining to the experience of care for children and young people with psychosis and schizophrenia using methodology described in Chapter 3.

Include unpublished data?	N/A
Dosage	N/A
Minimum sample size	N/A
Study setting	N/A
Databases searched	N/A
Database search dates	N/A
General search strategy used	N/A
Amendments to filter/ search strategy	N/A
Searching other resources	None
Existing reviews	The published sources of information that will be used are: • *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a) • *Schizophrenia* (NCCMH, 2010; NICE, 2009a)
Updated	No
Not updated	N/A
The review strategy	The principal aims of the topic group will be to: • Identify key issues and areas of concern for children and young people with psychosis and schizophrenia using NHS mental health services. • Review the underlying evidence and recommendations from *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011a) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) for their relevance to children and young people with psychosis and schizophrenia, bearing in mind the identified key issues and areas of concern. The topic group discussion will be fed back to the GDG who will take into account the key issues and areas of concern and the recommendations from *Service User Experience in Adult Mental Health*

	(NICE, 2011a) and *Schizophrenia* (NICE, 2009a) identified by the topic group as being relevant to children and young people with psychosis and schizophrenia. Recommedations from the guidelines used will be adapted using the methods set out in Chapter 3.

At risk mental states for psychosis and schizophrenia in children and young people

Topic	**At risk mental states in psychosis and schizophrenia in children and young people**
Scope	4.3.1 (a)
Review question(s)	**RQ A1:** In children and young people, what are the specific behaviours and symptoms that are associated with an increased risk of developing psychosis[1] and schizophrenia (at risk mental state)? **RQ B1:** For children and young people who are at risk of developing psychosis[1] and schizophrenia (at risk mental state), does the provision of pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes?
Sub-question(s)	**RQ A1**: Sub-questions: a) What is the course of these behaviours and symptoms? b) What are the specific behaviours and symptoms that prompt initial recognition of psychoses[1] or prompt diagnosis of schizophrenia?
Chapter	Chapter 5
Sub-section	None
Topic Group	None
Sub-section lead	N/A
Objectives	• To determine the specific behaviours and symptoms that are associated with an increased risk of developing psychosis and schizophrenia. • To evaluate if pharmacological, psychological or psychosocial and/or dietary interventions improve outcomes for children and young people who are at risk of developing psychosis and schizophrenia.

Criteria for considering studies for the review	
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Consideration should be given to the specific needs of children and young people with a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of psychosis, schizophrenia or bipolar disorder.
Intervention	For RCTs or systematic reviews of RCTs, pharmacological and psychological interventions will be considered. *Pharmacological interventions include:* all antipsychotic medication licensed in the UK for the treatment of children and young people with psychosis and schizophrenia, including considerations related to the age of children and young people (for example, dose modifications). Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia). Note that guideline recommendations will not normally fall outside licensed indications. Exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. • Amisulpride • Aripiprazole • Benperidol • Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol • Levomepromazine • Pericyazine • Paliperidone • Pimozide • Prochlorperazine • Promazine hydrochloride • Olanzapine • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate

	Psychological interventions include: • CBT • CRT • Counselling and supportive psychotherapy • Family intervention (including family therapy) • Psychodynamic psychotherapy and psychoanalysis • Psychoeducation • Social skills training • Arts therapies *Dietary interventions include:* • Any dietary/nutritional supplements
Comparison	Alternative management strategies: • Placebo • Treatment as usual • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Transition to psychosis • Time to transition to psychosis
Secondary outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes and cardiotoxicity)
Other outcomes	None
Study design	RCTs; systematic reviews
Include unpublished data?	Yes (if criteria met). The GDG will use a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG will not accept evidence submitted as commercial in confidence. However, the GDG recognises 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.

Dosage	Any
Minimum sample size	RCTs: >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	Any
Databases searched	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: CDSR, CENTRAL, DARE, HTA *Note:* any evidence resulting from generic guideline searches also mapped to RQ
Database search dates	Systematic review: 1995 to May 2012 RCT: inception of databases to May 2012
General search strategy used	[(Population terms – version 2) AND (at risk terms) AND (systematic review/RCT)] *Note:* any evidence resulting from generic guideline searches also mapped to RQ.
Amendments to filter/ search strategy	None
Searching other resources	• Hand-reference searching of reference lists of included studies. • GDG members will be asked to confirm that the list of included studies includes key papers. • Drug companies will be requested to provide relevant published and unpublished data.
Existing reviews	No
Updated	No
Not updated	N/A
The review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological, psychological, dietary and combination treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence.

	• The main review will focus on children and young people between the ages of 14 and 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.
Note. [1] Children and young people who are at risk of developing psychosis and those who have early psychosis but do not have a formal diagnosis of either schizophrenia or bipolar disorder.	

Treatment (psychological and psychosocial interventions)

Topic	**Psychological and psychosocial interventions for children and young people with psychosis and schizophrenia**
Scope	4.3.1 (b), (d)–(h) and (k)
Review question(s)	**RQ B11**[1]: Do the advantages and disadvantages of psychological or psychosocial interventions, compared with alternative management, differ between children and young people and adults with schizophrenia? **RQ B12**[1]: Are the advantages and disadvantages of combining particular psychological/psychosocial interventions with an antipsychotic, either concurrently or sequentially, different for children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia? **RQ B13**: Should the duration (and, where relevant, frequency) of an initial psychological/psychosocial intervention be different in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?

	RQ B14[1]: Is the most effective format for particular psychological/psychosocial interventions (for example, group or individual) the same for children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?
Sub-question(s)	**RQ B15**: Do the competencies or training requirements for practitioners to be able to deliver psychological/psychosocial interventions differ for those working with children and young people with psychosis and schizophrenia compared with those working with adults with psychosis and schizophrenia? **RQ B16**: Are there any different factors (including patient population, age, and so on) that predict the nature and degree of response to psychological/psychosocial interventions, which should be considered in children and young people with psychosis and schizophrenia that it is not necessary to consider in adults with psychosis and schizophrenia?
Chapter	Chapter 6
Sub-section	None
Topic Group	None
Sub-section lead	N/A
Objectives	To provide evidence-based recommendations regarding the psychological and psychosocial treatment and management of children and young people with psychosis and schizophrenia, including a review of the adult *Schizophrenia* guideline (NICE, 2009a, NCCMH, 2010) for its relevance to children and young people.
Criteria for considering studies for the review	
Population	**Inclusion**: Children and young people (aged 18 years and younger) with first episode psychosis. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion**: Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.

