PSYCHOSIS AND SCHIZOPHRENIA IN CHILDREN AND YOUNG PEOPLE

RECOGNITION AND MANAGEMENT

National Clinical Guideline Number X

National Collaborating Centre for Mental Health

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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 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 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 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 incorporate statements and recommendations based upon the consensus statements developed by the Guideline Development Group (GDG).

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

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

1.1.2 Uses and limitation of clinical guidelines

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

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

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

In using guidelines, it is important to remember that the absence of empirical evidence for the effectiveness of a particular intervention is not the same as evidence for ineffectiveness. In addition, and of particular relevance in mental health, evidence-based treatments are often delivered within the context of an overall treatment programme including a range of activities, the purpose of which may be to help engage the 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 Clinical Excellence (NICE) was established as a Special Health Authority for England and Wales in 1999, with a remit to provide a single source of authoritative and reliable guidance for service users, professionals and the public. NICE guidance aims to improve standards of care, diminish unacceptable variations in the provision and quality of care across the NHS, and ensure that the health service is person-centred. All guidance is developed in a

transparent and collaborative manner, using the best available evidence and involving all relevant stakeholders.

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

1.1.4 From national clinical guidelines to local protocols

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

1.1.5 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 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 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 Patient and Public Involvement Programme. The NICE Guidelines Technical Adviser provided advice and assistance regarding aspects of the guideline development process.

All GDG members made formal declarations of interest at the outset, which were updated at every GDG meeting. The GDG met a total of 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 and psychosocial interventions in the treatment of psychosis and schizophrenia in children and young people
- evaluate the role of specific 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 psychosis and schizophrenia
- promote the implementation of best clinical practice through the development of recommendations tailored to the requirements of the NHS in England and Wales.

1.2.4 The structure of this guideline

The guideline is divided into chapters, each covering a set of related topics. The first three chapters provide a summary of the clinical practice and research recommendations, and a general introduction to guidelines and to the methods used to develop them. 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 Text Box 1 for details).

Text Box 1: Appendices on CD-ROM

Clinical evidence study characteristics tables	Appendix 13
Clinical evidence forest plots	Appendix 14
Economic evidence methodology checklists	Appendix 15
Health economic evidence tables of published studies	Appendix 16
Clinical and health 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. This guideline relates specifically to those identified by the tenth edition of the International Classification of Diseases and Related Health Problems (ICD-10; World Health Organisation [WHO], 1992). These disorders are schizophrenia, schizoaffective disorder, schizophreniform disorder and delusional disorder. This guideline also addresses the population of children and young people considered at clinical high risk or prodromal for psychosis and schizophrenia. This guideline does not address the identification and management of other psychotic disorders, such as bipolar disorder or depressive psychosis and schizophrenia in adults, because they are covered by other guidelines.

2.1 THE DISORDER

2.1.1 Symptoms, presentation and patterns

Schizophrenia in children and young people is a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms (hallucinations, delusions, thought disorder and negative symptoms) that alter the child's perception, thoughts, affect and behaviour. Each child with the disorder will have a unique combination of symptoms and experiences.

Typically, in child and adolescent-onset schizophrenia there is a prodromal period characterised by some deterioration in personal functioning, which may follow an acute stress, distressing experience or physical illness (Garralda, 1984). The prodromal period includes concentration and memory problems, unusual uncharacteristic behaviour and ideas, unusual experiences and bizarre perceptual experiences, disturbed communication and affect, social withdrawal, apathy and reduced interest in daily activities. These are sometimes called 'negative symptoms'. This period is often insidious, can last up to 1 year (Werry *et al*., 1994) and lead to declining school performance. This insidious onset pattern together with the facts that positive symptoms, such as delusions, can be poorly systematised and thought disorganisation is common, can delay the diagnosis of schizophrenia in children.

The prodromal period is typically followed by an acute episode marked by hallucinations, delusions and behavioural disturbance. These are sometimes called 'positive symptoms' and are usually accompanied by agitation and distress (NICE, 2009a). A wide variety of anomalous perceptual experiences may occur at the onset of an episode of schizophrenia 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 young person. For example, a young person at the onset of illness may study their reflection in the mirror for hours because it looks strangely unfamiliar or 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 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, psychological and other interventions, the symptoms diminish and disappear for many young people; although a number of negative symptoms may remain. This phase, which can last for years, may be interrupted by recurrent acute episodes which 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 very early in the course of the illness in order to delay or possibly prevent the onset of schizophrenia. This focus on very early intervention and prevention in schizophrenia 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 2.8.1).

'At-risk mental states' (ARMS), or 'ultra high risk' (UHR) states, are characterised by help-seeking behaviour and the presence of attenuated positive schizophrenic symptoms, brief limited intermittent psychotic symptoms (BLIPS) 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 increased in these 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 ARMS/UHR is modest given that the majority of those identified do not become psychotic. Furthermore, most young people identified with ARMS have a mixture of other mental health problems (for example, depression, anxiety, substance misuse disorder, 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 ARMS/UHR states are best viewed as a dimension rather than a diagnostic category, including young people at one extreme 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 young people (false-positives) who do not develop psychosis.

2.1.3 Impairment and disability

Impairments associated with psychosis and schizophrenia include the consequences that occur from living with disabling psychotic symptoms, the adverse effects of poor physical health and drug treatments (see Section 2.1.5) 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 of young people are severely impaired requiring intensive social and psychiatric support (Hollis, 2000). The onset of schizophrenia in children and young people results in greater impairment than when schizophrenia first presents in adult life. This is in part because the nature of the disorder is more severe in 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 great; creating distress and disharmony in social interactions and relationships. For young adults, impairment is also seen in their occupational and 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 of cases making a full symptomatic recovery from the first psychotic episode. The short-term course for schizophrenia is worse than for other psychosis in young people with only 12% of young people with schizophrenia in full remission at discharge compared to 50% of cases with affective psychoses (Hollis & Rapoport, 2011). The short-term outcome for schizophrenia presenting in early life appears to be worse than that of first-episode adult patients (Robinson *et al.*, 1999). If full recovery does occur then it is most likely within the first 3 months of onset of psychosis. Early recovery appears important in determining outcome. Young people (adolescents) with schizophrenia who are still psychotic after 6 months have only a 15% chance of achieving full remission, while over half of all cases that make a full recovery have active psychotic symptoms for less than 3 months (Hollis & Rapoport, 2011).

About one fifth of children and young people with schizophrenia have a good outcome with only mild impairment. However, one third have severe impairment that requires intense social and psychiatric support (Hollis, 2000). A recent Israeli whole population study found that people younger than 17 years of age with schizophrenia 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 very frequently associated with significant impairments in many aspects of life including social, educational, vocational and family. 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 and the presence of negative symptoms. Premorbid functioning and negative symptoms at onset of psychosis provide better prediction of long-term outcome than categorical ICD-10 or DSM-IV diagnosis (Hollis & Rapoport, 2011).

Even though some 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 that it also requires external, material and psychosocial conditions that can facilitate the process (Kogstad *et al.*, 2011).

2.1.5 Diagnosis

This guideline is concerned both with the non-specific diagnosis of psychosis (including schizoaffective disorder, schizophreniform disorder and delusional disorder) and with the much more specific diagnosis of schizophrenia in children and young people. Although as full discussion of the issues of the diagnosis of psychosis and schizophrenia are outside the scope of this guideline, specific issues relating to children and young people will be described here.

The experience of a psychotic disorder challenges an individual's fundamental assumption that he/she can rely upon the reality of his/her thoughts and perceptions. This is often both frightening and emotionally painful for both the sufferer and for those close to him/her. For this experience then to be classified as a disorder and to acquire a diagnostic label may either be helpful in facilitating understanding or may be experienced as yet a further assault upon one's identity and integrity. Professionals need to be aware of both the positive and negative impacts of discussing a diagnosis. This has led to some professionals and user/carer groups questioning the usefulness of diagnosis and instead preferring to emphasise a narrative formulation of an individual's experiences.

The current concept of schizophrenia in children and adolescents 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) cases from children with a relatively 'late onset' psychosis which closely resembled schizophrenia (Kolvin, 1971; Kolvin *et al.*, 1971). Importantly, in DSM-III and ICD-9 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). First, a DSM-III-R diagnosis of schizophrenia in childhood and adolescence predicted a significantly poorer adult outcome compared to other

non-schizophrenic psychosis. Second, the diagnosis of schizophrenia showed a high level of stability, with 80% having the same diagnosis recorded at adult follow-up (Jarbin *et al*., 2003).

Both ICD-10 (World Health Organisation, 1992 and DSM-IV (American Psychiatric Association, 1994) describe similar symptom clusters necessary for the diagnosis of schizophrenia (see Section 2.1.1). Although ICD-10 only requires that these be present for a duration of 1 month whilst DSM-IV requires a total duration of illness of 6 months this difference is less than first seems as the ICD-10 duration refers to acute positive symptoms only whilst DSM-IV includes any period of non-specific impairment or attenuated (prodromal) symptoms which may precede an acute episode. In both DSM and ICD, 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 pre-pubertal children.

The majority of children and young people for whom a diagnosis of psychosis or of 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 can be made of schizophrenia (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 as 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 user/carer groups, it should only be used in those instances where criteria for a 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 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

Young people developing psychosis and schizophrenia can expect poorer physical health than the general population as they get older. Life expectancy may be reduced by 16 to 25 years (Brown *et al*., 2010; Parks *et al*., 2006). Whilst 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 NICE

guidance for adults with schizophrenia (NCCMH, 2010). However schizophrenia in young people tends to be a more disabling and persistent disorder (Hollis, 2003), bringing with it greater vulnerability to physical harm from both the disease 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 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 young people with schizophrenia are exposed to these risks comes mainly from antipsychotic treatment studies where such impacts may be even more important given these drugs are prescribed for lengthy periods over a critical developmental phase. Only one paediatric cohort study has examined this issue in 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 and metabolic disturbances. Changes were dose related with risperidone, whereas only adverse metabolic effects were dose related with olanzapine, and no dose relationship was observed with aripiprazole and quetiapine. This landmark study included young people aged 4 to 19 years with various mental disorders including schizophrenia and its findings are reinforced by two systematic reviews (De Hert *et al.*, 2011; Fedorowicz & Fombonne, 2005). A systematic review confined to adolescents with schizophrenia observed that while antipsychotics had similar efficacy, adverse effects varied between drugs (Kumra *et al.*, 2008). Overall, adolescents appear more vulnerable than adults to side effects of antipsychotic medication (weight gain, extrapyramidal symptoms, metabolic problems, prolactin elevation, and sedation).

Studies of first episode psychosis provide insights into a treatment naive young group, mostly in their late teens and twenties, and encompassing the under 18s (Kirkbride *et al.*, 2006). A systematic review of weight gain and cardiometabolic abnormalities is revealing (Foley & Morley, 2011). No difference in weight gain, blood pressure and cardiometabolic indices existed between first episode patients and controls prior to commencing antipsychotics. However, within 8 weeks from 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' antipsychotic drugs. Over a third of first episode patients experienced metabolic disturbance within by 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

underlining the importance clinically of being alert to the possibility of serious metabolic disturbance occurring in those on 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 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.

Whilst 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 harmful impacts. (Myles *et al*., 2012) found 59% of first episode patients with schizophrenia used tobacco at presentation, a rate six times higher than comparable non-psychiatric populations. Furthermore, in the general population 66% of current and past tobacco users commence smoking before the age of 18 (NHS Information Centre, 2010) whilst very few initiate smoking after their early twenties (Amos *et al*., 2009). Thus tobacco use in young people with psychosis is a substantial problem which then 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 adolescents (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 young people with emerging psychosis. Previously unexposed to antipsychotics, this group are particularly vulnerable to weight gain and cardiometabolic disturbances (Correll *et al*., 2009; Foley *et al*., 2011; Alvarez-Jimenez *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 commencing treatment (Correll *et al*., 2009; Foley *et al*., 2011). Notwithstanding the adverse metabolic effects of antipsychotics, young people with psychosis and schizophrenia often experience multiple cardiovascular risk factors, including poor nutrition, inadequate exercise, 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 of the order of 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 twenties. In an Australian sample of first episode psychosis, a third of new cases were aged between 15 and 19 years old (Amminger *et al*., 2006). Whilst male gender predominance has been described in pre-adolescent children (Russell *et al*., 1989), an equal sex ratio is more commonly reported in adolescents (Hollis, 2000).

2.3 POSSIBLE CAUSES OF SCHIZOPHRENIA

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.

Much of the research into the causes of schizophrenia has been based on adult populations and is consistent with a stress-vulnerability model. The stress-vulnerability model (Zubin & Spring, 1977) 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 adolescents as well as to 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 sub-optimally 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 rather simplistic 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/duplications that disrupt genes (Eckstrand *et al*., 2008; Rapoport, Addington & Frangou 2005; Walsh, McClellan *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 being present (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 (Aseneault *et al.,* 2002). So far, cannabis use 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 cases to have developed skills in assessment and diagnosis. The diagnosis of schizophrenia is to a large extent based on the effective communication by 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 only develops gradually before puberty, making the diagnosis of psychosis more difficult than in adolescents or adults and at times more likely to be based on behaviour than on subjective experiences.

Very early onset schizophrenia shows a high rate of insidious onset of illness (Ropcke & Eggers, 2005) in most cases over six 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, conduct problems (with aggression, truancy and firesetting) and developmental abnormalities within the autistic spectrum: these may be present in about one in four. 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 should 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. Such assessment in children should include their social, educational and health needs.

Assessment should include a detailed history, mental state and physical examination (Hollis, 2008). The developmental history should pay particular attention to pre-morbid functioning. Abnormal pre-morbid functioning is more common than in adult onset disorder or other child-adolescent-onset non-schizophrenic psychoses. (Hollis, 2003; Hollis, 1995; Jacobsen and Rapoport, 1998). Poor pre-morbid functioning is associated with negative symptoms (Hollis, 2003) and may be a predictor for poor prognosis (Hollis, 2000; Werry and McClellan, 1992; Vyas *et al.,* 2007).

The cognitive level of the child will influence their ability to both understand and express complex psychotic symptoms and make sense of subjective symptoms like hallucinations (Hollis, 2008; Ropcke & Eggers, 2005). Having an understanding of the child's cognitive functioning and whether he/she has 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). 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 a child who has immature language development with apparent loosening of associations and illogical thinking. Negative symptoms can appear very similar to non-psychotic language and social impairments can be confused with anhedonia or depression (Hollis, 2008).

Managing to assess a child's mental state can be a complex process. Understanding of the child's development and whether they have speech and language problems or learning disability will affect how the mental state is assessed 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. Assessment can be a lengthy process, engagement with the child and gaining their confidence may require a

number of meetings. Assessment should include a full mental health assessment to identify comorbid conditions. Childhood-onset schizophrenia can be comorbid with pervasive developmental disorder (Rapoport *et al.,* 2008).

Given the rarity of very early onset psychosis it is important that organic illness is excluded. Physical health care and baseline investigations should include detailed physical examination and blood investigations. MRI (magnetic resonance imaging) scanning of the brain should be considered in more complex presentations, EEG (electroencephalogram) if seizures are suspected and referral for a neurological opinion if neurodegenerative disorders are suspected (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 particular careful differentiation needs to be made between children with psychotic states and those with what is sometimes called multiple complex developmental disorder (MCDD) or multiple developmental impairment (MDI), 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.

Multidisciplinary assessment is beneficial in providing a holistic view of the child's needs. Base line psychometric testing can be helpful in assessment and for future educational planning.

Where diagnosis is reached, in collaboration with the child and their parent/carer a comprehensive care plan should be developed. Children should be involved at a level appropriate to their developmental functioning. Structured interviews and rating scales may be useful to monitor treatment.

2.4.2 Adolescents

The assessment of the adolescent thought to be possibly suffering from an emerging or frank psychotic disorder will in part vary according to the route he/she has taken to the healthcare professional. At one extreme, some young people will present themselves seeking help for their distress, impairment, or abnormal experience whilst others will be only unwilling participants who are referred or presented for assessment by someone else (usually a parent, carer or possibly teacher). Nonetheless engagement of the young person is crucial both to assessment and to subsequent intervention.

The assessment needs to flexible and adapted in terms of setting, the language, and the style of interviewing to the young person's developmental stage and age. 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 and particularly of abnormal belief systems and abnormal perceptions, thoughts and experiences. Physical health factors and a physical examination should not be overlooked (see Section 2.1.4). The role of substance use as both a causative and a comorbid/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 adolescence may result from an organic neuropsychiatric cause such as encephalitis, temporal lobe epilepsy, cerebral lupus, drug intoxication and rare neurodegenerative diseases 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 level of consciousness. In such cases physical investigations such as blood tests, EEG and MRI/CT (computed tomography) scan may be helpful in reaching a diagnosis.