Intervention	• Cognitive behavioural therapy (CBT) • Counselling and supportive psychotherapy • Family intervention (including family therapy) • Psychodynamic psychotherapy and psychoanalysis • Psychoeducation • Social skills training • Arts therapies
Comparison	Alternative management strategies: • Treatment as usual • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Remission
Secondary outcomes	None
Other outcomes	None
Study design	RCTs; systematic reviews
Include unpublished data?	Yes (if criteria met). The GDG will use a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG will not accept evidence submitted as commercial in confidence. However, the GDG recognises 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.
Number of sessions	Any

Minimum sample size	≥ 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	Any
Databases searched	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, ERIC, HTA, IBSS, Sociological Abstracts, SSA, SSCI – Web of Science Grey literature databases: HMIC, PsycBOOKS, PsycEXTRA
Database search dates	Systematic reviews: 1995 to May 2012 RCTs: inception of databases to May 2012
General search strategy used	Core/topic specific databases – generic search: [(population terms – version 1) AND (systematic review/RCT study design filters)] Grey literature databases – generic search: [(population search terms only – version 1)]
Amendments to filter/search strategy	None
Searching other resources	• Hand-reference searching of reference lists of included studies. • GDG members will be asked to confirm that the list of included studies includes key papers.
Existing reviews	The adult *Schizophrenia* guideline (NCCMH, 2010)
Updated	Yes
Not updated	N/A
The review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of psychological and psychosocial interventions. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and 18 years. The review will seek to identify whether modifications in treatment and management

	• of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

Note. [1] The following subgroups will be considered for each RQ:
a) Initial treatment (first episode psychosis)
b) Acute treatment (not first episode psychosis)
c) Treatment resistance
d) Remission
e) Maintaining and promoting recovery

Treatment (pharmacological interventions) for psychosis and schizophrenia in children or young people

Topic	**Pharmacological interventions for children and young people with psychosis and**
Scope	4.3.1 (c) – (h) and (k)
Review question(s)	**RQ B2**: Does the efficacy profile of continuous antipsychotic drug treatment, compared with alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children/young people and adults with schizophrenia?[1] **RQ B3**: Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared with adults with psychosis and schizophrenia (in particular, the metabolic, neurological and cognitive impairments)?[1]

	RQ B5a: For initial treatment in children and young people with schizophrenia: Should the dose/duration (and, where relevant, frequency) be different compared with adults? **RQ B6**: Are the same baseline measurements/monitoring procedures undertaken before initiating antipsychotic medication used in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?[1] **RQ B7**: For children and young people whose illness has not responded to pharmacological treatment, what is the next most effective treatment strategy and when do you decide to change treatment? Does this differ from adults with psychosis and schizophrenia? **RQ B8**: Does the most appropriate treatment strategy in people where antipsychotic medication is effective but not tolerated differ between children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?[1] **RQ B9**: Does the length of antipsychotic medication that is continued for prevention of relapse (maintaining and promoting recovery) differ between children and young people with psychosis and schizophrenia and adults with psychosis and schizophrenia? **RQ B10**: Does the risk of adverse effects associated with antipsychotic augmentation differ between children/young people and adults with psychosis and schizophrenia that is in remission?
Sub-question(s)	**RQ B4:** Do clinicians manage and monitor side effects of antipsychotic treatment differently in children and young people with psychosis and schizophrenia compared with adults with psychosis and schizophrenia?[1] **RQ B5b**: For initial treatment in children and young people with schizophrenia: Are there any different factors (including patient population, age, and so on) that predict the nature and degree of response to medication, which should be considered in children and young people with psychosis and schizophrenia that it is not necessary to consider in adults with psychosis and schizophrenia?
Chapter	Chapter 7

Sub-section	None
Topic Group	None
Sub-section lead	N/A
Objectives	To provide evidence-based recommendations regarding the pharmacological (antipsychotic) treatment and management of initial treatment in children and young people with psychosis and schizophrenia, including a review of the adult *Schizophrenia* guideline (NICE, 2009a; NCCMH, 2010) for its relevance to children and young people.
Criteria for considering studies for the review	
Population	**Inclusion:** Children and young people (aged 18 years and younger) with first episode psychosis. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion:** Study samples consisting only of individuals with a formal diagnosis of bipolar disorder.
Intervention	All antipsychotic medication licensed in the UK for the treatment of children and young people with psychosis and schizophrenia, including considerations related to the age of participants (for example, dose modifications). Off-label use may be considered if clearly supported by evidence (for example, those licensed only for adults with psychosis and schizophrenia). Note that guideline recommendations will not normally fall outside licensed indications. Exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. • Amisulpride • Aripiprazole • Benperidol • Chlorpromazine hydrochloride • Clozapine • Flupentixol • Haloperidol • Levomepromazine • Pericyazine • Paliperidone • Pimozide

	• Prochlorperazine • Promazine hydrochloride • Olanzapine • Quetiapine • Risperidone • Sulpiride • Trifluoperazine • Zuclopenthixol • Zuclopenthixol acetate
Comparison	Alternative management strategies: • Placebo • Psychological intervention • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Mental state (symptoms, depression, anxiety, mania) • Mortality (including suicide) • Global state • Psychosocial functioning • Social functioning • Leaving the study early for any reason • Adverse effects (including effects on metabolism, EPS, hormonal changes and cardiotoxicity) • Remission
Secondary outcomes	None
Other outcomes	None
Study design	RCTs; systematic reviews; observational studies
Include unpublished data?	Yes (if criteria met). The GDG will use a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG will not accept evidence submitted as commercial in confidence. However, the GDG recognises 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.

Dosage	Any
Minimum sample size	≥ 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	Any
Databases searched	**RQ B2 and RQ B5**: Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, ERIC, HTA, IBSS, Sociological Abstracts, SSA, SSCI – Web of Science Grey literature databases: HMIC, PsycBOOKS, PsycEXTRA **RQ B3**: Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: CDSR, CENTRAL, DARE
Database search dates	Systematic reviews: 1995 to May 2012 RCTs/observational studies: inception of databases to May 2012
General search strategy used	**RQ B2, B5, B6, B7, B8, B9**: Core/topic specific databases – generic search: [(population terms – version 1) AND (systematic review/RCT study design filters)] Grey literature databases – generic search: [(population search terms only – version 1)] **RQ B3, B4, B10**: [(population terms – version 1) AND (antipsychotic terms) AND (side effect terms) AND (observational study filter)]
Amendments to filter/ search strategy	None
Searching other resources	• Hand-reference searching of reference lists of included studies. • GDG members will be asked to confirm that the list of included studies includes key papers. • Drug companies will be requested to provide relevant published and unpublished data.

Existing reviews	The adult *Schizophrenia* guideline (NCCMH, 2010)
Updated	Yes
Not updated	N/A
The review strategy	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • In order to assess the possible side effects of antipsychotic medication, children and young people with psychosis and schizophrenia[1] will be included. In order to assess the efficacy of antipsychotic medication, children and young people with a formal diagnosis of schizophrenia will be included. • The main review will focus on children and young people between the ages of 14 and 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

Note. [1] The following subgroups will be considered:
a) Initial treatment (first episode psychosis)
b) Acute treatment (not first episode psychosis)
c) Treatment resistance
d) Remission
e) Maintaining and promoting recovery

Appendix 7

Cognition, employment and education

Topic	**Cognition, employment and education**
Scope	4.3.1 (i) and (j)
Review question(s)	**RQ C1a**: For children and young people with psychosis and schizophrenia are there any psychological or psychosocial interventions (CRT) that enhance cognition and/or improve engagement with education/occupational activities? **RQ C3**: What is the best way of providing educational opportunities to integrate/coordinate access to education/ employment opportunities for children and young people with schizophrenia: school, or a classroom in a CAMHS unit?
Sub-question(s)	**RQ C1b**: For children and young people with psychosis and schizophrenia, what are the competencies or training requirements for practitioners to be able to deliver such interventions?
Chapter	Chapter 8
Sub-section	None
Topic Group	None
Sub-section lead	N/A
Objectives	To provide evidence-based recommendations regarding interventions that may enhance cognition or improve engagement with education or occupational activities for children and young people and particularly those from black and minority ethnic groups.
Criteria for considering studies for the review	
Population	**Inclusion**: Children and young people (aged 18 years and younger) with first episode psychosis. Consideration will also be given to the specific needs of children and young people with psychosis and schizophrenia who have a mild learning disability and those from black and minority ethnic groups. **Exclusion**: Individuals with a formal diagnosis of bipolar disorder.
Intervention	• CRT • Psychoeducation • Social skills training

Comparison	Alternative management strategies • Treatment as usual • Waitlist • Any of the above interventions offered as an alternative management strategy
Primary outcomes	• Engagement with education/occupational activities • Educational attainment • Engagement with mental health services • Cognition (including social cognition)
Secondary outcomes	• Symptoms • Psychosocial functioning
Other outcomes	None
Study design	RCTs; systematic reviews
Include unpublished data?	Yes (if criteria met). The GDG will use a number of criteria when deciding whether or not to accept unpublished data. First, the evidence must be accompanied by a trial report containing sufficient detail to properly assess the quality of the data. Second, the evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Therefore, the GDG will not accept evidence submitted as commercial in confidence. However, the GDG recognises 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.
Dosage	N/A
Minimum sample size	>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	Any
Databases searched	Core databases: Embase, MEDLINE, MEDLINE In-Process, PsycINFO Topic specific databases: AEI, AMED, ASSIA, BEI, CDSR, CENTRAL, CINAHL, DARE, ERIC, HTA, IBSS, Sociological Abstracts, SSA, SSCI – Web of Science Grey literature databases: HMIC, PsycBOOKS, PsycEXTRA
Database search dates	Systematic review: 1995 to May 2012 RCT: inception of databases to May 2012

General search strategy used	Core/topic specific databases – generic search: [(population terms – version 1) AND (systematic review/RCT study design filters)] Grey literature databases – generic search: [(population search terms only – version 1)]
Amendments to filter/ search strategy	None
Searching other resources	• Hand-reference searching of reference lists of included studies. • GDG members will be asked to confirm that the list of included studies includes key papers.
Existing reviews	No
Updated	No
Not updated	N/A
• *The review strategy*	• Two independent reviewers will review the full texts obtained through sifting all initial hits for their eligibility according to the inclusion criteria outlined in this protocol. • The initial approach is to conduct a meta-analysis evaluating the benefits and harms of pharmacological treatment. However, in the absence of adequate data, the literature will be presented via a narrative synthesis of the available evidence. • The main review will focus on children and young people between the ages of 14 and 18 years. The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. • Unpublished data will be included when the evidence is accompanied by a trial report containing sufficient detail to properly assess the quality of the data. The evidence must be submitted with the understanding that data from the study and a summary of the study's characteristics will be published in the full guideline. Unpublished data will not be included when evidence submitted is commercial in confidence.

APPENDIX 8: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

This appendix can be found on the CD-ROM.

APPENDIX 9: TEMPLATE DATA EXTRACTION FORM FOR CLINICAL STUDIES AND REVIEWS

The following tables set out the fields that were used within the NCCMH data extraction database.

STUDY CHARACTERISTICS			
		Data to be extracted	**Instructions for data extraction**
Study information		Trial ID	Enter an ID for the trial (use the study ID for the first trial report, that is, enter first author and year (SMITH1992).
		Study ID	Use the first trial report. Enter first author and year (SMITH1992). Use lowercase letters to distinguish identical citations (SMITH1992a, SMITH1992b).
Context		Year (first results published)	Enter year of publication (see Study ID).
		Country	Select the name of the country where the study was based (or from which participants were recruited) or enter 'multiple'.
		Locality	Enter the name of the city or region where the study was based (or from which participants were recruited) or enter 'multiple sites'.
		Context quote	If relevant (for example, where there are multiple countries and/or sites), enter a quotation describing the study setting. You may include information about the different countries, area, the specific location, time, and so on. Enter 'N/A' if not applicable.

		Data to be extracted	**Instructions for data extraction**
Inclusion criteria		Recruitment location	From which setting(s) were participants recruited for the trial?
		Recruitment quote	Enter a quotation from the text describing the method of recruitment.
		Number of participants approached	How many people were contacted about participating in the study (for example, given a leaflet)? This is often 'not reported'.
		Number of participants randomised	How many people were randomly assigned to any group? Include participants who were later lost to follow-up, excluded during a run-in or washout, and so on. Enter 'not reported' if information could not be obtained.
		Run-in/washout period	If there was a run-in or washout phase, did it occur before or after participants had been assigned to groups?
		Run-in/washout exclusion rate %	What percentage of randomised participants was excluded during the run-in or washout? Enter as a decimal between 0 and 1. Do not round. Enter 'N/A' if there was no run-in. Enter 'not reported' if information could not be obtained.
		Run-in/washout quote	If applicable, enter a quotation describing the run-in or washout phase, or enter 'N/A'.
	Diagnosis	Assessor	Select individual who made the diagnostic assessment that led to inclusion into the study.
		Inclusion questionnaire 1	If participants had to score above or below a threshold on a questionnaire to be included, which questionnaire was used?