Physical investigations are also indicated prior to commencing antipsychotic drug treatment. These include measuring height, weight, pulse, blood pressure and depending, on the drug, an ECG (electrocardiogram) and baseline lipids, prolactin and glycosylated haemoglobin (Hb1Ac).

Collateral information from parents/carers (particularly around 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 present with 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 interventions, including psychosocial interventions, pharmacological interventions and interventions aimed at addressing physical health. Also, early engagement is

crucial as delays in receipt of a service have been shown to have a detrimental effect on longer term outcomes (The NHS Confederation, 2011).

Engaging a young person with these experiences may at times require considerable persistence and flexibility from professionals. The Early Psychosis Declaration (Rethink, 2004) 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'. It is important to consider who we are trying to engage in services. In addition to the child or young person, there is also a need to engage their family or others who are close to them. This is process may be made more challenging if the young person, or their family, does not share the professionals' view of what the main problems, 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 2.1.1.1) and are offered or receive a service from an 'Early Intervention in Psychosis Team'. 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' state needs to be balanced against the need to address the presenting problems in order to create a therapeutic alliance.

Psychosis can have a profound effect on the individual's judgment, their capacity to understand their situation and their capacity to 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) (Department of Health, 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 (Her Majesty's Stationery Office, 2007).

An important consideration is the requirement to manage young people with psychosis and schizophrenia in low-stigma and age-appropriate settings (The NHS Confederation, 2011, Department of Health, 2007), and to provide information that is age appropriate (*Achieving Equality and Excellence for Children*, Department of Health, 2010) and that supports the young person and their family in making informed decisions about treatment (Department of Health, 2011a) (see Section 2.6). Effective engagement for children and young people with psychosis and schizophrenia might be supported by minimising disruptive, developmentally inappropriate transitions. For example it makes little sense to have to transition a young person who entered an early intervention in psychosis (EIP) service at age 14 to CAMHS at age 17 because all EIP patients have to be transitioned after 3 years. 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 guidance.

2.6 LANGUAGE AND STIGMA

Stigma and discrimination can have negative effects on mental wellbeing in many ways. The stigma and discrimination associated with psychosis can: discourage people from seeking help, which may delay treatment; lead to social isolation, which can exacerbate problems; act as a mechanism of social exclusion, which hampers recovery; reduce employment and education opportunities; result in poorer physical healthcare, suicidality, and higher mortality rates (Thornicroft, 2006). Stigma among professionals towards schizophrenia and psychosis may also delay diagnosis and treatment (see Section 2.1.4). Psychosis is one of the most stigmatised mental health problems and people with psychosis are often stereotyped as dangerous and unpredictable (Thornicroft *et al.*, 2009). Furthermore, the public express the greatest desire for increased social distance from people with psychosis and studies have also shown that mental health staff also express a desire for social distance from and stereotype people with psychosis (Corrigan *et al.*, 2002); such discrimination from health professionals is important to service users and carers. 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 experience both shame of their diagnosis and fear of discrimination.

The use of language and terminology is one of the ways in which stigma can be influenced for better or worse. Throughout the guideline we use the term 'psychosis' as a short hand to describe experiences which 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; similarly 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 as the term 'psychosis' is can appear to be used interchangeably both to refer to 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 we reserve the term 'psychosis' to refer to psychotic disorder.

We use the term 'service user' for individuals who use mental health services. Diagnostic labels can be particularly divisive of opinion, with terminology such a 'schizophrenics' generally being recognised as unacceptable to service users; personal accounts of the impact of diagnosis emphasise that such a diagnosis is a label that is difficult to shed and it can take on a life of its own, dehumanizing and devaluing the individual (Bjorklund, 1996). Diagnosis can also be a cause of disempowerment for service users and the experience of being diagnosed can also

lead to the creation of a new identity as 'a schizophrenic', thus promoting social exclusion (Pitt *et al.*, 2009). Therefore, when referring to people with such diagnoses, we employ terminology such as 'people who meet criteria for a diagnosis of schizophrenia' rather than 'schizophrenic'.

2.7 ISSUES FOR FAMILIES AND CARERS

While developing the most appropriate and effective treatment for schizophrenia (or psychosis) with children and young people, it is important to remember that service users in this age group, along with their families or carers, may have different priorities and preferences for treatment than older service users (see Section 2.5). It will also be important to carefully consider the effectiveness or 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 carers full information about the relative costs and benefits of any recommended treatments (for example, long-term side-effects of anti-psychotics versus potential short-term reduction in psychological distress).

There may be important differences in the ways mental health staff engage and interact with children and young people and their carers, so it is important to draw from the experiences of those who work in child-specific mental healthcare contexts. Where possible, it will also be valuable to draw from the experiences of service users and carers themselves who have benefited from involvement with mental health services developed for children and young people.

As many children and young people offered treatment for schizophrenia (or psychosis) will still be in the direct care of families or other carers, it is important to consider developing treatments and treatment decision-making processes that involve families and carers as much as possible. At the same time though, 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.

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

Since the 1980s there has been an emerging consensus that schizophrenia presenting 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 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 which influence treatment approaches:

- 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.
- Children and young people with schizophrenia are more likely to have cognitive impairment, negative symptoms and less systematised delusions and hallucinations (possibly limiting the universal applicability of CBT approaches).
- The importance of families in providing care and supporting young people with schizophrenia (emphasising the importance of family interventions).

Until the 1990s most children and young people with psychosis and schizophrenia were managed on children's and adolescent inpatient units. General community CAMHS had relatively little experience or expertise with psychosis and schizophrenia, particularly as CAMHS services often ended at age 16 (just as the incidence of psychosis starts to take off). The last decade has seen a major change in service delivery with a shift towards community treatment and the development of EIP teams covering ages 14 to 35. EIP teams are generally managed by adult mental health services (AMHS) although some are nested within CAMHS. The benefits have included increased resources, interventions and expertise in psychosis targeted at a previously neglected age group. However, the challenge has been to integrate into EIP services the clinical expertise and training of CAMHS, which offers a developmental perspective, and to provide EIP services for children and young people in age-appropriate settings.

2.8.1 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 2.1.1.1). Yung and colleagues (Yung *et al.*, 1996) developed operational criteria to identify three subgroups possessing an 'at-risk mental state' (ARMS) for psychosis. Two subgroups specify state risk factors, defined by the presence of either transient psychotic symptoms, called Brief Limited Intermittent Psychotic Symptoms (BLIPS) or attenuated (subclinical) psychotic symptoms (AS). 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 this transition are needed because of the significant personal, social and financial costs associated with the development of psychosis. To date, there have been six randomised, controlled trials that have reported findings regarding outcomes associated with antipsychotic medication, omega-3 polyunsaturated fatty acids and / or psychological interventions; each using similar operational definitions of ARMS. These studies have been conducted in Australia (McGorry *et al.*, 2002; Yung *et al.*, 2011), North America (McGlashan *et al.*,

2006; Addington *et al.*, 2011), the UK (Morrison *et al.*, 2004, 2007) and Austria (Amminger *et al.*, 2010).

It is generally agreed that the research regarding interventions for at-risk mental states and sub-threshold psychotic experiences is in a state of clinical equipoise, and existing recommendations promote a clinical staging approach that utilises benign interventions such as monitoring of mental states, case management, social support and psychosocial interventions prior to consideration of 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, current clinical practice is likely to be highly variable according to local resources and service configurations, clinicians' attitudes and awareness of such recommendations, and this diversity of treatment approach is evident in the recent large international naturalistic cohort studies (Ruhrmann *et al.*, 2010; Cannon *et al.*, 2008).

2.8.2 Psychological and psychosocial interventions

Prior to the introduction of neuroleptic medication for schizophrenia in the 1950s and 1960s, analytical psychotherapies based on the work of Fromm-Reichan (1950) and 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 in the hospital (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.

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 interventions to prevent relapse (Leff *et al.*, 1982; Lobban & Barrowclough, 2009). Family interventions 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 affective disorders sparked a renewed interest in 'talking therapies' for psychosis. One of the key progenitor studies was the work of Chadwick & 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.*, 2004) and of specific symptoms such as hallucinations (Chadwick & Birchwood, 1994); and applying the assumptions and techniques of CBT to psychosis (for example, Kingdon and 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, trauma symptoms). CBT has been developed further to reduce the likelihood of relapse, including young people with a first episode of psychosis (Alvarez-Jimenez *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 rarely available in NHS services. A specific cognitive behavioural approach that aims to enhance compliance with medication was also developed towards the mid 1990s and is now commonly known as 'adherence therapy' (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 high relevance for young people with psychosis (Killackey *et al*., 2008).

2.8.3 Pharmacological treatment

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 psycho education for the user and the 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 adolescents (Vitiello *et al.,* 2009) with evidence also of a change of use from 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; 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 continuing 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 adolescents 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 randomised control trials (RCTs) (Armenteros & Davies, 2006; Kennedy *et al.*, 2007) confirming the efficacy of anti-psychotic medication in children and adolescents. Antipsychotic medication is effective in reducing the positive symptoms of psychosis (hallucinations, delusions, thought disorder), however, the effect size is modest (ES= 0.2 to 0.3) according to Cohen's criteria (Cohen, 1992). Furthermore, there is limited evidence to suggest efficacy of these medications against negative symptoms of psychosis (lack of motivation, poverty of thought etc.). The relative lack of efficacy is a concern as 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 between adults and younger users, some important differences exist. Younger users are more sensitive to the effects of medication (Correll, 2011), and therefore initiation of treatment is particularly important. One should start with a low dose of anti-psychotic medication, whenever possible, and gradually titrate upwards over a period of several days to weeks. Although drug metabolism may be more rapid in adolescents than in adults (suggesting the possible need for higher doses) the use of higher than British National Formulary (BNF) doses of antipsychotics does not appear effective, with only indirect evidence for high-dose olanzapine (Kumra *et al.*, 2008) and such practice is not recommended unless guided by drug levels (for example, when treating with clozapine)

Psycho education for the user and family 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 in decisions upon the use of medication are important, as is continuity of care, especially across the transition of adolescence to early adulthood.

2.8.4 Organisation of care

Community Child and Adolescent Mental Health Services (CAMHS) and Early Intervention in Psychosis (EIP)

The policy implementation guide (Her Majesty's Stationery Office, 2001) for EIP services recommended that such services should provide for young people aged 14-35 thus providing a new challenge to the organisation and delivery of services for adolescents. Prior to this young people presenting with psychotic symptoms or first episode psychosis were seen in community CAMHS. CAMHS were directed by the National Service Framework for Children, Families and Maternity Services (Department of Health, 2004) 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. EIP teams thus potentially provided an additional resource for young people presenting with a putative psychotic disorder. However, the relationship between CAMHS and EIP/AHMS was not explicit and hence there has been considerable variation in provision.

The most recent report on this subject 'joint working at the interface' Early Intervention in Psychosis and Specialist Child and Adolescent Mental Health Services by Rethink illustrates that this continues to be the case despite some models of good practice (Rethink, 2011). This report recommends an agreed protocol for managing young people under the age of 18 with psychosis which should be embedded within every day 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 we are still needing these recommendations some 10 years later. In the original policy implementation guideline there was a recommendation of 0.1 WTE child and adolescent psychiatrist as part of the EIP service.

In 2004, a group of international experts published a paper with recommendations on the involvement of CAMHS in EIP services (Marshall *et al.*, 2004). Key points from this were that there was a strong consensus that Early Intervention services should have close links with CAMHS and be supported with under 16 prescribing. There was also a good consensus that EIP services should integrate CAMHS and AMHS and that EIP services should have at least one representative from CAMHS and have designated sessions from Child and Adolescent Psychiatry and employ youth workers. Despite this an audit of EIP services in England in 2005 (Pinfold *et al.*, 2007), found that only 16% of EIP teams had dedicated input from CAMHS or youth workers. 25% of EIP teams did not see young people under the age of 16 years.

It is most unfortunate that this audit has not been replicated in its original format to inform us how things are now some 6 years later. 'Joint working at the interface' found that of staff working in EIP/AMHS, 91% reported that they had not received training to work with young people aged under 14. 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 the 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 Adolescent Psychiatrist as an integral EIP team member rather than relating to potentially, eight different CAMHS and Consultant Psychiatrists. This has been cited as a model of good practice in review of the implementation of Part 9 of the NSF in 2006 (Department of Health, 2006a) and has been presented as a case study in 'joint working at the interface'. This is not to say that this is the preferred model to integrating EIP and CAMHS. What is likely to be the predominant model nationally is that young people with psychotic symptoms are referred to CAMHS or EIP services but may receive care comprising components of both. For example, young people may be most likely to receive care co-ordination from EIP services and psychiatric input from CAMHS.

Admission to hospital

A child or young person suffering from schizophrenia or other psychotic disorder may be admitted to a range of different types of inpatient environment**.** In part this will depend upon clinical features for example, age (child or adolescent), nature/purpose of admission (planned, crisis, or emergency), level of disturbance/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 (Her Majesty's Stationery Office, 2007) have make it much less likely that that a child or young person will be admitted to an adult mental health setting unless this is clearly appropriate to their very specific needs.

Child and adolescent mental health inpatient units are characterised by their emphasis upon meeting the developmental needs of the individual and upon minimising the impacts of the disorder and the admission upon the individual'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. However the range of provision that exists in AMHS for managing acute presentations in or out of hospital (for example, crisis resolution, home treatment, acute admission, psychiatric intensive care) is less well developed in child and

adolescent mental health services and partnership/provision from other non-NHS-based willing 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 patient'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, 2008) provides the appropriate framework within which this should take place.

2.8.5 Pre-pubertal children

Treatment in pre-pubertal children requires clinicians to be confident in the assessment of the young person's competence and level of understanding. Treatment is generally offered within the framework of the consent of those holding parental responsibility for the young person. However it is good practice to involve and inform the child in a manner that is appropriate to their developmental level. Information leaflets using simple language and information may be helpful. Children may require several discussions and opportunities to ask questions about their illness and the treatments that they are being offered. Parents/carers should be expected to be actively involved in the treatment package. Occasionally treatment may be required within the framework of the Mental Health Act.

Treatment involves a multimodal treatment package including pharmacotherapy, family therapy, psycho education and cognitive behavioural therapy targeted at symptoms (Hollis, 2008; Kennedy *et al.,* 2009).

There is some evidence that childhood-onset schizophrenia improves with treatment with antipsychotic medications. (Kennedy *et al.,* 2009; James, 2010) 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). Within current drug licensing regulation children are often being treated using licensed medication for an unlicensed indication given that many antipsychotic drugs are not licensed for use in the younger age group. It is good practice to inform parents/carers of this fact and give them an opportunity to ask questions.

Physical healthcare, base line investigations and on-going monitoring for the side effects of drug treatment should form part of the treatment package. Children may be more sensitive to the side effects of antipsychotic medication (Correll, 2008; James 2010; Kumra *et al.,* 1996). Weight, blood pressure, blood tests (full blood count, liver function tests, fasting lipids, cholesterol, blood sugar and prolactin levels) should be monitored at 3 to 6 monthly intervals.

Children may come to attention either in a Community CAMHS service or through paediatric services. Community CAMHS services generally provide the initial treatment package. Inpatient care may become necessary for clarification of diagnosis, detailed assessment or management of risk. This would usually be provided in a specialist children's inpatient tier 4 CAMHS service. In the absence of the availability of a suitable CAMHS inpatient provision, children may be admitted to a paediatric ward. Strong links between the community CAMHS service and the inpatient paediatric service should be maintained during treatment. Protocols across services may help to clarify lines of responsibility for care and treatment.

2.8.6 Primary–secondary care interface

Pathways to specialist care can be particularly problematic for people presenting with psychosis under the age of 18. A study of first time presentations in adolescents in central Scotland (study population 1.75 million) reported 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 GP (general practitioner) involvement with fewer legal detentions, reported previously (Cole *et al*., 1995; Burnett *et al*., 1999) suggesting that GP involvement 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 involvement in the pathway can reduce distress and treatment delay, paradoxically GPs may hold negative opinions about providing care for people with 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 patients a year (Simon *et al*., 2005) and the proportion under 18 would be fewer still as 20% of first episodes are aged under 20 and 5% under 16 years (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. However, 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 specialist early intervention 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 issue concerns difficulties in addressing downstream physical disorders due to poor organisation of health services and an on-going 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 (Macklin *et al*., 2007; Buckley *et al*., 2005; Morrato *et al*., 2009; Nasrallah *et al*., 2006) and was recently also confirmed in children (Morrato *et al*., 2010). European screening and monitoring guidelines for diabetes and cardiovascular risk in schizophrenia were mentioned but offered no specific guidance on the risks in children and adolescents (De Hert *et al*., 2009). A more recent systematic review targeting children and adolescents concluded that good collaboration between 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).