		Data to be extracted	**Instructions for data extraction**
		Inclusion cut-off questionnaire 1	If participants had to score above (>) or below (<) a threshold on a questionnaire to be included, what score was required? Enter N/A if no questionnaire used. Enter 'not reported' if a questionnaire was used but the required value is not reported.
		Inclusion questionnaire 2	If participants had to score above or below a threshold on a second questionnaire to be included, which questionnaire was used?
		Inclusion cut-off questionnaire 2	If participants had to score above (>) or below (<) a threshold on a questionnaire to be included, what score was required? Enter 'N/A' if no questionnaire was used. Enter 'not reported' if a questionnaire was used but the required value is not reported.
		Diagnosis criteria	Where possible, select the specific DSM or ICD criteria used to include participants.
		Diagnosis	Select the inclusion criteria diagnosis. For studies including more than one diagnosis select either 'Psychosis - mixed, including bipolar disorder' or 'Psychosis - mixed, not including bipolar disorder'.
		Diagnosis format	Select the method by which participants were assessed. For studies with several screening steps (for example, questionnaire then diagnostic interview), select the first method on the list.

		Data to be extracted	**Instructions for data extraction**
		Diagnosis duration	If participants had to have a disorder for some period of time to be included, enter the duration requirement in months. If there was no reported duration requirement, enter 'N/A'.
		Diagnosis sub-group category	Select subgroup category used to include participants (may not be reported).
		Diagnosis sub-group category quote	If you have entered 'unclear' add a quote to support this.
		Minimum age (years)	Enter the minimum age (in years) inclusion criteria.
		Maximum age (years)	Enter the maximum age (in years) inclusion criteria.
		Inclusion quote	Include any other information about the inclusion criteria (for example, duration requirement, required comorbidities, and so on). Do not duplicate information captured in other fields related to the inclusion and exclusion criteria.
Exclusion criteria		Bipolar disorder excluded?	Were individuals excluded from the study if they had a diagnosis of bipolar disorder?
		Substance-induced psychotic disorder excluded?	Were individuals excluded from the study if they had a substance-induced psychotic disorder?
		Substance dependence disorder excluded?	Were individuals excluded from the study if they had a substance dependence disorder?

		Data to be extracted	Instructions for data extraction
		Other psychiatric diagnoses excluded?	Were individuals excluded from the study if they had any other psychiatric diagnosis? Do not duplicate information captured in other fields related to diagnostic exclusions.
		Other psychiatric exclusions quote	Enter a quote describing any other exclusions relating to the diagnosis.
		Neurological impairment excluded?	Were individuals with a neurological impairment excluded from the study?
		Risk of suicide excluded?	Were individuals considered at risk of suicide excluded from the study?
		Mild learning disability excluded?	Were individuals with a mild learning disability excluded from the study?
		Physical health exclusions?	Were individuals with any physical health conditions excluded from the study (for example, heart disease, diabetes)? This does not include pregnancy.
		Physical health quote	Enter a quote describing any other physical health conditions.
		Previous antipsychotic medication	How did the study handle applicants who had previously used antipsychotic medication?
		Current antipsychotic medication	How did the study handle applicants who were currently using antipsychotic medication?
		Current medication for 'other psychiatric' conditions	How did the study handle applicants who were currently using other psychiatric medication (other = not antipsychotic)?

		Data to be extracted	Instructions for data extraction
		Current medication for physical or neurological conditions	How did the study handle applicants who were currently using medication for physical health conditions (for example, heart disease) or neurological conditions (for example, epilepsy)?
		Medication quote	If applicable, enter a quotation describing the relevant criteria, or enter 'N/A'.
		Other exclusions quote	If there were any other exclusion criteria, enter them here. Examples include pregnancy and breast feeding. Do not duplicate information extracted elsewhere.
Group assignment		Number of groups	To how many groups were participants assigned?
		Randomisation unit	What was the unit of randomisation. (Most trials randomise individuals, but some assign GP surgeries, schools, households or other units that include more than one person.)
		Number of cluster	If the trial randomised individuals, enter 'N/A'. If the trial randomised another unit, enter the number of units assigned (for example, if 200 children were randomised by assigning 10 classrooms, enter 10).
Participant demographics		Mean age (years)	Enter the mean age (years) of participants assigned to any group. Do not round. Enter 'not reported' if information cannot be obtained.
		Lower age range (years)	Enter the age (in years) of the youngest participant in the study. Do not round. Enter 'not reported' if information cannot be obtained.

		Data to be extracted	Instructions for data extraction
		Upper age range (years)	Enter the age (in years) of the oldest participant in the study. Do not round. Enter 'not reported' if information cannot be obtained.
		Sex (% male)	Enter the percentage of participants that were male.
		Mean duration of disorder	Enter the mean duration of the disorder in the study as number of months. Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		Mean age of onset (years)	Enter the mean age (in years) of onset of the disorder. Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		Ethnicity (% white)	Enter the percent of participants in the study who were white as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		Previous antipsychotic medication %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if data cannot be obtained. Enter 'unclear' if previous psychiatric treatment is referred to but specifics are not reported.
		Current antipsychotic medication %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if data cannot be obtained. Enter 'unclear' if current antipsychotic treatment is referred to but specifics are not reported.

		Data to be extracted	**Instructions for data extraction**
		Current 'other psychiatric' medication %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if data cannot be obtained. Enter 'unclear' if current 'other psychiatric' treatment is referred to but specifics are not reported. Other psychiatric = not antipsychotic.
		Current medication for physical or neurological conditions %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if data cannot be obtained. Enter 'unclear' if current physical or neurological treatment is referred to but specifics are not reported.
		Medication quote	If categorical data were converted to continuous data, give the number in each category.
		Previous psychological treatment %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if data cannot be obtained. Enter 'unclear' if previous psychological therapy is referred to but specifics are not reported.
		Current psychological treatment %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if data cannot be obtained. Enter 'unclear' if current psychological therapy is referred to but specifics are not reported.
		Psychological therapy quote	Enter quote describing previous or current psychological therapy.
		Comorbidities %	Enter as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.