Reluctant as GPs may be to deal with these patients' mental health issues, at least they are more likely to accept physical healthcare as a core role (Lester *et al*., 2005). Furthermore the Quality and Outcomes Framework [QOF, 2011/12] (NHS Employers and British Medical Association, 2011) has incentivised annual physical health checks for people with psychosis since 2004, reinforced by the NICE *Schizophrenia* guideline for adults (NICE, 2009a) which allocates overall responsibility to primary care for managing physical healthcare. However, both QOF and NICE guidance have not prioritised 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 understand and weigh the trade-offs of improved mental health symptoms versus increased risks to physical health.

Given that modifiable cardiovascular risk appears within months of commencing treatment (Foley and Morley , 2011) the onus should arguably shift towards a prevention and early intervention approach to cardiovascular risk by those specialist services responsible for the critical early phase (Phutane *et al*., 2011). However, simply issuing more guidance, for instance, to early intervention 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 EDUCATION AND YOUNG PEOPLE WITH EARLY ONSET PSYCHOSIS OR SCHIZOPHRENIA (EOS)

This section is divided into three subsections, the first discusses the onset of the psychosis. The second subsection discusses education and the young person who is unwell with early onset psychosis. The third section discussed education for young people recovering from psychosis.

2.9.1 The development of early-onset psychosis and its impact in school

Early onset psychosis is relatively uncommon in young people of aged between 13 and 18. It is estimated that out of 1000 secondary school pupils, up to three of the pupils might be expected to be at risk of developing early-onset psychosis. The staff in secondary schools should be aware that some of their pupils are likely to develop early–onset psychosis particularly precipitated around times of stress such as public examinations.

There are a number of signs which can indicate that at 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 or year heads or others with pastoral responsibilities should be alert for changes in mood or demeanour that are persistent, that is they last for more than three weeks.

At this point school staff should consult with pupils, parents and carers and share their concerns. As a consequence of the sharing of concerns, 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 and if there is no improvement, they may well ask if the pupil and her/his carers would accept referral to CAMHS or the relevant early intervention in psychosis (EIP) team.

2.9.2 Education while the young person is unwell

A young person, the young person 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 experience the world. 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 derided for their differing view of reality, the accompanying mocking or bullying behaviour will exacerbate the fear and isolation that the young person with psychosis will feel. 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.

The experiences of those in school who work with a young person developing psychosis could also be fearful about the impact of the disorder unless they have had specific experiences of working alongside an individual with psychosis or schizophrenia. Educators have a responsibility to deal with any fearful feelings that they may have through seeking the support through a supervisory process perhaps from the school educational psychologist or other mental health workers to address the issues arising from and feelings evoked by the development of psychosis or schizophrenia in a school pupil or college student.

For many young people, as the illness progresses the continuation of full time education may become increasingly difficult. The young person with psychosis or schizophrenia may be unable to sustain long periods of academic work and the many interactions that comprise a school day. In these circumstances some 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 young person with psychosis in advance of a breakdown of school placement and consequent emergency admission to some alternate provision. A rushed and hasty process will only add to the fear felt by the young person with psychosis.

2.9.3 The young person recovering from psychosis or schizophrenia

When the young person is recovering, it is appropriate that they should in time be able to return to full time education. School staffs must prepare for re-admission and must be quietly welcoming for the young person returning. Environments with high levels of expressed emotion are known to increase the likelihood of a relapse into schizophrenia, and so pastoral staff who are aware of those classes with high expressed levels of emotion within the school should, in consultation with the young person, structure a timetable to avoid or minimise exposure to such classes. At the same time it may be appropriate to provide opportunities for quiet and a 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 SCHIZOPHRENIA

Among all mental health disorders, patients suffering from schizophrenia suffer some of the highest financial and emotional strain. The disease places an immense burden on both the individuals suffering from the disorder as well as their caretakers and also makes potentially large demands on the healthcare systems of several countries.

In 1990 the World Health Organization (WHO) ranked schizophrenia as the ninth leading cause of disability among all known diseases. Disability Adjusted Life Years (DALYs) assessment indicators such as non-fatal health outcomes as well as the premature mortality ration for the disease rank it as the 26th leading cause of global economic burden and the ninth leading cause of DALYs for ages 15 to 44 years (Murray and Lopez, 1996).

The disorder has been shown to place a substantial economic burden on the global healthcare system as well as society in general. According to Wu and colleagues (2005), the reported total cost of coping with schizophrenia in the US amounted to US $62.7 billion in 2002. 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 with direct healthcare service use, while 12% has often been incurred by other non-healthcare services coping with schizophrenic patients. Several national studies conducted in Europe in the 1990s revealed schizophrenia to be directly linked with long-lasting health, social and financial implications, not only for those suffering from the disorder but also for their families, caregivers and society as a whole (Knapp *et al.*, 2004b).

The cost of treatment of people with schizophrenia is incredibly high, especially for patients who require inpatient treatment and other psychiatric care facilities. A study conducted by Mangalore and Knapp (2007) reveals the estimated societal cost for coping with schizophrenia at £6.7 billion, only in England (2004-2005 prices). Of this total, approximately £2 billion comprised of the direct costs of treatment and care that fell upon the public exchequer, this amounts to nearly 30% of the total cost of the disease. The remaining £4.7 billion constituted indirect costs borne by society. Other costs, including the lost cost of productivity for patients owing to unemployment, absence from work and premature mortality have been estimated at £3.4 billion and the cost of care givers has been estimated roughly at £32 million. Other unanticipated costs allocated for such disorders included the cost of informal care and private expenditures borne by families that have been estimated at roughly £615 million. In addition, the cost attributed to the criminal justice system for its services rendered in association with any psychiatric episodes amounts to nearly £1 million. Here, one must also factor in the costs associated with administration relating to all the above mentioned payments which have, so far, been marked at £14 million. Based on these estimates, the annual average cost borne by a schizophrenic patient in England can easily exceed £55,000.

There is a necessary distinction to be made when allocating economic costs to people with schizophrenia. Traditionally, first time diagnosed patients have been shown to contend with a considerably lower financial burden than chronic patients. According to Davis and Drummond (1994), the lifetime total direct and indirect financial costs borne by people with schizophrenia who have suffered from a single episode can range from £8,000 and for those suffering 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 (1990/91 prices). Guest and Cookson (1999) revised this estimate after factoring in the estimated average costs borne by a newly diagnosed patient at around £115,000 over the first 5 years following their diagnosis. This amounts to nearly £23,000 annually, where 49% of the cost is directly attributed to indirect losses owed to lost productivity.

As is the case with most psychiatric disorders, unemployment is a potential consequence for most people suffering from schizophrenia. The loss of jobs places considerable burden on patients and a recent review reported the rate of unemployment among people suffering from schizophrenia between 4 and 27% in the UK. Stigmatization has been cited as the leading barrier to employment for this

demography. Unemployment rates were higher for newly diagnosed patients compared with those living with established schizophrenia, however, a majority of people presenting to services for the first time were already unemployed (Marwaha and Johnson, 2004). According to Guest and Cookson (1999) between 15 and 30% of people suffering from schizophrenia find themselves 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 have been marked from between £412 million for newly diagnosed patients over the first 5 years to £1.7 billion annually for chronic patients (Davis and Drummond, 1994).

The use of hospital inpatient care is often significant and in the financial year 2006-07, 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, 2008a). 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 on the disease. Lang and colleagues (1997a) reported that providing inpatient care amounted to 59% of the total cost of health and social care for schizophrenic patients. Perhaps the cost that is most often overlooked and the hardest to allocate for schizophrenia includes the costs associated with informal care of patients. Family members and friends often provide care for people with schizophrenia and this places substantial burdens on their health, time, finances and employment status. Guest and Cookson (1999) estimated that at least 1.2 to 2.5% of care givers in the UK quit their jobs to look after dependents suffering from the disorder. Measuring this cost in exact financial terms is problematic, however, it does form a significant component of the total economic costs linked with the disease. 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 patients suffering mental health problems amounted to £3.9 billion.

It is clear that apart from the obvious emotional and mental strain borne by people with schizophrenia and their family there is a substantial economic burden that both patients, the healthcare system and society needs to contend with. Efficient use of available healthcare resources is essential to maximize benefits for this demographic. Financial costs borne by mental health patients cause considerable strain on their existing condition and for those caring for them and an efficient management of public healthcare services and finances in this regard could go a long way to reduce the emotional stress and other implications that inevitably face people suffering from schizophrenia.

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 health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG), with support from the National Collaborating Centre for Mental Health (NCCMH) staff, undertook the development of a patient-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 guidance.
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.

3.3 THE GUIDELINE DEVELOPMENT GROUP

During the consultation phase, members of the GDG were appointed by an open recruitment process. GDG membership consisted of professionals in psychiatry, clinical psychology, nursing 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 economics literature searches, reviewed and presented the evidence to the GDG, managed the process, and contributed to drafting the guideline.

3.3.1 Guideline development group meetings

Eleven GDG meetings were held between 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 group of service users and carer representatives from service user and carer organisations formed a small topic group to undertake guideline work in the area of experience of care. 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, 2011) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) for their relevancy 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, 2011) 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 Chapter 3, 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 who 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 most particularly 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 advisors

Special advisors, who had specific expertise in one or more aspects of recognition and management 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 advisors.

3.3.5 National and international experts

Specific national and international expert researchers in the area under review were identified through the literature search and through the experience of the GDG members. These experts were contacted to identify unpublished or soon-to-be published studies, to ensure that up-to-date evidence was included in the development of the guideline. They informed the GDG about completed trials at the pre-publication stage, systematic reviews in the process of being published, studies relating to the cost effectiveness of treatment and trial data if the GDG could be provided with full access to the complete trial report. Appendix 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 1).

Table 1: Features of a well-formulated question on effectiveness intervention – the PICO guide

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

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

To help facilitate the literature review, a note was made of the best study design type to answer each question. There are four main types of review question of relevance to NICE guidelines. These are listed in Table 2. For each type of question, the best primary study design varies, where 'best' is interpreted as 'least likely to give misleading answers to the question'.

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

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

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

Type of question	Best primary study design
Effectiveness or other impact of an intervention	Randomised controlled trial (RCT); other studies that may be considered in the absence of RCTs are the following: internally/externally controlled before and after trial, interrupted time-series
Accuracy of information (for example, risk factor, test, prediction rule)	Comparing the information against a valid gold standard in 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)

3.5 SYSTEMATIC CLINICAL LITERATURE REVIEW

The aim of the clinical literature review was to systematically identify and synthesise relevant evidence from the literature in order to answer the specific review questions developed by the GDG. Thus, clinical practice recommendations are evidence-based, where possible, and, if evidence is not available, informal consensus methods are used (see Section 3.5.7) and the need for future research is specified.

3.5.1 Methodology

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

- *British Medical Journal* (*BMJ*) Clinical Evidence
- Clinical Policy and Practice Program of the New South Wales Department of Health (Australia)
- The Cochrane Collaboration
- Grading of Recommendations: Assessment, Development and Evaluation (GRADE) Working Group (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 (AHRQ).

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 randomised controlled trials (RCTs), and conducted in the following databases and websites:

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

Parts of existing NICE guidelines were updated if relevant to any specific review question. Other relevant guidelines were assessed for quality using the AGREE instrument (AGREE Collaboration, 2003). The evidence base underlying high-quality existing guidelines was utilised and updated as appropriate. Further information about this process can be found in *The Guidelines Manual* (NICE, 2009b).

Systematic literature searches

After the scope was finalised, a systematic search strategy was developed to locate all the relevant evidence. The balance between sensitivity (the power to identify all studies on a particular topic) and specificity (the ability to exclude irrelevant studies

from the results) was carefully considered, and a decision made to utilise a broad approach to searching to maximise retrieval of evidence to all parts of the guideline. Searches were restricted to systematic reviews, RCTs and, where appropriate, observational studies, and conducted in the following databases:

- Allied and Complementary Medicine (AMED) Australian Education Index (AEI)
- British Education Index (BEI)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Cochrane Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Education Resources in Curriculum (ERIC)
- Embase
- Health Management Information Consortium (HMIC)
- HTA database (technology assessments)
- International Bibliography of Social Sciences (IBSS)
- MEDLINE / MEDLINE In-Process
- PsycBOOKS
- PsycEXTRA
- Psychological Information Database (PsycINFO)
- Social Science Citation Index
- Sociological Abstracts
- Social Services Abstracts (SSA).

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 the population 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 the reference management software and duplicates removed. Records were then screened against the eligibility criteria of the reviews before being quality appraised (see below). The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

Search filters

To aid retrieval of relevant and sound studies, study design filters were used to limit a number of searches to systematic reviews, randomised controlled trials, and where

necessary, observational studies. The search filters for systematic reviews and randomised controlled trials 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 data sets.

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 the study information database. More specific eligibility criteria were developed for each review question and are described in the relevant clinical evidence chapters. Eligible systematic reviews and primary-level studies were critically appraised for methodological quality, using NICE study quality 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 topic groups took into account the following factors when assessing the evidence:

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

It was the responsibility of 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 and outcome data were extracted from all eligible studies that met the minimum quality criteria, using Review Manager 5 (Cochrane Collaboration, 2011) and Excel-based forms (see Appendix 13). This included aspects of the NICE quality checklists which look to assess and address study bias.

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

Where possible, outcome data 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 re-calculated if ITT had not been used. When making the calculations if there was good evidence that those participants who ceased to

engage in the study were likely to have an unfavourable outcome, early withdrawals were included in both the numerator and denominator. Adverse effects were entered into Review Manager as reported by the study authors because it is usually not possible to determine whether early withdrawals had an unfavourable outcome.

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

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

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

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

3.5.4 Synthesising the evidence from comparative effectiveness studies

Meta-analysis

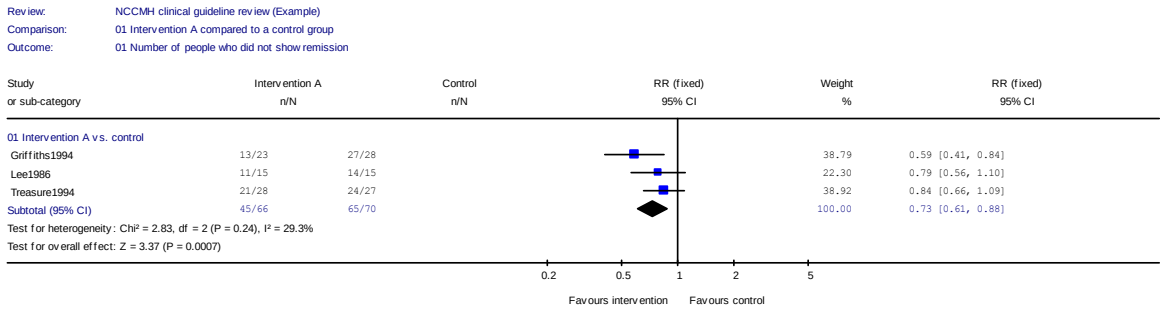
Where possible, meta-analysis was used to synthesise evidence from comparative effectiveness studies using Review Manager. If necessary, re-analyses of the data or sub-analyses were used to answer review questions not addressed in the original studies or reviews.

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

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

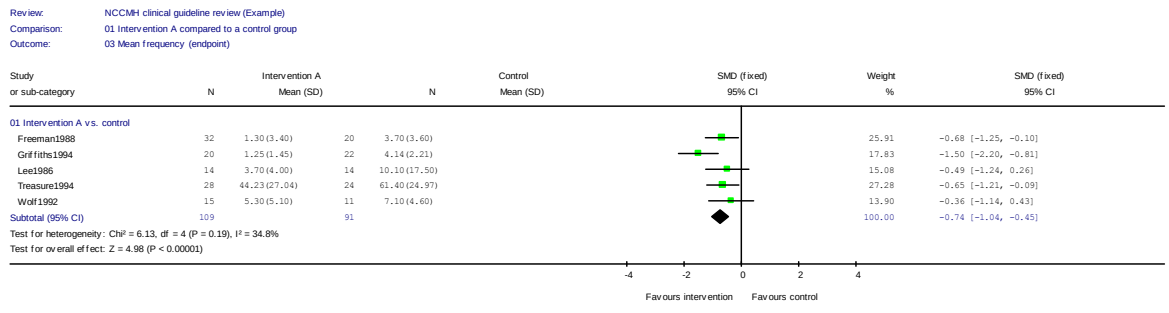
The CI shows a range of values within which it is possible to be 95% confident that the true effect will lie. If the effect size has a CI that does not cross the 'line of no effect' then the effect is commonly interpreted as being statistically significant.