		Data to be extracted	Instructions for data extraction
		Comorbidities quote	If categorical data were converted to continuous data, give the number in each category.
		% Bipolar disorder	If individuals with bipolar disorder were included, enter % with bipolar disorder as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		% Substance-induced psychotic disorder	If individuals with substance-induced psychosis were included, enter % as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		% Substance dependence disorder	If individuals with substance-induced psychosis were included, enter % as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		% Neurological impairment	If individuals with a neurological impairment were included, enter % as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		% Risk of suicide	If individuals considered at risk of suicide were included, enter % as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.
		% Mild learning disability	If individuals with a mild learning disability were included, enter % as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained.

		Data to be extracted	Instructions for data extraction
		% Physical health condition	If individuals with a physical health condition (for example, heart disease, diabetes) were included, enter % as a decimal between 0 and 1. Do not round. Enter 'not reported' if information cannot be obtained. Do not report pregnancy here.
		Physical health quote	If individuals with a physical health condition (for example, heart disease, diabetes) were included enter a quote describing the physical health conditions present.
		Other demographics	Enter any other important demographic information by listing what other demographic data were collected (do not enter data here). Do not duplicate information in other columns.
Sequence generation		Randomisation method	How was the randomisation sequence generated?
		Quote	Where possible, enter a quotation to support your judgement about risk of bias.
		Risk of bias	Sequence truly random = Low risk. Method not specified = Unclear. Not an RCT = High risk.
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.
Allocation concealment		After recruitment	Were participants allocated to groups after the inclusion and exclusion criteria had been applied and the participants had given informed consent?

		Data to be extracted	Instructions for data extraction
		Impervious to influence	Was the allocation sequence impervious to influence? Ideally, the generation and administration of the sequence should be separate. Good methods might include sealed opaque envelopes or phoning a statistician.
		Risk of bias	After recruitment and impervious to influence = Low risk. Method not specified = Unclear. Allocated before recruitment, sequence known, sequence tampered = High risk.
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.
		Quote	Where possible, enter a quotation to support your judgement about risk of bias.
Blinding (performance and detection bias)	Participants	Participant blind	Were participants blind (unaware) of which treatment they were receiving?
		Quote	Where possible, enter a quotation to support your judgement about risk of bias.
		Risk of bias	Participants aware of assignment = High risk. Participants unaware = Low risk. Most psychological therapy trials will be high risk.
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.

		Data to be extracted	Instructions for data extraction
	Providers	Provider contact	Did researchers or practitioners have contact with the participants during the trial?
		Provider blind	Were providers blind (unaware) of which treatment they were giving?
		Quote	Where possible, enter a quotation to support your judgement about risk of bias.
		Risk of bias	No provider contact = Low risk. Providers unaware (blind) = Low risk. Provider contact + providers aware (not blind) = High risk.
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.
	Outcome assessors	Outcome assessors	Did the study include outcomes rated by an assessor (that is, not self-report or objective outcomes). Examples include clinical interview or other clinician ratings.
		Assessors blind	Were assessors blind (unaware) of which treatment the participants were receiving?
		Quote	Where possible, enter a quotation to support your judgement about risk of bias.
		Risk of bias	No assessor rated outcome = Low risk. Assessors unaware (blind) = Low risk. Assessor rated outcomes + assessors aware (not blind) = High risk.

		Data to be extracted	**Instructions for data extraction**
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.
Missing outcome data (cases not included in analysis)		Dropout reasons	Were the reasons for dropout similar across groups?
		Dropout rate	Were the rates of dropout similar across groups?
		Method of analysis	What method was used to account for missing data in the analyses? Per-protocol = participants excluded after the trial started. Available case = analysed all who provide data. LOCF = replace missing values with baseline data. Other imputation.
		Quote	Where possible, enter a quotation to support your judgement about risk of bias.
		Risk of bias	Is the method for handling missing data likely to result in an over- or under-estimation of treatment effects? Yes = High risk. No = Low risk.
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.

		Data to be extracted	**Instructions for data extraction**
Selective outcome reporting		Trial registered	Was the trial registered? Drug trials within the last decade should be registered even if they do not report a registration number.
		Registration number	If the trial was registered, record the registration number.
		Outcomes reported	Were all measured outcomes reported in sufficient detail to include in a meta-analysis?
		Quote - if unclear	Where possible, enter a quotation to support your judgement about risk of bias.
		Risk of bias	Outcomes/time points registered and reported in full = Low risk. Not registered = Unclear (unless authors confirm that all outcomes are reported). Outcomes/times missing = High risk.
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.
Other bias		Quote	Use this section sparingly. Where possible, enter a quotation to support your judgement about risk of bias.
		Stopped early	Was the trial stopped early (for example, because the intervention was thought to be beneficial or harmful)?
		Risk of bias	Use this section sparingly.

		Data to be extracted	**Instructions for data extraction**
		Direction	If high or unclear risk of bias, which group did the bias favour? For low risk of bias, enter 'N/A'. If necessary due to true uncertainty, enter 'unclear'.
Funding publication type		Funding source	How was the study funded? Enter name of funder or quote acknowledgements.
		Publication status	Were main sources of information for the trial published or unpublished papers?
		Unpublished data included in study?	Was unpublished data included in study?
		Unpublished description quote	If the review includes unpublished data (including outcomes or information about the methods), provide a quotation from the author or describe the information that may not be otherwise available to readers.

INTERVENTIONS			
		Data to be extracted	**Instructions for data extraction**
Study information		Trial ID	Enter an ID for the trial (use the study ID for the first trial report, that is, enter first author and year [SMITH1992]).
	Missing data	Number randomised	How many participants were assigned to this group? Include those who were later excluded for any reason.

		Data to be extracted	**Instructions for data extraction**
		Number post-treatment	How many participants were analysed at post-treatment? Include those who provided data but did not complete treatment AND those for whom data were imputed.
		Number follow-up	How many participants were analysed at follow-up? Include those who provided data but did not complete treatment AND those for whom data were imputed.
	Time	Contact hours	During the treatment period, how much contact did participants have with researchers or clinicians? Enter as hours (do not round) or 'not reported' if relevant. (Exclude assessments before and after treatment for research purposes only.)
Intervention component		Specific group	Select the specific type of treatment or control group.
		Specific group name	Name of the intervention or control group. Include reference to treatment manual if relevant.
		Format	Select the format of the intervention. For medication or no treatment, select 'N/A'.
		Group size	Select the format of the intervention. For medication or no treatment, select 'N/A'.
		Dose	Enter drug dose in mg. For studies of variable or escalating dose, enter the optimal or mean dose. If range only reported, add range. For psychological intervention studies enter 'N/A'.