Figure 1: Example of a forest plot displaying dichotomous data



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

Figure 2: Example of a forest plot displaying continuous data



Heterogeneity

To check for consistency of effects among studies, both the I^2 statistic and the chi-squared test of heterogeneity, as well as a visual inspection of the forest plots were used. The I^2 statistic describes the proportion of total variation in study estimates that is 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 confidence interval 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 (FE) and random effects (RE) models were compared for differences.

3.5.5 Grading the quality of the evidence

For questions about interventions, the GRADE approach was used to grade the quality of evidence for each outcome. The approach is described briefly below, but for further information please see the GRADE website: www.gradeworkinggroup.org. The guideline 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 3 for an example of an evidence profile). The GRADE approach is based on a sequential assessment of the quality of evidence, followed by judgment about the balance between desirable and undesirable effects, and subsequent decision about the strength of a recommendation.

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

- randomised trials without important limitations provide high quality evidence

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

For each outcome, quality may be reduced depending on five factors: limitations, inconsistency, indirectness, imprecision and publication bias. For the purposes of the guideline, each factor was evaluated using criteria provided in Table 4.

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

Table 3: Example of an evidence profile

Outcome or Subgroup	STUDY ID	Design	ROB	Inconsistency	Indirectness	Imprecision	Other considerations	Number of studies / participants	Effect Estimate (SMD or RR)	Quality	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
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* 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 (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Serious risk of reporting bias.

Table 4: 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 confidence intervals around the estimate of the effect.	If either of the following two situations were met: • the optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) was not achieved • the 95% confidence interval 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.

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.

3.5.6 Presenting the data to the guideline development group

Study characteristics tables, forest plots (where appropriate) generated with Review Manager (version 5.0) 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 5). Where meta-analysis was not

appropriate and/or possible, this was reported in the included study characteristics table for each primary-level study.

Table 5: Example of a summary of findings table

Outcome or Subgroup	STUDY ID	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	QUALITY
Total Symptoms (SMD)	Insert Study ID	K=4; N=516	-0.32 [-0.52, -0.13] *	(P = 0.31); I^2 = 16%	Low[1,5]
Global State (SMD)	Insert Study ID	K=3; N=400	-0.38 [-0.58, -0.18]*	(P = 0.44); I^2 = 0%	Very low[1,2,5]
Response (RR)	Insert Study ID	K=1; N=98	1.43 [0.95, 2.17]	N/A	Very low[1,3-5]

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* 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 (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Serious risk of reporting bias.

3.5.7 Extrapolation

When answering review questions, it may be necessary to consider extrapolating from another data set where direct evidence from a primary data set[2] is not available. In this situation, the following principles were used to determine when to extrapolate:

- a primary data is absent, of low quality or is 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(s) is in the view of the GDG available which may inform the review question.

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

- the population under consideration shares the same diagnosis as the population under review (either at-risk for psychosis and schizophrenia; or

[2] A primary data set is defined as a data set which contains evidence on the population and intervention under review

diagnosed with psychosis and schizophrenia) but differ in age. Specifically, studies had to meet the following population criteria to be eligible for extrapolation:
  - The study sample included individuals <18> years, but the mean age of the study sample was <25 years.
- the interventions under consideration in the view of the GDG have one or more of the following characteristics:
  - share a common mode of action (e.g., the pharmacodynamics of drug; a common psychological model of change - operant conditioning)
  - be feasible to deliver in both populations (e.g., in terms of the required skills or the demands of the health care system)
  - share common side effects/harms in both populations.
- the context or comparator involved in the evaluation of the different data sets shares some common elements which support extrapolation
- the outcomes involved in the evaluation of the different data sets shares some common elements which support extrapolation (for example, improved mood or a reduction in challenging behaviour).

When the choice of the non-primary data set 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 data set and be guided in these decisions by the principles for the use of extrapolation
- in all areas of extrapolation data sets should be assessed against the principles for determining the choice of data sets. 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 data set 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

In the absence of appropriately designed, high-quality research an informal consensus process was adopted.

Informal consensus

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 regarding the review question. The process involved a number of steps:

1. A description of what is known about the issues concerning the clinical 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 may include studies that did not directly address the review question but were thought to contain relevant data.
4. Recommendations were then developed and could also be sent for further 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. 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, cognitive behaviour therapy (CBT) and pharmacological intervention 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 health technology assessment 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 health technology assessment 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 the population 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 were combined with a search filter for health economic studies. For searches generated in topic-specific databases (EconLit, HTA, NHS EED) search terms for psychosis and schizophrenia in children 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 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 inclusion criteria of the reviews before being quality appraised. The unfiltered search results were saved and retained for future potential re-analysis to help keep the process both replicable and transparent.

Search filters

The search filter for health economics is an adaptation of a pre-tested strategy designed by Centre for Reviews and Dissemination (CRD) 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. Full details of the filter are provided in Appendix 8.

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 accompanying respective GRADE clinical evidence profiles in Appendix 17.

3.6.5 Results of the systematic search of economic literature

The titles of all studies identified by the systematic search of the literature were screened for their relevance to the topic (that is, economic issues and information on health-related quality of life in 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 (3 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

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 the current context. In addition, there are a number of other reasons why it was desirable to reuse recommendations published in NICE guidelines, including to:

- Increase the efficiency of guideline development and reduce duplication of activity between guidelines.
- 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.
- 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
- 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 *adaption*. 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.

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 by the GDG to be sufficiently similar to that associated with the recommendation in the original guideline
- the recommendation can 'standalone' 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.

Adaptation

When adaption 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, young people to adults) 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 from *Schizophrenia* (NICE, 2009a) or *Service User Experience* (NICE, 2011):

- 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 'standalone' 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 health care setting(s) that are the focus of the guideline. This may inform the re-drafting or re-structuring 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 GDG would move to the 'incorporate and adapt' method.

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 or re-writing and re-structuring.
In evidence chapters where incorporation and adaption have been used, tables are provided that set out the original recommendation, the new recommendation, and the reasons for adaption.

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 development group and society, the requirements to prevent discrimination and to promote equality[3], and the GDG's awareness of practical issues (Eccles *et al.,* 1998; NICE, 2009b).

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

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

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
- highlighting factual errors in the pre-publication check.

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 and others were responded to, and the guideline updated as appropriate (see Appendix 4 for a list of stakeholders who submitted comments during consultation).

Following the consultation period, the GDG finalised the recommendations and the NCCMH produced the final documents. These were then submitted to NICE for the pre-publication check where stakeholders are given the opportunity to highlight factual errors. Any errors are corrected by the NCCMH, then the guideline is formally approved by NICE and issued as guidance to the NHS in England and Wales.

4 ACCESS TO AND THE DELIVERY OF SERVICES, AND THE EXPERIENCE OF CARE, FOR CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS OR SCHIZOPHRENIA

4.1 INTRODUCTION

There is great emphasis on clinical practice and service organisation to deliver effective clinical interventions, however it is well known that there are significant social and ethnic inequalities regarding access to and benefit from such effective clinical interventions. As described in Chapter 2, psychosis and schizophrenia in children and young people is likely to have a negative impact on relationships, as this is a vulnerable period of development and the adverse social impact of an illness can be particularly devastating. More attention is now rightly focused on ensuring early access to and delivery of effective services and interventions for psychosis, to reduce periods of untreated psychosis, and also to ensure prompt and precise diagnosis, and quicker recovery to minimise social deficits, following the onset of illness.

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 or 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 or 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, 2011) 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 6. A full review protocol can be found in Appendix 7, and further information about the search strategy can be found in Appendix 8.

Table 6: Summary review protocol for the review of access to and delivery of services and the experience of care for children and young people with psychosis and schizophrenia

Review question	**RQC2** *Access to and delivery of services:* a) For children and young people with psychosis and schizophrenia, do specialised intensive services (early intervention in psychosis [EIP] services; specialised CAHMS) improve access and engagement with mental health services for children and young people with schizophrenia (particularly from black and minority ethnic groups)? *Experience of care:* b) 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 and 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 meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when 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 schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	• Specialised intensive services (CAMHS, EIP)
Comparison	Alternative management strategies
Primary outcomes	• Symptoms • Psychosocial functioning
Secondary outcomes	• None
Electronic databases	Mainstream databases: Embase, MEDLINE, PreMEDLINE, 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

4.2.1 Sources of information considered

The GDG advised the 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 schizophrenia. The search for RCTs and systematic reviews confirmed this - no RCTs or systematic reviews investigating intensive services (child and adolescent mental health services [CAMHS] or early intervention in psychosis [EIP] services) for children and young people with psychosis or schizophrenia were identified. The GDG therefore sought to develop recommendations using a consensus-based approach detailed in Chapter 3. 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 pertaining to the findings and expert opinion regarding current practice. Section 4.3 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, 2011) 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 in this process, a topic group of service users and carer representatives was formed in accordance with the methods set out in Chapter 3. The aims of the topic groups were to identify key issues and areas of concern for children and young people in their experience of care using NHS mental health services; and to review and assess the recommendations from the *Service User Experience in Adult Mental Health* (NCCMH, 2012; NICE, 2011) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) guidelines for their relevancy to children and young people with psychosis and schizophrenia, specifically in relation to issues and concerns identified (see Chapter 3 for further information on topic groups). The narrative review, outcome of the topic group discussion and GDG consensus informed the incorporation and adaption of recommendations from other guidelines (see Chapter 3 for detailed methodology regarding incorporation and adaptation). Section 4.4 sets out the findings of the topic group and further detail regarding the development of the recommendations for the experience of care of children and young people with psychosis and schizophrenia.

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

4.3.1 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 Tier2/3 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 child and adolescent mental health disorders. 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 young people with psychosis and schizophrenia. 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), drug treatments 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 adult mental health services (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 in young people.

Early intervention in psychosis services

Early intervention in psychosis (EIP) services are a community service approach with focus on the care and treatment of people in the early phase of psychosis or schizophrenia (usually up to 3 years) and 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 a 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, a first episode of 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 these specialised services which engage and deliver treatment to people with a first episode of psychosis 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 of cost benefit (NICE, 2009b). Moreover *No Health without Mental Health* (Department of Health, 2011b) highlights two principles relevant to adolescents with psychosis:

- take a life-course view (Executive summary 1.2)
- shift the focus of services towards promotion of mental health, prevention of mental illness and early identification and intervention as soon as mental illness arises (Section 7.13).

In considering the role of EIP services in supporting young people with emerging psychosis 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 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) with a first episode of psychosis (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).

Of particular relevance to young people is a Scottish study examining a large representative group of people under the age of 18 presenting with a first episode of psychosis to mainstream mental health services (Boeing *et al.,* 2007). Out of 103 patients, 86 had 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. This is what the *NHS Plan* (Department of Health, 2000) had set out to achieve in England some years previously by developing EIP services.

Another ambition of the *NHS Plan* (Department of Health, 2000) was to avoid the service transition issues that impede care pathways between CAMHS and AMHS. These were investigated in the TRACK study (Singh *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 this age group 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. Duration of untreated psychosis (DUP) has been well studied since the landmark Northwick Park study (Johnstone *et al.,* 1986) first revealed that longer DUP 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 National Collaborating Centre for Mental Health (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. Of the essential service ingredients the study 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 adolescents 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 of the disorders.

Tier 4

Inpatient services can form an important part of the care for young people with psychosis 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 young children or adolescents specifically, and the 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 which 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 (Her Majesty's Stationery Office, 2007) to mandate treatment and therefore staff working in these hospital settings need to be familiar with its operation and safeguards.

A full range of treatments may include psychopharmacology, cognitive behavioural therapy (CBT) and family interventions (including psychoeducation for parents and the patient). 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. Patients with psychosis may be subject to the care programme approach (CPA) to ensure continuity of care. The CPA documentation should include an up-to-date risk assessment and details on medication and emergency contact numbers.

During the inpatient stay the patient needs age appropriate education and, given the metabolic side effects of antipsychotics, nutritional advice and an emphasis upon physical activity is important. 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 patients and families.

The interface between primary and secondary care

The emerging distress of a first episode of psychosis will cause many young people, often supported by their families, to seek help from their general practitioner (GP). The nature of their presentation, the symptomatology and changes in psychosocial functioning, are in essence similar to how an adult may present. However, what may make recognition difficult is the low frequency of such an encounter for an individual GP. Given that about 20% of first episodes of psychosis occur in those under 20 years 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 of psychosis is against a backdrop of increasing psychological distress through adolescence, with 20% experiencing a diagnosable depressive episode by the age of 18 years (Lewinsohn *et al.*, 1993). It has been estimated that more than a third of GP attendees aged 13 to 16 years have evidence of a current or recent psychiatric disorder (Kramer & Garralda, 2000). Concerns over acquiring a psychiatric label or receiving treatment may explain why 50% of young people who perceived themselves to have more serious psychological difficulties, avoided raising these issues in the consultation, thereby potentially impeding GP recognition (Martinez *et al.*, 2006).

Presentations of psychosis in young people should also be seen within a 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 health professional (Kramer & Garralda, 1998). Moreover, parents and families often accompany the young person or present themselves to the GP with a related problem, one study showing that 77.5% of young people who consult 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 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 request 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 with an emerging serious mental illness is that many will also be embarking on a path towards serious physical illness, including cardiovascular disorders (see Chapters 4 and 7). Despite these future physical consequences, there is evidence that systematic screening and monitoring may often be lacking for 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

Whilst most 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 young people for whom this does not apply as they are 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 child and adolescent mental disorders and it is important that the clinician assesses this and pitches their approach and interventions accordingly.

Young people living in custody or in local authority secure care can have particularly elevated rates of mental disorder 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. Within England there is a network of specially commissioned secure inpatient mental health beds (NHS Specialised Services, 2012) and arrangements in place for rapid transfer from custody to one of these beds (Department of Health, 2011c).

Transition to adult services

Young people with psychosis or schizophrenia often face problems when moving from CAMHS to AMHS. The result of poorly developed transition services 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 mental health transition can also affect parents and carers, having implications for the whole family.

Young people aged 16 and 17 are making the transition to adulthood, and so 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.

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

4.3.2 Evidence Summary

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. Within these teams some input from trained child and adolescent mental health service (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 adolescents with psychosis and schizophrenia and it is important that children and young people 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 the care for these individuals forming part of a comprehensive care package. When a child or young person needs hospital care, it should be provided in 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 individuals of compulsory school age a full educational programme should be accessible, while in hospital.

Children and young people with psychosis or schizophrenia often face problems when moving from CAMHS to adult mental health services (AMHS). 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 and therefore transition should be planned and structured carefully, and discussed with the child or young person and their parents or carers.

Finally, this population 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 important for children and young people with psychosis and schizophrenia.

4.4 EXPERIENCE OF CARE

The NICE *Service User Experience in Adult Mental Health* (NICE, 2011) guidance 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: access to community care, assessment (non-acute), community care, assessment and referral in crisis, hospital care, discharge and transfer of care and detention under the Mental Health Act.

While it is expected that health and social care professionals will consult *Service User Experience in Adult Mental Health* (NICE, 2011) 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 the treatment of people with a 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* (NICE, 2011) 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.

4.4.1 Method

A topic group of GDG members and NCCMH staff was convened consisting of four service user and carer representatives from service user and carer organisations, and five NCCMH staff members (the facilitator, systematic reviewer, research assistant, 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, 2011) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) for their relevancy 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 4.3.

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, 2011) 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 Chapter 3, Section 3.7.

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

The topic group of service users and carers discussed what they judged to be some of the key issues and areas of concern for children and young people with psychosis or schizophrenia using NHS mental health services. They drew on their own experience, considered the reviews in Section 4.3 and identified the following eight key issues and areas of concern:

- Stigma
  - The impact of clinical language and clinical setting; and the need to recognise that stigma can come from medical models.
- 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 offer regular communication 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.
- 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)
  - With regard to young people who are of a sufficient developmental level, they should be asked if they would like their parents or carers involved
- Access to emergency/crisis teams
  - There is a gap in provision of crisis services
  - The need to provide geographically accessible and age appropriate settings (that is, close to family and friends)
  - The need to provide home treatment.
- Education
  - Assessment of needs
  - The need to support children and young people to be in education.
- Transition
  - Continuity of care
  - The need for clear handover.
- 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 procedures and what leads to restraining a patient); and the need to provide debriefs following an incident such as restraint of another patient.
- 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.