		Data to be extracted	**Instructions for data extraction**
		Dose type	Was the dose stable throughout the study (fixed) or could participants/clinicians change the dose? For psychological interventions enter 'N/A'.
		Dose quote	If the dose was not fixed, enter a quotation describing the way in which it was adjusted during the trial. For psychological interventions enter 'N/A'.
		Hours	Enter psychological interventions as total hours of contact excluding assessment for research purposes. For pharmacological interventions enter 'N/A'.
		Frequency	Enter psychological interventions as total hours of contact excluding assessment for research purposes. For pharmacological interventions enter 'N/A'.
		Duration	Enter psychological interventions as total hours of contact excluding assessment for research purposes. For pharmacological interventions enter 'N/A'.
		Intervention setting	Where did participants receive treatment?
		Provider	Who provided the intervention?
		Group quote	If possible, include a quotation describing the intervention or control condition. You do not need to duplicate information that is adequately captured in other fields.

		Data to be extracted	**Instructions for data extraction**
	Timepoint	Weeks post-randomisation	At what time was the outcome measured? Calculate the weeks since randomisation. To convert months to weeks, do not multiply months x 4; instead, calculate M/12x52.
		Phase	At what phase in the study were these data collected? Note that a study may include multiple follow-up assessments.
Mean and standard deviation (SD)		Intervention mean	Enter the group mean. Do not enter change scores here.
		Intervention SD	Enter the SD for the mean. Do not enter SD for a change score.
		Intervention sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Control mean	Enter the group mean. Do not enter change scores here.
		Control SD	Enter the SD for the mean. Do not enter SD for a change score.
		Control sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).

		Data to be extracted	**Instructions for data extraction**
		Direction	Does this outcome favour the intervention group or control group? *Hint:* If lower scores represent a better outcome (for example, reduced symptoms) and the intervention mean is lower than the control mean, select 'favours intervention'.
Mean and standard error (SE)		Intervention mean	Enter the group mean. Do not enter change scores here.
		Intervention SE	Enter the SE for the mean. Do not enter SE for a change score.
		Intervention sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Control mean	Enter the group mean. Do not enter change scores here.
		Control SE	Enter the SE for the mean. Do not enter SE for a change score.
		Control sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Direction	Does this outcome favour the intervention group or control group?

		Data to be extracted	Instructions for data extraction
			Hint: If lower scores represent a better outcome (for example, reduced symptoms) and the intervention mean is lower than the control mean, select 'favours intervention'.
Events		Intervention events	Enter the number of events for each group. Use this format for events that can happen once for each group. Do not enter events that can occur multiple times for each person (see formats for rate).
		Intervention sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Control events	Enter the number of events for each group. Use this format for events that can happen once for each group. Do not enter events that can occur multiple times for each person (see formats for rate).
		Control sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).

		Data to be extracted	**Instructions for data extraction**
Mean difference, SD		Intervention difference	Enter the within group mean difference (for example, change from baseline).
		Intervention SD	Enter the SD of the within group change.
		Intervention sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Control difference	Enter the within group mean difference (for example, change from baseline).
		Control SD	Enter the SD of the within group change.
		Control sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Direction	Does this outcome favour the intervention group or control group? *Hint*: If lower scores represent a better outcome (for example, reduced symptoms) and the intervention mean is lower than the control mean, select 'favours intervention'.
Mean difference, SE		Intervention difference	Enter the within group mean difference (for example, change from baseline).

		Data to be extracted	**Instructions for data extraction**
		Intervention SE	Enter the SE of the within group change.
		Intervention sample size	Enter the size of the sample for each intervention.
		Control difference	Enter the within group mean difference (for example, change from baseline).
		Control SE	Enter the SE of the within group change.
		Control sample size	Enter the number of people represented in this analysis. The N may differ across outcomes/times. Include people for whom data have been imputed (for example, by LOCF).
		Direction	Does this outcome favour the intervention group or control group? *Hint*: If lower scores represent a better outcome (for example, reduced symptoms) and the intervention mean is lower than the control mean, select 'favours intervention'.

APPENDIX 10: SEARCH STRATEGIES FOR THE IDENTIFICATION OF HEALTH ECONOMIC EVIDENCE

This appendix can be found on the CD-ROM.

APPENDIX 11: METHODOLOGY CHECKLIST FOR ECONOMIC STUDIES – TEMPLATE

This checklist is designed to determine whether an economic evaluation provides evidence that is useful to inform the decision-making of the GDG. It is not intended to judge the quality of the study *per se* or the quality of reporting. For further information about how to complete the checklist, see *The Guidelines Manual* (NICE, 2009b).

Study identification *Including author, title, reference, year of publication*			
Guideline topic:			**Question no:**
Checklist completed by:			
Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case). This checklist should be used first to filter out irrelevant studies.		**Yes/ Partly/ No/Unclear/ NA**	**Comments**
1.1	Is the study population appropriate for the guideline?		
1.2	Are the interventions appropriate for the guideline?		
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?		
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?		
1.5	Are all direct health effects on individuals included?		
1.6	Are both costs and health effects discounted at an annual rate of 3.5%?		
1.7	Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?		

1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?		
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?		
1.10	Overall judgement: Directly applicable/ Partially applicable/Not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments:			

Section 2: Study limitations (the level of methodological quality). This checklist should be used once it has been decided that the study is sufficiently applicable to the context of the clinical guideline.		**Yes/Partly/ No/Unclear/ NA**	**Comments**
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?		
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?		
2.3	Are all important and relevant health outcomes included?		
2.4	Are the estimates of baseline health outcomes from the best available source?		
2.5	Are the estimates of relative treatment effects from the best available source?		
2.6	Are all important and relevant costs included?		
2.7	Are the estimates of resource use from the best available source?		

2.8	Are the unit costs of resources from the best available source?		
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?		
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?		
2.11	Is there no potential conflict of interest?		
2.12	Overall assessment: Minor limitations/Potentially serious limitations/ Very serious limitations		
Other comments:			

APPENDIX 12: HIGH PRIORITY RESEARCH RECOMMENDATIONS

The GDG has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1. **What are the long-term outcomes, both psychotic and non-psychotic, for children and young people with attenuated or transient psychotic symptoms suggestive of a developing psychosis, and can the criteria for 'at risk states' be refined to better predict those who will and those who will not go on to develop psychosis?**

The suggested programme of research would be in two phases. First, a systematic review and meta-analysis of prospective observational studies/cohorts of children and young people identified at high or ultra-high risk of developing psychosis would be undertaken. The review would identify risk and protective factors most strongly associated with the later development of psychotic and non-psychotic outcomes. Second, the factors identified in the first phase would be used to identify a large cohort of children and young people with these factors and to evaluate the effectiveness of these refined criteria for predicting the later development of psychotic and non-psychotic outcomes.

Why this is important
A major problem with trials of treatments for populations of children and young people deemed to be 'at risk' or 'at ultra-high risk' of developing psychosis is identifying the precise symptoms and/or behaviours or (risk) factors that are most strongly associated with the development of psychosis; and conversely, which (protective) factors are likely to be associated with a lowered risk of later psychosis. At present, identified factors have a low predictive value, with only about 10 to 20% of children and young people who have been identified as at high risk of going on to develop psychosis. If these risk and protective factors could be refined, it would be possible to better target children and young people who are most at risk, and reduce the numbers of those thought to be 'at risk' who do not go on to later develop psychosis.

2. **What is the clinical and cost effectiveness of omega-3 fatty acids in the treatment of children and young people considered to be at high risk of developing psychosis?**

The suggested programme of research would need to test out, using an adequately powered, multicentre randomised controlled design, the likely benefits and costs of using omega-3 fatty acids for children and young people at high risk of developing psychosis. The outcomes considered should include transition to psychosis, quality of life, symptomatic and functional improvements, treatment acceptability, side effects and self-harm. There should be follow-up at 3 years. The trial should also estimate the cost effectiveness of intervening.

Why this is important
A number of interventions have been trialled in an attempt to avert the development of psychosis, including drugs, psychological treatments and other interventions. A relatively recent, moderate-sized randomised controlled trial of omega-3 fatty acids has shown the best evidence of any intervention, to date, at reducing the rates of transition from 'high risk' states to a sustained psychosis. However, this is a single trial, which is underpowered, undertaken in one centre and lacks any health economic analysis.

3. What is the clinical and cost effectiveness for family intervention combined with individual CBT in the treatment of children and young people considered to be at high risk of developing psychosis and their parents or carers?

The suggested programme of research would need to test out, using an adequately powered, multicentre, randomised controlled design, the likely benefits and costs of providing family intervention, combined with individual CBT, for children and young people at high risk of developing psychosis and their parents or carers. The outcomes considered should include transition to psychosis, quality of life, symptomatic and functional improvements, treatment acceptability and self-harm. There should be follow-up at 3 years. The trial should also estimate the cost effectiveness of intervening.

Why this is important
A number of interventions have been trialled in an attempt to avert the development of psychosis, including drugs, psychological treatments and other interventions. After the first episode of psychosis, family intervention as an adjunct to antipsychotic medication substantially and significantly reduces relapse rates. A single small trial combining CBT family treatment with individual CBT without antipsychotic treatment suggested an important reduction in transition rates to the first psychosis.

4. What is the clinical and cost effectiveness of psychological treatment alone, compared with antipsychotic medication and compared with psychological treatment and antipsychotic medication combined, for young people with first episode psychosis?

The programme of research would compare the clinical and cost effectiveness of psychological treatment alone, compared with antipsychotic medication, and compared with psychological intervention and antipsychotic medication combined, for young people in the early stages of psychosis using an adequately powered study with a randomised controlled design. The combination of psychological interventions most likely to have an impact would be family intervention and individual CBT. The key outcomes should include symptoms, relapse rates, quality of life, treatment acceptability, experience of care, level of psychosocial functioning and the cost effectiveness of the interventions.

Why this is important
The personal and financial cost of psychosis and schizophrenia to the person, their family and friends, and to society is considerable. The personal cost is reflected in a suicide

rate of nearly 15% amongst people with schizophrenia, and a lifelong unemployment rate that varies between 50 and 75%, depending on geographical location, and reduced life expectancy. The additional cost to the healthcare system for one person with schizophrenia is estimated to reach over £50,000 per year, on average, throughout their life.

Currently, the mainstay of treatment is antipsychotic medication, but the potential adverse effects are such that there is considerable impetus to develop alternative treatment strategies to allow either lower doses or to remove the need for medication entirely. It has been recognised that psychological interventions as an adjunct to antipsychotic medication have an important part to play in the treatment of schizophrenia. NICE clinical guideline 82[246] identified family intervention and CBT as adjunct treatments and current evidence suggests that these interventions are cost saving. However, evidence for adjunctive family intervention and CBT is lacking in children and young people with psychosis. Furthermore, there has been one recent positive trial of CBT as a first-line treatment, without antipsychotics, for young people in the early stages of psychosis.

5. What is the clinical effectiveness of clozapine for children and young people with schizophrenia with symptoms unresponsive to antipsychotic medication and psychological treatment combined?

The suggested programme of research would need to test out, using an adequately powered, randomised controlled design, the likely benefits of using clozapine, compared with another antipsychotic, for children and young people with symptoms of schizophrenia unresponsive to antipsychotic medication and psychological treatment combined. The outcomes considered should include quality of life, symptomatic and functional improvements, treatment acceptability, side effects and length of hospitalisation.

Why this is important

Currently, about 30% of people with schizophrenia have symptoms that do not respond adequately to treatment with an antipsychotic. Although precise figures are unavailable, especially for children and young people, smaller percentages of people do not respond when a second, alternative, antipsychotic and an adequate course of psychological treatment have been tried. For these people, clozapine, which has a different dopamine receptor subtype blocking profile from other antipsychotics, has become an important treatment option in adults. However, evidence is lacking (only one study) about the effectiveness of clozapine for 'treatment-resistant schizophrenia' in children and young people.

6. What is the most effective management strategy for preventing the development of excessive weight gain and metabolic syndrome associated with the use of antipsychotic medication in children and young people?