4.4.3 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 4.3, that although the Service User Experience in Adult Mental Health guidance (NCCMH, 2012; NICE, 2011) 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 or 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 4.4.2, 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 considering the narrative review conducted in Section 4.3; in all cases the adaptation retained the original meaning and intent of the recommendations.

Table 7 contains the original recommendations from *Service User Experience in Adult Mental Health* (NICE, 2011) 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 2 the numbers refer to the recommendations in the NICE guideline.

Table 7: Recommendations from *Service User Experience in Adult Mental Health* for inclusion

Original recommendation from Service User Experience in Adult Mental Health	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.	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.	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.	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.	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
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.	1.1.6 Work in partnership with children and young people with psychosis or schizophrenia and their 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.	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), with no significant adaptation required.	• 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-	1.1.7 When working with children and young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity:	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	• Communication

management • maintain continuity of individual therapeutic relationships wherever possible • offer access to a trained advocate.	• aim to foster their autonomy, promote active participation in treatment decisions and support self-management and access to peer support • maintain continuity of individual therapeutic relationships wherever possible • offer access to a trained advocate.	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.	
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).	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).	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	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,	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	• Involvement of parents or carers

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.	including developmental level, and should not happen only once.	and cognitive capacity. The last sentence of the original recommendation was removed because it had been covered by another recommendation developed by the GDG (1.1.11).	
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: • 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.	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.	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 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 three bullet points were included in a separate recommendation (1.1.13)	• Involvement of parents or carers
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 including any relevant 'Understanding NICE guidance' booklets • ensure that comprehensive	1.1.13 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 'Understanding NICE	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 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	• Communication • Involvement of parents or carers

information about other support groups, such as third sector, including voluntary, organisations, is made available.	guidance' booklets • support groups, such as third sector, including voluntary, organisations.	should include biomedical and psychosocial perspectives on causes and treatment.	
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.	1.1.14 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.	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
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.	1.1.15 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.	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.	1.1.16 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.	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	1.1.17 When working with children and young people with psychosis or schizophrenia and their parents or carers: • take into account that stigma 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 stigma, with no significant	• Stigma

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.	discrimination are often associated with using mental health services • be respectful of and sensitive to children and young peoples' 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.	adaptation required	
1.2.5 Local mental health services should work with primary care and local third sector, including voluntary, organisations to ensure that: • 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.	1.1.21 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.	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
1.7.1 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: • such changes, especially discharge, are discussed and planned carefully	1.1.23 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	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. Based on the expert opinion of the GDG,	• Communication • Transition

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.	transfer from child and adolescent mental health services (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.	this recommendation was adapted to account for the possible transfer of young people from CAMHS to adult mental health services 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 • 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	1.3.2 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 side effects, to promote discussion and shared	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 importance of discussion and provision of information during the assessment process), with no significant adaptation required	• Communication

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.	understanding • offer support after the assessment, particularly if sensitive issues, such as childhood trauma, have been discussed.		
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.	1.3.5 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 parent or carer 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.	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 as physical health problems are a particular issue in people with schizophrenia; 'caring for dependants' was removed as it was felt that this was unlikely to be an activity that many children and young 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.	• Communication • Education

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.	1.3.6 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.	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) • 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.	1.3.7 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.	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 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 the roles of primary and secondary care professionals should be involved given that the child or young person's care was likely to be shared between them.	• Access to emergency/ • crisis teams
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	1.3.9 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	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.	1.4.12 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.	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.	1.4.13 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, and other occupations and leisure activities, wherever possible.	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
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.	1.4.14 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.	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	1.4.15 Consider the support and care needs of parents or carers of children or young people in crisis. Where needs are	The GDG considered this recommendation to be relevant to the care of children and young people with psychosis or	• Involvement of parents or carers

they are met when it is safe and practicable to do so.	identified, ensure they are met when it is safe and practicable to do so.	schizophrenia because it pertained to the key issue of access to emergency/crisis teams with no significant adaptation required	• Access to emergency/ • crisis teams
1.6.2 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.	1.4.18 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.	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).	1.4.19 Undertake shared decision-making routinely with children or young people with psychosis or schizophrenia in hospital, including, whenever possible, those who are subject to the Mental Health Act (1983; amended 1995 and 2007).	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
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	1.4.21 Ensure that children and young people with in hospital continue to have access to a wide range of meaningful and culturally appropriate occupations and activities 7 days per week, and not	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	• Hospital care

include creative and leisure activities, exercise, self- care and community access activities (where appropriate). Activities should be facilitated by appropriately trained health or social care professionals.	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.	significant adaptation required	
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.	1.4.22 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.	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 •

Schizophrenia

The topic group and GDG also appraised the *Schizophrenia* (NCCMH, 2010; NICE, 2009a) guideline for adult service users 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 or schizophrenia and addressed some of the key issues and concerns they had identified in Section 4.4.2, 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 4.3; in all cases the adaptation retained the original meaning and intent of the recommendations.

Table 8 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 2 the numbers refer to the recommendations in the NICE guideline.

Table 8: Recommendations from *Schizophrenia* for inclusion

Original recommendation from *Schizophrenia*	**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 • negotiating skills for working with families of people with schizophrenia • conflict management and conflict resolution.	1.1.19 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.	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 (1.1.11) Based on expert opinion, the GDG preferred the term 'mental health problems' to 'abnormal mental states' because they felt it was less stigmatising.	• Stigma
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	1.1.20 Healthcare professionals inexperienced in working with children and young people with psychosis or schizophrenia from diverse ethnic and cultural backgrounds, and their parents or	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	• Stigma

professionals who are experienced in working transculturally.	carers, should seek advice and supervision from healthcare professionals who are experienced in working transculturally.	no significant adaptation required	
1.1.2.4 Mental health services should work with local voluntary BME 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.	1.1.22 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.	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.	1.3.4 Routinely monitor for other coexisting mental health problems, including depression and anxiety, and substance misuse, particularly in the early phases of treatment.	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.	
1.4.1.1 Develop and use practice case registers to monitor the physical and mental health of people with schizophrenia in primary care.	1.6.1 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.	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
1.4.1.4 Treat people with schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance.	1.6.4 Treat children and young people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance where available.	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	• Physical health needs

		recommendation because only NICE guidance for type 1 diabetes is appropriate for children and young people.	
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.	1.6.5 Healthcare professionals in secondary care should ensure, as part of the care programme approach (CPA), that children and young people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 1.6.2–1.6.4. Healthcare professionals in secondary care should continue to maintain responsibility for monitoring and managing any side effects of antipsychotic medication.	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 effects of medication.	• Physical health needs
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.	1.6.6 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.	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
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.	1.6.7 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	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.	

	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.		

4.4.4 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, 2011), twenty-seven recommendations from that guidance were considered relevant and important to the experience of care of children and young people with psychosis or 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 or 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 or 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. The GDG also considered the narrative review set out in Section 4.3 regarding hospital care.

Four recommendations were identified as being relevant to the experience of parents and carers, particularly the issue of 'involvement of parents or carers' 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.

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 (BME) groups with psychosis or 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 or schizophrenia. The GDG also considered the narrative review set out in Section 4.3 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 *Schizophrenia* (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 or 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 BME groups conducted for the *Schizophrenia* guideline (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 '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 or schizophrenia.

4.5 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, 2011) and *Schizophrenia* (NICE, 2009a) that were relevant to children and young people with psychosis or 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, Section 3.7. All adapted recommendations are listed in Table 7 and Table 8, 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 4.3), and why 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 or schizophrenia to address particular issues that were not covered by either *Service User Experience in Adult Mental Health* (NICE, 2011) or *Schizophrenia* (NICE, 2009a). New recommendations were considered important in five areas of treatment and management of children and young people with psychosis and schizophrenia: care across all phases; referral from primary care; assessment and care planning; treatment options for first episode psychosis; hospital care; and promoting recovery and providing possible future care in primary care. The GDG adopted an informal consensus approach as outlined in Chapter 3 (see Sections 3.5.6 and 3.5.7) to develop these recommendations.

In considering care across all phases the GDG agreed, based on the narrative review conducted in Section 4.3, 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. The GDG was mindful that professionals should use simple, jargon-free language and explain any clinical language, and use communication aids if needed. The GDG wished to emphasise that health and social care professionals working with children and young people with psychosis or 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. They should be able to assess capacity and competence and understand how to apply all relevant legislation including Children Act (1989; amended 2004), the Mental Health Act (1983; amended 1995 and 2007) and the Mental Capacity Act (2005). Considering the evidence that people from black and minority ethnic groups with psychosis or 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.

In discussing referral from primary care, and based on the narrative review of service provision, 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 consultant psychiatrist with training in child and adolescent mental health in either CAMHS or EIP services, where they should receive a multidisciplinary assessment covering psychiatric, psychosocial, developmental, physical health, social, educational and economic domains.

The GDG was of the opinion that care planning should involve consideration of educational input that is commensurate with the child or young person's capacity to engage with educational activity; and liaison with the child or young person's school was considered important in order to provide education at home where necessary.

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.

It was agreed by the whole GDG, based on the narrative review conducted in Section 4.3 and via informal consensus methods, that the distance of inpatient units from the child or young person's family home could impact the child or young person and their parents, carers and other family members and should be considered before referral for hospital care is arranged. In addition, community-based alternatives should be considered, but where inpatient admission was avoidable, parent and carers should be provided with support following admission. Hospital care should include access to a full educational programme (meeting the National Curriculum); and promote physical healthcare such as diet, exercise and smoking cessation.

An important issue for the GDG to consider, based on the narrative review conducted in Section 4.3 and via informal consensus, was the responsibility for physical healthcare of children and young people with psychosis or schizophrenia. They judged that GPs and other primary healthcare professionals should monitor their physical health at least once a year. 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

Finally, and based on the narrative review conducted in Section 4.3 , 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.

4.6 RECOMMENDATIONS

4.6.1 Working safely and effectively with children and young people

4.6.1.1 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.

4.6.1.2 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), the Mental Health Act (1983; amended 1995 and 2007[4]) and the Mental Capacity Act (2005), in the care and treatment of children and young people.

4.6.1.3 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. [5]

4.6.1.4 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. [6]

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

4.6.2.1 Work in partnership with children and young people with psychosis or schizophrenia and their parents or carers. Offer help, treatment and care in an atmosphere of hope and optimism. Take time to build trusting,

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

[5] Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

[6] Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

supportive, empathic and non-judgemental relationships as an essential part of care.[7]

4.6.2.2 When working with children and young people with psychosis or schizophrenia of an appropriate developmental level, emotional maturity and cognitive capacity:

- aim to foster their autonomy, promote active participation in treatment decisions, and support self-management, and access to peer support
- maintain continuity of individual therapeutic relationships wherever possible
- offer access to a trained advocate.[8]

4.6.2.3 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). [9]

4.6.2.4 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. [10]

4.6.2.5 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. [11]

4.6.3 Communication and information

4.6.3.1 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

[7] Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
8 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
9 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
10 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
11 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

- managing issues relating to information sharing and confidentiality as these apply to children and young people.

When a young person is 'Gillick competent' ask them what information can be shared before speaking to their parents or carers.

4.6.3.2 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.

4.6.3.3 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 'Understanding NICE guidance' booklets
- support groups, such as third sector, including voluntary organisations. [12]

4.6.3.4 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. [13]

4.6.3.5 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. [14]

12 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
13 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
14 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

4.6.3.6 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. [15]

4.6.4 Culture, ethnicity and social inclusion

4.6.4.1 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 peoples' 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. [16]

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

- provide and work proficiently with interpreters if needed
- offer a list of local education providers who can provide English language teaching for children and young people and their parents or carers who have difficulties speaking and understanding English.

4.6.4.3 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. [17]

15 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
16 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

4.6.4.4 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.[18]

4.6.4.5 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. [19]

4.6.4.6 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. [20]

4.6.5 Transfer and discharge

4.6.5.1 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 child and adolescent mental health services (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

17 Adapted from 'Schizophrenia' (NICE clinical guideline 82).
18 Adapted from 'Schizophrenia' (NICE clinical guideline 82).
19 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
20 Adapted from 'Schizophrenia' (NICE clinical guideline 82).

supported during the referral period and arrangements for support are agreed beforehand with them. [21]

4.6.6 Referral from primary care

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

4.6.7 Assessment and care planning in secondary care

4.6.7.1 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
- 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 side effects, to promote discussion and shared understanding
- offer support after the assessment, particularly if sensitive issues, such as childhood trauma, have been discussed. [22]

4.6.7.2 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)
- psychological and psychosocial, including social networks and relationships
- developmental (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions)
- physical health and history (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])

21 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
22 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

- educational and occupational (attendance at school or college, educational attainment, employment and functional activity)
- economic (family's economic status).

4.6.7.3 Routinely monitor for other coexisting mental health problems, including depression and anxiety, and substance misuse, particularly in the early phases of treatment. [23]

4.6.7.4 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 parent or carer 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.

4.6.7.5 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.[21]

4.6.7.6 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. [24]

23 Adapted from 'Schizophrenia' (NICE clinical guideline 82).
24 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

4.6.7.7 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. [25]

4.6.8 Treatment options for first episode psychosis

4.6.8.1 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, 2006) or 'Depression in children and young people' (NICE, 2005).

4.6.9 Referral in crisis

4.6.9.1 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. [26]

4.6.9.2 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
- make early plans to help the child or young person maintain their day-to-day activities, including education, work, and other occupations and leisure activities, wherever possible. [27]

4.6.9.3 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. [28]

4.6.9.4 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. [29]

25 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
26 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
27 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
28 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
29 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

4.6.10 Hospital care

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

4.6.10.2 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.

4.6.10.3 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

Make sure there is enough time for the child or young person and their parents or carers to ask questions. [30]

4.6.10.4 Undertake shared decision-making routinely with children or young people with psychosis or schizophrenia in hospital, including, whenever possible, those who are subject to the Mental Health Act (1983; amended 1995 and 2007). [31]

4.6.10.5 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.

4.6.10.6 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

30 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
31 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).

access activities (where appropriate). Activities should be facilitated by appropriately trained educational, health or social care professionals. [32]

4.6.10.7 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. [33]

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

4.6.11 Early post-acute period

4.6.11.1 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.

4.6.12 Primary care

4.6.12.1 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. [34]

4.6.12.2 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.

4.6.12.3 Children and young people with psychosis or schizophrenia at increased risk of developing cardiovascular disease and/or diabetes (for example, with elevated blood pressure, raised lipid levels, smokers, increased waist measurement) should be identified at the earliest opportunity and monitored for the emergence of these conditions.

4.6.12.4 Treat children and young people with psychosis or schizophrenia who have diabetes and/or cardiovascular disease in primary care according to the appropriate NICE guidance where available.[35] [36]

4.6.12.5 Healthcare professionals in secondary care should ensure, as part of the care programme approach (CPA), that children and young people with psychosis or schizophrenia receive physical healthcare from primary care as described in recommendations 4.6.12.2 to 4.6.12.4. Healthcare professionals in secondary care should continue to maintain responsibility

32 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136).
33 Adapted from 'Service user experience in adult mental health' (NICE clinical guideline 136)..
34 Adapted from 'Schizophrenia' (NICE clinical guideline 82).
35 See 'Type 1 diabetes' (NICE clinical guideline 15).
36 Adapted from 'Schizophrenia' (NICE clinical guideline 82).

for monitoring and managing any side effects of antipsychotic medication.[37]

4.6.12.6 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. [38]

4.6.12.7 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. [39]

4.6.12.8 Children and young people with psychosis or schizophrenia who are being treated in an early intervention in psychosis service should remain in that service for 3 years whatever their age of entry.

[37] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[38] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[39] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

5 AT-RISK STATES OF PSYCHOSIS IN CHILDREN AND YOUNG PEOPLE: RECOGNITION AND MANAGEMENT

5.1 INTRODUCTION

Over the past two 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 of this effort, 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 (Loebal *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 early intervention in psychosis (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 individuals 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 (Klosterkotter *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. Effective interventions are desirable because of the significant personal, social and financial costs associated with psychosis. To date, there have been nine randomised controlled trials (RCTs), each using similar operational definitions of 'at-risk', which have reported findings regarding outcomes associated with antipsychotic medication, omega-3 polyunsaturated fatty acids and/or psychological interventions including cognitive therapy. These studies have been conducted in Australia (McGorry *et al.*, 2002; Phillips *et al.* 2009), North America (Addington *et al.,* 2011; McGlashan *et al.*, 2006)and Europe (Amminger *et al.,* 2010; Bechdolf *et al.*, 2012; Morrison *et al.,* 2007; Morrison *et al.,* 2004) 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, an antipsychotic medication can be combined with a psychological therapy such as cognitive therapy, or several psychosocial interventions may be combined (such as cognitive therapy, cognitive remediation and family intervention). 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 9 (further detail on the review protocol can be found in Appendix 7; and further information about the search strategy can be found in Appendix 8).