The suggested programme of research would be in two parts: (1) a longitudinal cohort study (a national observational database of at least 12 months' duration) to determine

[246]NICE, 2009a.

the incidence and predictors of adverse physical effects of antipsychotic medication; (2) a randomised controlled trial of behavioural and/or medical approaches to reduce weight gain and the risk of metabolic syndrome associated with antipsychotic medication.

Why this is important

Rapid weight gain associated with antipsychotic medication and poor physical health (smoking, lack of exercise) leading to type 2 diabetes and metabolic syndrome are major sources of morbidity and premature mortality in young people with psychosis and schizophrenia. Most evidence of adverse effects comes from short-term studies of antipsychotics (maximum 8 to 12 weeks). In contrast, very little is known about the longer-term adverse effects of these drugs. Evidence is needed both on longer-term adverse effects as well as on effective early intervention strategies that reduce these risk factors and improve physical health outcomes.

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12 ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
AEI	Australian Education Index
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AIMS	Abnormal Involuntary Movement Scale
AMED	Allied and Complementary Medicine Database
AMHS	adult mental health services
ASSIA	Applied Social Services Index and Abstracts
BARS	Barnes Akathisia Rating Scale
BEI	British Education Index
BMA	British Medical Association
BMI	body mass index
BMJ	*British Medical Journal*
BNF(C)	*British National Formulary (for Children*)
BP	blood pressure
BPM	beats per minute
BPRS (-P)	Brief Psychiatric Rating Scale (-Psychotic Subscale)
CAARMS	Comprehensive Assessment of At Risk Mental States
CAMHS	child and adolescent mental health services
CBT	cognitive behavioural therapy
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CGI	Clinical Global Impression scale
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPA	care programme approach
CRT	cognitive remediation therapy
C&TP	care and treatment plans (Wales)
DARE	Cochrane Database of Abstracts of Reviews of Effects
DSM (-III, -III-R,-IV, -V)	*Diagnostic and Statistical Manual of Mental Disorders* (3rd edition, 3rd edition revised, 4th edition, 5th edition)
DUP	duration of untreated psychosis
EBSCO	Elton B. Stephens Company (publisher of journal article databases)
ECG	electrocardiogram
EconLit	American Economic Association's electronic bibliography
ECT	electroconvulsive therapy
EEG	electroencephalogram

EIP	early intervention in psychosis
EIS	early intervention service
Embase	Excerpta Medica database
EPPIC	Early Psychosis Prevention and Intervention Centre, Australia
EPS	extrapyramidal symptom
ERIC	Education Resources in Curriculum
FGA	first generation antipsychotic
GAF	Global Assessment of Functioning
GDG	Guideline Development Group
GP	general practitioner
GRADE	Grading of Recommendations: Assessment, Development and Evaluation
HbA1c	glycosylated haemoglobin
HMIC	Health Management Information Consortium
HMSO	Her Majesty's Stationery Office
HPC	Health Professions Council
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IAPT	Improving Access to Psychological Therapies
IBSS	International Bibliography of Social Sciences
ICER	incremental cost-effectiveness ratio
ICD (-9, -10)	*International Classification of Diseases* (9th revision, 10th revision)
IPS	individual placement and support
IQ	intelligence quotient
ITT	intention-to-treat
K	number of studies
LOCF	last observation carried forward
MEDLINE	Medical Literature Analysis and Retrieval System Online
MRI	magnetic resonance imaging
n/N	number of participants
N/A	not applicable
NCCMH	National Collaborating Centre for Mental Health
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NIACE	National Institute of Adult Continuing Education
NICE	National Institute for Health and Care Excellence

NIHR	National Institute for Health Research
NOS	not otherwise specified
OASIS	Outreach and Support in South London
OIS	optimal information size
ONS	Office for National Statistics
p/P	probability
PANSS	Positive and Negative Syndrome Scale
POMH-UK	Prescribing Observatory for Mental Health, United Kingdom
p.r.n.	*pro re nata* (as required)
PsycBOOKS	A full-text database of books and chapters in the American Psychological Association's electronic databases
PsycEXTRA	A grey literature database, which is a companion to PsycINFO
PsycINFO	Psychological Information Database
PSYRATS	Psychotic Symptoms Rating Scale
PUFA	omega-3 fatty acid
QALY	quality-adjusted life year
QOF	Quality and Outcomes Framework
QT(c)	the interval between Q and T waves in the electrocardiogram (corrected)
RCT	randomised controlled trial
RQ	review question
RR	relative risk
SAS	Simpson-Angus Extrapyramidal Side Effects Scale
SD/sd	standard deviation
SE	standard error
SFS	Social Functioning Scale
SGA	second generation antipsychotic
SIGN	Scottish Intercollegiate Guidelines Network
SIPS	Structured Interview for Prodromal Symptoms
SMD	standardised mean difference
SPC	summary of product characteristics
SSA	Social Services Abstracts
SSCI	Social Sciences Citation Index
TSH	thyroid stimulating hormone
UKU	Udvalg for Kliniske Undersøgelser (Neurologic subscale)

"As a child psychiatrist I am all too aware that when the onset of psychosis and schizophrenia is in childhood and adolescence the effects can be devastating. This is why this guideline is to be championed. It provides invaluable advice for this vulnerable group, especially intervening early before a psychotic episode fully develops, and will be an important tool in promoting recovery.'

Professor Sue Bailey, President of the Royal College of Psychiatrists
and Consultant Child and Adolescent Forensic Psychiatrist,
Forensic Adolescent Consultation and Treatment Services (FACTS),
Greater Manchester West Mental Health NHS Foundation Trust

There is a worse prognosis for psychosis and schizophrenia when onset is in childhood or adolescence, and this new NICE guideline puts much-needed emphasis on early recognition and assessment of possible psychotic symptoms. For the one-third of children and young people who go on to experience severe impairment as a result of psychosis or schizophrenia the guideline also offers comprehensive advice from assessment and treatment of the first episode through to promoting recovery.

This guideline reviews the evidence for recognition and management of psychosis and schizophrenia in children and young people across the care pathway, encompassing access to and delivery of services, experience of care, recognition and management of at-risk mental states, psychological and pharmacological interventions, and improving cognition and enhancing engagement with education and employment.

The guideline contains full details about the methods used and all the evidence on which the recommendations were based, including further data on a CD-ROM:

- characteristics of included studies
- profile tables that summarise both the quality of the evidence and the results of the evidence synthesis
- all meta-analytical data presented as forest plots
- detailed information about how to use and interpret forest plots.

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