Table 9: Clinical review protocol for the review of at-risk mental states in children and young people

Review question	**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): 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? **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 and/or psychological or psychosocial interventions improve outcomes?
Objectives	To provide evidence-based recommendations, via GDG consensus, regarding early recognition and management of at-risk mental states before a formal diagnosis of psychosis or schizophrenia has been made.
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 meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. Consideration will be given to individuals 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(s)	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 or 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. Licensed antipsychotics include: • 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 • Cognitive remediation • Counselling and supportive psychotherapy • Family interventions (including family therapy) • Psychodynamic psychotherapy and psychoanalysis • Psychoeducation • Social skills training • Art therapies
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 events (including effects on metabolism; extrapyramidal side effects; hormonal changes; and , cardiotoxicity)
Electronic databases	Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic-specific databases (see Appendix 8) Note: any evidence resulting from generic guideline searches also mapped to RQ
Date searched	SR: 1995 to May 2012 RCT: inception of databases to May 2012
Study design	RQA1 (a) and (b): Systematic reviews RQB1: 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.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 younger than 13 years need to be made.

5.3 RECOGNITION OF AT-RISK MENTAL STATES

5.3.1 Studies considered

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 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 (FUSAR-POLI2012). The GDG therefore decided to conduct a narrative review to address the review questions and to inform an informal consensus based approach, as detailed in Chapter 3, to develop recommendations. In brief, this process involved full group discussion about the narrative review, the evidence reported in the systematic review (FUSAR-POLI2012), 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 meet criteria for 'at-risk' mental state as being at high risk of developing psychosis.

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 possessing an 'at-risk mental state' for psychosis. 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 have been within a specified age range (usually 14 to 30 years) known to be at greatest risk for the 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 first episode psychosis suggest that over 75% make contact with general practitioners (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-POLI2012 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 (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:

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

A basic symptoms criterion is based on self-perceived disturbances and assessments included a further 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 DSM, the ICD 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%-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% (CI, 25.0% to 29.7%) and 27.5% (24.3% to 30.9%) respectively. However when transition was defined according to DMS-III, DMS-IV or ICD-10, significant variance in risk was observed across studies and the risk was higher than that observed 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 who meet criteria for at-risk mental states as being at high risk of developing psychosis. 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 identify individuals 'at risk' for developing psychosis, including brief limited intermittent psychotic symptoms, attenuated (subclinical) psychotic symptoms and trait-plus-state factors. Several measures exist to measure at-risk states and, despite variation in transition rates between studies employing different measures, these instruments correctly identify people who later developed psychosis. However, the variability in transition rates suggest that the criteria for 'at-risk states' need further refinement in order to better predict those who will and those who will not go on to develop psychosis. 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 may be needed to investigate the influence of sampling strategies on rates of transition to psychosis.

5.4 PHARMACOLOGICAL INTERVENTIONS

5.4.1 Studies considered

Three RCTs (N = 234) providing relevant clinical evidence met the eligibility criteria for this review. Of these, one study contained unpublished data (PHILLIPS2009) and two studies were published in peer-reviewed journals between 2002 and 2011. All studies contained a sample in which some participants were under 18 and the mean age was 25 years or younger. Further information about both included and excluded studies can be found in Appendix 13.

Of the three included trials, there was one involving a comparison of olanzapine to placebo, two involving a comparison of risperidone plus CBT to supportive counselling and one comparing risperidone plus CBT to placebo plus CBT (see Table 10) for a summary of the study characteristics). The full evidence profiles and associated forest plots can be found in Appendix 13 and Appendix 14, respectively.

Table 10: 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]	(1) Not reported (2) CAARMS[2]	CAARMS2
Diagnosis	At-risk mental state	Ultra-high risk mental state	Ultra-high risk mental state
Age: Mean (range)	17.8 (range 12 to 36)	(1) 20 (range 14 to 28) (2) 17.9 (not reported)[3]	17.9 (not reported)[3]
Sex (% male)	65	(1) 58 (2) 39[3]	39[3]
Ethnicity (% Caucasian)	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); SC: 5.9(4.3). (2) Up to of 35 hours of CBT or SC	Up to 35 hours
Treatment length (weeks)	52	(1) 26 (2) 52	52
Treatment follow-up (weeks)	104	(1) 156 to 208 (2) 52	52
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. N = Total number of participants
[1]Structured Interview for Prodromal Symptoms
[2] Comprehensive assessment of at-risk mental states
[3] In whole study (N = 115; PHILLIPS2009 is a three way comparison evaluating risperidone, CBT and SC)

5.4.2 Olanzapine versus placebo

Efficacy

One study (N = 60) compared olanzapine with placebo. By week eight, more people taking olanzapine compared with placebo transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder), but the difference was not statistically significant (RR = 10.31, 0.60 to 178.62). At 1-year post-treatment 16 participants had transitioned to psychosis and there was no significant difference between groups (RR = 0.43, 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 11 and Table 12.

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, 0.88 to 2.88). Participants taking olanzapine gained significantly more weight (SMD = 1.18, 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, 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 12 and Table 12.

Table 11: Summary evidence profile 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	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)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; 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/min; 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 (beats/min; SMD)	MCGLASHAN2003	K = 1, N = 59	0.37 [-0.15, 0.88]	N/A	Very low[1,2,3]	Appendix 14a (3.3)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours placebo
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Table 12: Summary evidence profile 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	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. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation and allocation concealment and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

5.4.3 Risperidone plus CBT versus supportive counselling

Efficacy

Two studies (N = 130) compared risperidone plus CBT against supportive counselling. By the end of treatment 26 participants had transitioned to psychosis (defined as the development of a DSM-IV psychotic disorder) and there was no significant difference between groups (SMD = 0.48, 0.17 to 1.32). By 52 weeks' follow-up and 156 to 208 weeks' follow-up, one study (MCGORRY2002) reported that 16 out of 59 participants, and later 22 out of 59 participants, transitioned to psychosis. However, there was still no significant difference between groups (SMD = 0.54, 0.23 to 1.30 and SMD = 0.75, 0.39 to 1.46 respectively). 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 efficacy 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 = 1.16, 0.60 to 2.25). Evidence from each reported outcome and overall quality of evidence are presented in Table 13, Table 14 and Table 15.

Side effects

Six out of the 21 participants for whom side effect data were reported experienced extrapyramidal symptoms (as measured by the Udvalg for KliniskeUndersogelser Neurologic Scale, see Appendix 14a [6.2]). However, observing only six events, there was no significant difference between groups at post-treatment (RR = 0.55, 0.13 to 2.38) (see Table 13).

Table 13: Summary evidence profile for outcomes reported for risperidone plus CBT versus supportive at post-treatment

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 1, N = 101	-0.13 [-0.53, 0.26]	(P = 1.00); I^2 = 0%	Very low[1,2,3]	Appendix 14a (5.1)
Positive symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 101	-0.16 [-0.55, 0.23]	(P = 0.93); I^2 = 0%	Very low[1,2,3]	Appendix 14a (5.2)
Negative symptoms (SMD)	MCGORRY2002 PHILLIPS2009	K = 2, N = 101	-0.03 [-0.59, 0.52]	(P = 0.16); I^2 = 48%	Very low[1,2,3]	Appendix 14a (5.3)
Depression (SMD)	MCGORRY2002	K = 1, N = 59	-0.32 [-0.83, 0.20]	N/A	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 = 102	-0.08 [-0.47, 0.31]	(P = 0.88); I^2 = 0%	Very low[1,2,3]	Appendix 14a (5.8)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	0.48 [0.17, 1.32]	(P = 0.19); I^2 = 43%	Very low[1,2,3]	Appendix 14a (5.9)
Leaving the study early for any reason (RR)	MCGORRY2002 PHILLIPS2009	K = 2, N = 130	1.16 [0.60, 2.25]	N/A [no events observed by MCGORRY2002]	Very low[1,2,3]	Appendix 14a (6.1)
Extra pyramidal symptoms (RR)	PHILLIPS2009	K = 1, N = 21	0.55 [0.13, 2.38]	N/A	Very low[1,2,3]	Appendix 14a (6.2)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, participants and providers unblind to psychological intervention, trial registration not found, uneven sample sizes and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Table 14: Summary evidence profile for outcomes reported for risperidone plus CBT versus supportive at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total symptoms (SMD)	MCGORRY2002	K = 1, N = 59	0.21 [-0.30, 0.73]	N/A	Very low[1,2,3]	Appendix 14a (7.1)
Positive symptoms (SMD)	MCGORRY2002	K = 1, N = 59	0.21 [-0.30, 0.72]	N/A	Very low[1,2,3]	Appendix 14a (7.2)
Negative symptoms (SMD)	MCGORRY2002	K = 1, N = 59	-0.06 [-0.57, 0.45]	N/A	Very low[1,2,3]	Appendix 14a (7.3)
Depression (SMD)	MCGORRY2002	K = 1, N = 59	0.14 [-0.37, 0.65]	N/A	Very low[1,2,3]	Appendix 14a (7.4)
Mania (SMD)	MCGORRY2002	K = 1, N = 58	0.00 [-0.52, 0.52]	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	K = 1, N = 59	0.04 [-0.47, 0.55]	N/A	Very low[1,2,3]	Appendix 14a (7.8)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	MCGORRY2002	K = 1, N = 59	0.54 [0.23, 1.30]	N/A	Very low[1,2,3]	Appendix 14a (7.9)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, participants, providers and raters unblind to psychological intervention, trial registration could not be found and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Table 15: Summary evidence profile for outcomes reported for risperidone plus CBT versus supportive at 156 to 208 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	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 (8.1)
Positive symptoms (SMD)	MCGORRY2002	K = 1, N = 41	-0.04 [-0.66, 0.58]	N/A	Very low[1,2,3]	Appendix 14a (8.2)
Negative symptoms (SMD)	MCGORRY2002	K = 1, N = 41	-0.24 [-0.87, 0.38]	N/A	Very low[1,2,3]	Appendix 14a (8.3)
Depression (SMD)	MCGORRY2002	K = 1, N = 41	0.23 [-0.39, 0.86]	N/A	Very low[1,2,3]	Appendix 14a (8.4)
Mania (SMD)	MCGORRY2002	K = 1, N = 41	-0.36 [-0.98, 0.27]	N/A	Very low[1,2,3]	Appendix 14a (8.5)
Anxiety (SMD)	MCGORRY2002	K = 1, N = 41	0.14 [-0.49, 0.76]	N/A	Very low[1,2,3]	Appendix 14a (8.6)
Psychosocial functioning (SMD)	MCGORRY2002	K = 1, N = 41	-0.15 [-0.77, 0.47]	N/A	Very low[1,2,3]	Appendix 14a (8.7)
Quality of life (SMD)	MCGORRY2002	K = 1, N = 41	-0.08 [-0.71, 0.54]	N/A	Very low[1,2,3]	Appendix 14a (8.8)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	MCGORRY2002	K = 1, N = 59	0.75 [0.39, 1.46]	N/A	Very low[1,2,3]	Appendix 14a (8.9)
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 (8.10)
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 (9.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, participants, providers and raters unblind to psychological intervention, trial registration could not be found and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

5.4.4 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 (SMD 1.02, 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 = 0.80, 0.33 to 1.95). Evidence from each reported outcome and overall quality of evidence are presented in Table 16.

Side effects

Five out of the 23 participants for whom side effect data were reported experienced extrapyramidal symptoms (as measured by the Udvalg for Kliniske Undersogelser Neurologic Scale, see Appendix 14a [11.2]). However, there was no significant difference between groups (RR = 0.87, 0.18 to 4.24). Evidence from each reported outcome and overall quality of evidence are presented in Table 16.

5.4.5 Clinical evidence summary

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

Table 16: Summary evidence profile 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	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 (10.1)
Positive symptoms (SMD)	PHILLIPS2009	K = 1, N = 51	-0.07 [-0.62, 0.48]	N/A	Very low[1,2,3]	Appendix 14a (10.2)
Negative symptoms (SMD)	PHILLIPS2009	K = 1, N = 51	0.12 [-0.43, 0.67]	N/A	Very low[1,2,3]	Appendix 14a (10.3)
Psychosocial functioning (SMD)	PHILLIPS2009	K = 1, N = 52	0.24 [-0.31, 0.78]	N/A	Very low[1,2,3]	Appendix 14a (10.4)
Quality of life (SMD)	PHILLIPS2009	K = 1, N = 51	-0.23 [-0.78, 0.33]	N/A	Very low[1,2,3]	Appendix 14a (10.5)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	PHILLIPS2009	K = 1, N = 87	1.02 [0.39, 2.67]	N/A	Very low[1,2,3]	Appendix 14a (10.6)
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 (11.1)
Extrapyramidal symptoms (RR)	PHILLIPS2009	K = 1, N = 23	0.87 [0.18, 4.24]	N/A	Very low[1,2,3]	Appendix 14a (11.2)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation, allocation concealment, participants and providers unblind to psychological intervention, trial registration not found, uneven sample sizes and available case analysis).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

5.5 DIETARY INTERVENTIONS

5.5.1 Studies considered

One RCT (N = 81) providing relevant clinical evidence met the eligibility criteria for this review. Post-treatment data were identified in a systematic review (MARSHALL2011), whilst follow-up data were published in a peer-reviewed journal in 2010 (AMMINGER2010, see Table 17 for a summary of the study characteristics). The full evidence profiles and associated forest plots can be found in Appendix 13 and Appendix 14, respectively.

Table 17: 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/MARSHALL2011
Screening tool	PANSS1
Diagnosis	Ultra-high risk mental state
Age: Mean (range)	16.4 (not reported)
Sex (% male)	33
Ethnicity (% Caucasian)	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
Note. N = Total number of participants [1]Positive and Negative Symptom Scale	

5.5.2 Omega-3 fatty acids versus placebo

One study compared omega-3 polyunsaturated fatty acids (ω-3 PUFAs) versus 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, 0.02 to 0.95). However, there were only eight events in total. This effect was maintained at 12 months' follow-up (RR = 0.18, 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 positive (SMD = -2.08, -2.63 to -1.54) and negative symptoms of psychosis (SMD = -2.22, -2.77 to -1.66), depression (SMD = -0.56, -1.01 to -0.12) and psychosocial functioning (SMD = -1.28, -1.76 to -0.80) also favoured omega-3 fatty acids at 12 months' follow-up. Effects on total symptoms of psychosis, however, were not significant (SMD = -1.26, -1.74 to 0.78) and dropout was low (only five events; see Appendix 14a [13.1]) and similar between groups (RR = 1.46, 0.26 to 8.30). Evidence from each reported outcome and overall quality of evidence are presented in Table 18 and Table 19.

Table 18: Summary evidence profile 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	Forest Plot
Transition to psychosis (RR)	AMMINGER2010/ MARSHALL2011	K = 1, N = 76	0.13 [0.02, 0.95]*[1]	N/A	Low[2, 3]	Appendix 14a (12.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours omega-3 fatty acids
[1]Serious risk of bias (including dropout not reported therefore, an available case analysis has been used)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Table 19: Summary evidence profile 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	Forest Plot
Total symptoms (SMD)	AMMINGER2010	K = 1, N = 81	-1.26 [-1.74, 0.78]	N/A	Low[1, 2]	Appendix 14a (13.1)
Positive symptoms (SMD)	AMMINGER2010	K = 1, N = 81	-2.08 [-2.63, -1.54]*	N/A	Low[1, 2]	Appendix 14a (13.2)
Negative symptoms (SMD)	AMMINGER2010	K = 1, N = 81	-2.22 [-2.77, -1.66]*	N/A	Low[1, 2]	Appendix 14a (13.3)
Depression (SMD)	AMMINGER2010	K = 1, N = 81	-0.56 [-1.01, -0.12]*	N/A	Low[1, 2]	Appendix 14a (13.4)
Psychosocial functioning (SMD)	AMMINGER2010	K = 1, N = 81	-1.28 [-1.76, -0.80]*	N/A	Low[1, 2]	Appendix 14a (13.5)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	AMMINGER2010	K = 1, N = 81	0.18 [0.04, 0.75]*	N/A	Low[1, 2]	Appendix 14a (13.6)
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 (14.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours omega-3 fatty acids
[1] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[2]Serious risk of reporting bias

5.5.3 Clinical evidence summary

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

Five RCTs (N = 599) providing relevant clinical evidence met the eligibility criteria for this review. Of these, two contained some unpublished data (MORRISON2004 and PHILLIPS2009) and the remaining were published in peer-reviewed journals between 2004 and 2012. All studies contained a sample in which some participants were under 18 and the mean age was 25 years or younger. Further information about both included and excluded studies can be found in Appendix 14.

Of the five included trials, four studies compared individual CBT with supportive counselling and one compared a multi-modal intervention entitled integrated psychological therapy with supportive counselling (see Table 20 for a summary of the study characteristics). The full evidence profiles and associated forest plots can be found in Appendix 13 and Appendix 14, respectively.

Table 20: Study information table for trials of psychosocial interventions

	CBT versus supportive counselling	Integrated psychological therapy versus supportive counselling
Total no. of studies (N)	4 (N = 471)	1 (N = 128)
Study ID	(1) ADDINGTON2011 (2) MORRISON2004 (3) MORRISON2011 (4) PHILLIPS2009	BECHDOLF2012
Screening tool	(1) SIPS[1] (2) PANSS[2] (3)(4) CAARMS[3]	ERIraos[4]
Diagnosis	Ultra high/high risk mental state	Early initial prodromal state
Age: Mean (range)	(1) 20.9 (not reported) (2) 22 (range 16 to 36) (3) 20.7 (range 14 to 34) (4) 17.9 (not reported)[5]	25.8 (not reported)
Sex (% male)	(1) 71 (2) 67 (3) 63 (4) 39[5]	66
Ethnicity (% Caucasian)	(1) 57 (2) Not reported (3) 88 (4) Not reported	Not reported
Sessions of therapy	(1) CBT and SC: up to 20 sessions (2) CBT: 26; SC: 13 (3) CBT: 26; SC: not reported (4) Up to of 35 hours	25 individual therapy sessions; 15 group sessions; 12 cognitive remediation sessions; three information and counselling of relatives sessions
Treatment length (weeks)	(1) 26 (2) 52 (3) 26 (4) 52	52
Treatment follow-up (weeks)	(1) 78 (2) 156 (3) 104 (4) 52	104
Setting	(1) Specialist clinic/ward (2) Not reported (3) Not reported (4) Specialist clinic/ward	Specialist clinic/ward
Country	(1) Canada (2) UK (3) UK (4) Australia	Germany

Note. N = Total number of participants.
[1]Structured Interview for Prodromal Symptoms
[2] Positive and Negative Symptom Scale
[3] Comprehensive Assessment of At-risk Mental States
[4]Early Recognition Inventory
[5]In whole study (N = 115; PHILLIPS2009 is a three way comparison evaluating risperidone, CBT and SC).

5.6.2 CBT versus supportive counselling

Four RCTs (ADDINGTON2011, MORRISON2004, MORRISON2011, PHILLIPS2009; N = 471) compared CBT with supportive counselling. By the end of treatment all studies reported that CBT did not significantly reduce transition to psychosis (defined as the development of a DSM-IV psychotic disorder) compared with supportive counselling (RR = 0.71, 0.38 to 1.34), observing 35 events in total. Furthermore, between-group differences remained insignificant at both 52 weeks' (RR = 0.55, 0.23 to 1.29) and 78 weeks' or more follow-up (RR = 0.88, 0.70 to 1.09). All studies reported mean endpoint scores and at post-treatment there were no between-group differences on total symptoms of psychosis (SMD = -0.00, -0.21 to 0.21). However, at 52 weeks' follow-up a small effect was found for CBT (SMD = 0.30, -0.56 to -0.05). Combined effects at post-treatment and follow-up on positive and negative symptoms of psychosis, depression, psychosocial functioning and quality of life were also not significant. At post-treatment 79 out of 250 participants in the CBT group, and 87 out of 219 participants in the supportive counselling group, had dropped out (see Appendix 14a [16.1]). However, this difference was not statistically significant (RR = 0.71, 0.38 to 1.34) and remained insignificant at both 52 weeks (RR = 0.98, 0.74 to 1.31) and 78 weeks' or more follow-up (RR = 1.01, 0.79 to 1.28). Evidence from each reported outcome and overall quality of evidence are presented in Table 21, Table 22 and Table 23.

Table 21: Summary evidence profile for outcomes reported for CBT versus supportive counselling at post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest Plot
Total symptoms (SMD)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009	K = 4, N = 350	-0.00 [-0.21, 0.21]	(P = 0.89); I^2 = 0%	Low[1,2]	Appendix 14a (15.1)
Positive symptoms (SMD)	ADDINGTON2011 MORRISON2004 PHILLIPS2009	K = 3, N = 154	-0.15 [-0.48, 0.17]	(P = 0.94); I^2 = 0%	Low[1,2]	Appendix 14a (15.2)
Negative symptoms (SMD)	ADDINGTON2011 MORRISON2004 PHILLIPS2009	K = 3, N = 154	0.10 [-0.22, 0.42]	(P = 0.93); I^2 = 0%	Low[1,2]	Appendix 14a (15.3)
Depression (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 236	0.04 [-0.21, 0.30]	(P = 0.50); I^2 = 0%	Low[1,2]	Appendix 14a (15.4)
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 172	0.01 [-0.28, 0.31]	N/A	Low[1,2]	Appendix 14a (15.5)
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 (15.6)
Quality of life (SMD)	MORRISON2011 PHILLIPS2009	K = 2, N = 185	0.02 [-0.27, 0.31]	(P = 0.70); I^2 = 0%	Low[1,2]	Appendix 14a (15.7)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011* MORRISON2004 MORRISON2011 PHILLIPS2009	K = 4, N = 469	0.62 [0.31, 1.22]	(P = 0.36); I^2 = 6%	Moderate[1]	Appendix 14a (15.8)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011 PHILLIPS2009	K = 4, N = 469	0.71 [0.38, 1.34]	(P = 0.0008); I^2 = 82%	Low[1,3]	Appendix 14a (16.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* 15 weeks during treatment
[1]Serious risk of bias (including unclear sequence generation, participants, providers and outcome assessors unblind, trial registration could not be found, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3] $I^2 \geq 50\%$, $p<.05$

Table 22: Summary evidence profile 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	Forest Plot
Total symptoms (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 239	-0.30 [-0.56, -0.05]*	(P = 0.42); I^2 = 0%	Low[1,2]	Appendix 14a (17.1)
Positive symptoms (SMD)	ADDINGTON2011	K = 1, N = 51	-0.27 [-0.82, 0.29]	N/A	Low[1,2]	Appendix 14a (17.2)
Negative symptoms (SMD)	ADDINGTON2011	K = 1, N = 51	0.06 [-0.49, 0.61]	N/A	Low[1,2]	Appendix 14a (17.3)
Depression (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 234	-0.01 [-0.26, 0.25]	(P = 0.43); I^2 = 0%	Low[1,2]	Appendix 14a (17.4)
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 188	0.15 [-0.15, 0.44]	N/A	Low[1,2]	Appendix 14a (17.5)
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 (17.6)
Quality of life (SMD)	MORRISON2011	K = 1, N = 134	-0.10 [-0.44, 0.24]	N/A	Low[1,2]	Appendix 14a (17.7)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011 MORRISON2011	K = 2, N = 339	0.55 [0.23, 1.29]	(P = 0.27); I^2 = 19%	Low[1,2]	Appendix 14a (17.8)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2011	K = 2, N = 339	0.98 [0.74, 1.31]	(P = 0.75); I^2 = 0%	Low[1,2]	Appendix 14a (18.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours CBT
[1]Serious risk of bias (including unclear sequence generation, participants, providers and outcome assessors unblind, trial registration could not be found, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Table 23: Summary evidence profile 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	Forest Plot
Total symptoms (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 116	-0.17 [-0.53, 0.20]	(P = 0.56); I^2 = 0%	Low[1,2]	Appendix 14a (19.1)
Positive symptoms (SMD)	ADDINGTON2011	K = 1, N = 54	0.02 [-0.53, 0.57]	N/A	Low[1,2]	Appendix 14a (19.2)
Negative symptoms (SMD)	ADDINGTON2011	K = 1, N = 54	-0.10 [-0.65, 0.45]	N/A	Low[1,2]	Appendix 14a (19.3)
Depression (SMD)	ADDINGTON2011 MORRISON2011	K = 2, N = 112	-0.05 [-0.46, 0.37]	(P = 0.27); I^2 = 19%	Low[1,2]	Appendix 14a (19.4)
Anxiety (social; SMD)	MORRISON2011	K = 1, N = 58	-0.46 [-0.99, 0.06]	N/A	Low[1,2]	Appendix 14a (19.5)
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 (19.6)
Quality of life (SMD)	MORRISON2011	K = 1, N = 48	0.40 [-0.17, 0.98]	N/A	Low[1,2]	Appendix 14a (19.7)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	ADDINGTON2011 MORRISON2004 MORRISON2011	K = 3, N = 397	0.88 [0.70, 1.09]	(P = 0.42); I^2 = 0%	Low[1,2]	Appendix 14a (19.8)
Leaving the study early for any reason (RR)	ADDINGTON2011 MORRISON2004 MORRISON2011	K = 3, N = 397	1.01 [0.79, 1.28]	(P = 0.86); I^2 = 0%	Low[1,2]	Appendix 14a (20.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including unclear sequence generation, participants, providers and outcome assessors unblind, trial registration could not be found, missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

5.6.3 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, cognitive remediation and family treatments, in the absence of antipsychotic medication. Transition to psychosis was defined as either the development of attenuated or transient symptoms (subthreshold psychosis) or a DSM-IV psychotic disorder. At 1-year post-treatment fewer people receiving integrated psychological therapy transitioned (RR = 0.20, 0.05 to 0.86), but there were only 13 events and the effect was no longer significant when dropouts in both groups were assumed to have transitioned (RR = 0.67, 0.34 to 1.31). Again, the effect was maintained at 2 years' follow-up (RR = 0.34, 0.12 to 097) unless dropouts were assumed to have transitioned (RR = 0.71, 0.38 to 1.31). Importantly, 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). Dropout was similar between groups at 1 year (RR = 1.55, 0.68 to 3.53) and 2 years (RR = 0.95, 0.61 to 1.49) post-treatment. Other symptoms were not reported as outcomes, although the PANSS and GAF were recorded at baseline. Evidence from each reported outcome and overall quality of evidence are presented in Table 24 and Table 25.

Table 24: Summary evidence profile 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	Forest Plot
Transition to psychosis (RR)	BECHDOLF2012	K = 1, N = 113	0.20 [0.05, 0.86]*	N/A	Very low[1,2,3]	Appendix 14a (21.1)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	BECHDOLF2012	K = 1, N = 128	0.67 [0.34, 1.31]	N/A	Very low[1,2,3]	Appendix 14a (21.2)
Leaving the study early for any reason (RR)	BECHDOLF2012	K = 1, N = 128	1.55 [0.68, 3.53]	N/A	Very low[1,2,3]	Appendix 14a (22.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours integrated psychological therapy
[1] Serious risk of bias (participants, providers and outcome assessors unblind, missing data).
[2] Optimal information size (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 25: Summary evidence profile 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	Forest Plot
Transition to psychosis (RR)	BECHDOLF2012	K = 1, N = 113	0.34 [0.12, 0.97]*	N/A	Very low[1,2,3]	Appendix 14a (23.1)
Sensitivity analysis: transition to psychosis (assuming dropouts transitioned; RR)	BECHDOLF2012	K = 1, N = 128	0.71 [0.38, 1.31]	N/A	Very low[1,2,3]	Appendix 14a (23.2)
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 (24.1)

Note. ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference. *Favours integrated psychological therapy
[1] Serious risk of bias (participants, providers and outcome assessors unblind, missing data).
[2] Optimal information size (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

Five RCTs (N = 599) investigated the efficacy of psychological interventions in young people at risk of developing psychosis or schizophrenia. Four trials (N = 471) compared CBT with supportive counselling and the findings suggest that CBT is no more effective at preventing transition to psychosis. Furthermore, CBT was found to be no more effective 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 authors failed to 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 conclusion can be drawn.

5.7 HEALTH ECONOMIC EVIDENCE

Systematic literature review

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

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. 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 (CAU), which did not include any provision of specialised mental health interventions. The data on CAU was obtained from the same geographical area of south London. The decision analytic model was developed for a period of 1 year 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 CMHT contacts), 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 (OASIS and LEO).

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.

The OASIS study showed that probability of transition to psychosis with an EIP service is 0.20 as compared with 0.35 probability of transition to psychosis 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 early intervention 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 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 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 (2009) 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 pharmacology 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 pharmacology 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-base 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.

One of the health economics studies reviewed conducted a cost effectiveness analysis of an early intervention service for people at high risk of psychosis. The two-year study did not show cost effectiveness for early intervention, however, the psychotic disorders can be lifelong.

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 in the 'at-risk' stage, prior to the development of psychosis. 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 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 or schizophrenia. However, this is often a highly comorbid, help-seeking group that requires support and treatment and as a result, outcomes pertaining to 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.

Similarly, for all but one of the psychological interventions there was no clear evidence that transition could be altered. 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 on applying an intention-to-treat analysis (that is, dropouts assumed to be transition) the effect was lost. Nevertheless, this assumption may not be correct in this context, as 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 thus will be harder to locate. An important additional consideration is that there is good evidence that family interventions are effective in reducing relapse rates in both first episode psychosis and in established schizophrenia. Importantly, family interventions were a key component of integrated psychological therapy. As the strongest evidence for preventing a psychotic episode recurring is for family interventions, rather than for individual cognitive behavioural therapies, the use of family interventions to prevent the first occurrence of a psychosis in those at high risk of developing a psychosis certainly warrants independent investigation.

Finally, one small RCT indicated that omega-3 fatty acids may be effective in preventing transition from at-risk mental states to development of psychosis (even when an intention-to-treat analysis is used, that is, dropouts assumed to be transition) and improving symptoms of psychosis, depression and psychosocial functioning in young people. There is not sufficient evidence on which to recommend the use of omega-3 fatty acids, however, given 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.

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 treatments. The harms associated with intervening include stigma, a fear of becoming psychotic (because that is why they have been included in the trial/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 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 (individual or family 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 problems, which led to a high risk of bias for almost all of the studies that were considered to be of low/very low quality and difficult to interpret. Such problems included: (a) small sample sizes, (b) lack of outcome assessor blinding, (c) use of available case analysis, rather than ITT analysis; and (d) likely publication bias. Furthermore, there is some suggestion that amongst this high risk group, the number of transitions increases over 3 years and then settles. Therefore, trials require longer follow-up periods.

In summary, the GDG decided not to recommend any treatments for child and young people at risk of developing psychosis delivered with the aim of reducing the risk of transition to psychosis. Instead, it was deemed important to treat presenting psychotic and associated symptoms to reduce current distress and monitor individuals for up to 3 years. Further research was considered necessary; based on the evidence for the first episode that family interventions can prevent relapse, and

the promise shown in the trial on integrated psychological therapy (which included a family treatment), a large multicentre RCT of family interventions with a cost-effectiveness analysis should be undertaken.

5.9 RECOMMENDATIONS

5.9.1 Referral from primary care

5.9.1.1 When a child or young person experiences transient 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 and 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 are not sufficient for a diagnosis of psychosis or schizophrenia, consider:

- treatments recommended in NICE guidance for any recognised conditions such as anxiety, depression, emerging personality disorder or substance misuse, or

- individual or family cognitive behavioural therapy (CBT) to decrease distress (delivered as set out in recommendation 6.5.15.1)

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 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 13 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 13 for further details.)
- What are the long-term outcomes, both psychotic and non-psychotic, for children and young people with prodromal 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 13 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 adolescents with psychosis, 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 urban upbringing and residence in unstable, fragmented neighbourhoods (Kirkbride *et al*., 2010); and the impact that low self-esteem can have on the way in which individuals with psychotic experience appraise its meaning.

Demand for psychological therapies in general has also grown, culminating in the Department of Health's IAPT (Improving Access to Psychological Therapies) 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, which are the subject of this guideline.

6.1.1 Developmental processes and the emergence of psychosis

The familiar notion that the onset of psychosis coincides with the 'first psychotic episode' as now understood to be something of a misnomer; 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 NEMESIS project (Kuepper *et al*., 2011) and the UK AESOP study (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 the experience of childhood abuse or neglect. Affective dysregulation has been shown to be a dimension that is both highly co-morbid with psychosis (now argued 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 those with adolescent onset tend to fare worse in this regard. Prospective studies of social disability and recovery have shown that early functional and vocational recovery, rather than psychosis 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 (Alvarez-Jimenez *et al.*, 2011). These developmental processes can inform wider foci of interventions in adolescent psychosis embracing: the family; developmental trauma and their sequelae; affective dysfunction; substance misuse and peer social engagement.

6.1.2 Aims of psychological therapy and psychosocial intervention

The aims of psychological therapy and psychosocial intervention in children and young people with psychosis are therefore numerous. These should include interventions to improve symptoms but also those that address vulnerability, which 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; dealing with the sequelae of abuse and neglect including attachment formation.

Further considerations need to be given to very young 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 – especially at acute phases of illness – to adapt expectations from the child in line with the severity of the symptoms will be especially important in this age group. Rehabilitation back into school will require careful assessment of what school environment will best meet the child's general needs, associated developmental deficits and psychiatric co-morbidity and sequelae.

6.1.3 Competence to deliver psychological therapies

For the purpose of implementing these guidelines in practice, it is important to have an understanding of the therapists' level of competence in the psychological therapy trials that were included. Each of the psychological therapy papers was reviewed for details of training or level of competence of the therapists delivering the intervention.

Psychological therapies delivered to younger children in particular, must be appropriate for their cognitive and developmental level. Therapists delivering these

interventions must have training in working with children and young people at all developmental levels.

6.2 CLINICAL REVIEW PROTOCOL FOR THE REVIEW OF PSYCHOLOGICAL THERAPY IN THE TREATMENT AND MANAGEMENT OF 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 26 below (further detail on the review protocol can be found in Appendix 8 and further information about the search strategy can be found in Appendix 9).

Table 26: Clinical review protocol for the review of psychological therapy in the treatment and management of schizophrenia in children and young people

Component	Description
Review question	**RQB11*** Do the advantages and disadvantages of psychological or psychosocial interventions, compared with alternative management differ between children/young people and adults with schizophrenia? **RQB12*** 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 schizophrenia compared with adults with schizophrenia? **RQB13** Should the duration (and where relevant frequency) of an initial psychological/ psychosocial intervention be different in children and young people with schizophrenia compared with adults with schizophrenia? **RQB14*** Is the most effective format for particular psychological/ psychosocial interventions (for example group or individual) the same for children and young people with schizophrenia compared with adults with schizophrenia? *The following subgroups will be considered for each RQ: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission[1] e) Maintaining and promoting recovery[1]
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding the psychological and psychosocial treatment and management of children and young people with psychosis or schizophrenia, including a review of NICE

	Clinical Guidance 82 for its relevance to children and young people.
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 meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. Consideration will also be given to the specific needs of children and young people with schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusions:** 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 • Art therapies
Comparison	Alternative Management Strategies • Treatment as usual (TAU) • Wait-list • 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	Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic specific databases and grey literature (see Appendix 8)
Date searched	SR: 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 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 aged 13 years and younger need to be made.
[1] Evidence not found	

6.3 STUDIES CONSIDERED FOR REVIEW

The adult guideline, *Schizophrenia* (NCCMH, 2010; NICE, 2009a), included a broad range of different types of psychological and psychosocial interventions including cognitive behavioural therapy, cognitive remediation, counselling and supportive therapy, family interventions, psychodynamic and psychoanalytic therapy, psychoeducation, social skills training, adherence therapy and arts therapies. For children and young people with psychosis and schizophrenia, only one RCT (N=30) was identified that provided relevant clinical evidence which met the eligibility criteria for this review and was conducted in individuals <18 years (APTER1978). A further eight RCTs (N = 618) were identified in samples that included individuals <18years>, but with a mean age <25 years, which provided relevant clinical evidence and met the eligibility criteria for this review. Data from these studies was included and extrapolated. These included cognitive behavioural therapy, family interventions and a specialised treatment as usual (EPPIC). Given the limited evidence in children and young people, this evidence was considered alongside the evidence reported in the adult *Schizophrenia* guideline (NCCMH, 2010) and recommendations were developed accordingly.

All RCTs in children and young people were published in peer-reviewed journals between 1978 and 2012. An additional 194 studies were reviewed by full text and excluded from the analysis. Further information about both included and excluded studies can be found in Appendix 14.

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 patient 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, drama therapy and music therapy.

6.4.2 Studies considered

One RCT (N = 30) compared individual body movement therapy with group body movement therapy (BMT) and a non-specific dance therapy control (see

Table 27 for a summary of the study characteristics). It was conducted in a sample of children and young people aged 13 to 18 years old with acute psychosis and published in a peer-reviewed journal in 1978. No data could be extracted and analysed and so results are reported narratively in this review.

Table 27: Summary study characteristics 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(s)	APTER1978
Diagnosis	Acute psychosis (BP not specified)
Age	Range: 13-18
Sex (% male)	50%
Ethnicity (% Caucasian)	Not reported
Treatment length (weeks)	12
Length of follow-up (weeks)	12
Setting	Inpatient
Country	Unclear

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

Efficacy data could not be extracted from APTER1978 and the only outcome of interest reported was global improvement (as measured by the Clinical Global Impression Scale). Authors stated that global improvement tended to favour the two treatment groups (individual and group BMT) over the control group, but that this effect failed to reach statistical significance.

6.4.4 Clinical evidence summary - 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. No data could be extracted and analysed.

As a result, no robust conclusions about the efficacy of arts therapies in this population can be made.

6.4.5 Clinical evidence summary - adults

This review contained six RCTs (N = 382) comparing arts therapy with any control. 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 From evidence to recommendations

This review identified extremely limited data investigating the efficacy of art therapies in children and young people. 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 is 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 guideline, *Schizophrenia* (NCCMH, 2010), considered arts therapies, provided by a Health Professions Council (HPC) registered arts therapist to be cost effective at both the lower (£20,000 per QALY) and upper (£30,000 per QALY) NICE cost-effectiveness threshold. 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 incorporate and adapt from the adult guideline, *Schizophrenia* (NCCMH, 2010; NICE, 2009a) based on the methodological principles outlined in Chapter 3 and recommend the use of art therapies for children and young people with psychosis or 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 28 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 2 the numbers refer to the recommendations in the NICE guideline.

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

Table 28: Adapted recommendations for the use of arts therapies in the treatment and management of children and young people with psychosis and schizophrenia

Original recommendation from *Schizophrenia*	**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.	1.4.6 Consider arts therapies (for example, dance movement, drama, music or art 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.	This recommendation was adapted because the GDG wished to make it clear that the term 'arts therapies' covers a range of interventions. No other significant adaptation 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 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	1.4.7 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	This recommendation was adapted because the GDG wished 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 required.

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.	• 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.	
1.4.3.4 Consider offering arts therapies to assist in promoting recovery, particularly in people with negative symptoms.	1.6.12 Consider arts therapies (see recommendation 1.4.6) to assist in promoting recovery, particularly in children and young people with negative symptoms.	This recommendation was adapted to conform with changes to NICE style for recommendations ('consider' rather than 'consider offering'). No other significant adaptation required.
[1]Recommendation also appears in sections 6.10 and 6.14		

6.4.7 Recommendations

6.4.7.1 Consider arts therapies (for example, dance movement, drama, music or art 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. [40]

6.4.7.2 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. [41]

[40] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[41] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

6.4.7.3 Consider arts therapies (see recommendation 6.4.7.1) to assist in promoting recovery, particularly in children and young people with negative symptoms.

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.

In addition, 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 29 for a summary of the study characteristics). All studies were conducted in children and young people aged 25 years and younger and published in peer reviewed journals between 2003 and 2012. One study (MAK2007) compared CBT with waitlist, two studies (HADDOCK2006, JACKSON2009) compared CBT with treatment as usual, and one study compared CBT with supportive counselling (HADDOCK2006). The remaining three studies (JACKSON2009, POWER2003, URBEN2012) were conducted in a specialist Early Psychosis Prevention and Intervention Centre (EPPIC), in Australia. All participants in these studies received treatment as usual (TAU) by the EPPIC centre, which was considered by the GDG to be highly specialised. One study compared CBT with befriending (JACKSON2009), one study compared CBT for acutely suicidal participants with EPPIC TAU (POWER2003) and finally, one study compared CBT plus clozapine with clozapine alone, in participants who had not adequately responded to treatment with at least one atypical antipsychotic (EDWARDS2012). Two studies (HADDOCK2006, MAK2007) reported outcomes in insufficient detail to allow for extraction and analysis, one of which (HADDOCK2006) was a subanalysis of an RCT (LEWIS2002) designed to evaluate the effectiveness of CBT, supportive counselling and treatment as usual in the UK. It compared the efficacy of treatments in participants aged 21 years and younger (N = 71) with those aged over 21 years (N = 238).

Table 29: Summary study characteristics for trials comparing CBT

	CBT(individual) versus waitlist	**CBT(individual) versus TAU**	**CBT(individual) versus supportive counselling**	**CBT(individual) + EPPIC TAU versus befriending + EPPIC TAU**	**CBT(individual) + EPPIC TAU versus EPPIC TAU in acutely suicidal participants**	**CBT(individual) + clozapine + EPPIC TAU versus clozapine + EPPIC TAU**
Total no. of studies (N)	1 (N = 48)	2 (N = 269)	1 (N = 207)	1 (N = 62)	1 (N = 56)	1 (N = 25)[1]
Study ID(s)	MAK2007	(1) JACKSON2009* (2) HADDOCK2006	HADDOCK2006	JACKSON2008*	POWER2003*	EDWARDS2012*
Diagnosis	Schizophrenia	(1) First episode psychosis (BP not specified). (2) Schizophrenic disorders	Schizophrenic disorders	First episode psychosis (including BP)	Acutely suicidal first episode psychosis mixed (BP not specified)	First episode psychosis (excluding BP) that had not adequately responded to treatment
Age (mean)	24	(1) 23.3 (2) Not reported	Not reported	22.3	Range: 15-29	21.4
Sex (% male)	56	(1) 74 (2) Not reported	Not reported	73	Not reported	71
Ethnicity (% Caucasian)	Not reported	(1) 71 (2) Not reported	Not reported	Not reported	Not reported	Not reported
Mean (range) medication dose (mg/day)	N/A	N/A	N/A	N/A	N/A	CLZ: 326.12 (NR) CLZ+CBT: 281.28 (NR)
Sessions of therapy	Minimum 20	(1) Maximum of 26	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 setting	(1) Non-specified psychiatric setting (2) Inpatient and outpatient	Inpatient and outpatient	Specialist clinic/ward	Specialist clinic/ward	Specialist clinic/ward
Country	China	(1) Australia (2) Great Britain	Great Britain	Australia	Australia	Australia

Note. *Extractable outcomes. [1]EDWARDS2012 had four treatment arms: clozapine (CLZ), CLZ+CBT, thioridazine (TDZ), and TDZ+CBT (N = 48). However, two arms (TDZ and TDZ+CBT) contained a pharmacological intervention not included in the review protocol.

6.5.3 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 PSE-9), negative symptoms (FIS), depression (measured using the BDI) and psychosocial functioning (measured using the GAF). 25% of the whole sample discontinued study, but drop-out 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 the waitlist control, the results did not reach statistical significance.

6.5.4 CBT versus treatment as usual

Two studies (HADDOCK2006, JACKSON2009; N = 269) compared individual CBT with treatment as usual (TAU) 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's follow-up, effects on depression were not significant (SMD = -0.29, -0.87 to 0.30 and SMD = -0.05, -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 participants in the TAU group, but the difference was not statistically significant (see forest plots in Appendix 14b [1.2]). Evidence from each reported outcome and overall quality of evidence are presented in Table 30 and Table 31.

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 TAU. Authors reported that there were no significant age x therapy interactions on psychotic symptoms (as measured by the PANSS) or social functioning (as measured by the SFS), at 3 months' post-treatment or 18 months' follow-up.

Table 30: Summary evidence profile for outcomes reported for CBT versus TAU at 26 weeks' post-treatment

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Depression (SMD)	JACKSON 2009	K = 1, N = 46	-0.29 [-0.87, 0.30]	N/A	Low[1,2]	Appendix 14b (1.1)
Leaving the study early for any reason (RR)	JACKSON 2009	K = 1, N = 66	1.94 [0.85, 4.43]	N/A	Low[1,2]	Appendix 14b (1.2)
Note ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.						

[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Table 31: Summary evidence profile for outcomes reported for CBT versus TAU at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Depression (SMD)	JACKSON 2009	K = 1, N = 46	-0.05 [-0.65, 0.54]	N/A	Low[1, 2]	Appendix 14b (2.1)
Leaving the study early for any reason (RR)	JACKSON 2009	K = 1, N = 66	1.77 [0.89, 3.52]	N/A	Low[1, 2]	Appendix 14b (2.2)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

6.5.5 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 (LEWIS2002), evaluating the effectiveness of CBT, supportive counselling 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 sub-scale scores (F [1,147] = 6.44, P = 0.012), and a trend towards a significant interaction on PSYRATS delusions sub-scale 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 age x therapy interactions were found for social functioning (as measured by the SFS). The authors suggest that supportive counselling is more effective than both CBT and TAU at reducing positive symptoms in younger participants. Furthermore, they suggest the opposite pattern for older participants. At 18 months' follow-up they purport 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 CBT versus EPPIC TAU

One study (JACKSON2008) (N = 62) compared CBT plus treatment as usual in an Early Psychosis Prevention and Intervention Centre (EPPIC TAU) with befriending plus EPPIC TAU. 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's follow-up effects on symptoms of psychosis and social functioning were not significant, and dropout was similar between groups (RR = 0.57, 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 suicides and eight participants were hospitalised (see Appendices 15b [4.4] and 15b [4.5], respectively). However, this difference is not statistically significant. Evidence from each reported outcome and overall quality of evidence are presented in

Table 32 and Table 33.

Table 32: Summary evidence profile for outcomes reported for CBT versus EPPIC TAU at 14 weeks' post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Symptoms: positive (SMD)	JACKSON 2008	K = 1, N = 62	-0.05 [-0.55, 0.45]	N/A	Very low[1,2,3]	Appendix14b (3.1)
Symptoms: negative (SMD)	JACKSON 2008	K = 1, N = 62	-0.46 [-0.96, 0.05]	N/A	Very low[1,2,3]	Appendix14b (3.2)
Social functioning (SMD)	JACKSON 2008	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)	JACKSON 2008	K = 1, N = 62	0.57 [0.19, 1.76]	N/A	Very low[1,2,3]	Appendix14b (3.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found)
[2] Optimal information size (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 and 8.1% of participants were receiving ECT

Table 33: Summary evidence profile for outcomes reported for CBT versus EPPIC TAU at 52 weeks' follow-up

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Symptoms: positive	JACKSON	K = 1, N = 62	-0.08 [-0.58, 0.42]	N/A	Very	Appendix

(SMD)	2008				low[1,2,3]	14b (4.1)
Symptoms: negative (SMD)	JACKSON 2008	K = 1, N = 62	-0.37 [-0.87, 0.13]	N/A	Very low[1,2,3]	Appendix 14b (4.2)
Social functioning (SMD)	JACKSON 2008	K = 1, N = 62	-0.08 [-0.58, 0.41]	N/A	Very low[1,2,3]	Appendix 14b (4.3)
Relapse (RR; number of participants requiring hospitalisation)	JACKSON 2008	K = 1, N = 57	5.00 [0.25, 100.08]	N/A	Very low[1,2,3]	Appendix 14b (4.4)
Suicide (number of participants; assuming drop outs did not commit suicide) (RR)	JACKSON 2008	K = 1, N = 62	1.35 [0.65, 2.80]	N/A	Very low[1,2,3]	Appendix 14b (4.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear allocation concealment, only raters were blind, trial registration not found)
[2] Optimal information size (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 and 8.1% of participants were receiving ECT

6.5.7 CBT (individual) versus EPPIC TAU 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 a first episode psychosis. The CBT based intervention was called LifeSpan therapy and specifically aimed to reduce participants' suicidality. Similarly 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 program, 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 difference between groups in quality of life (SMD = -0.04, -0.54 to 0.47 and SMD = 0.03, -0.66 to 0.71 respectively). There were no suicides at 10 weeks' post-treatment however, during the follow-up period authors report that one participant from each group committed suicide (RR = 0.81, 0.05 to 12.26). Dropout at 10 weeks was higher in the CBT group (10 participants versus 4 but the difference was not statistically significant (RR = 2.02, 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 34 and Table 35.

Table 34: Summary evidence profile for outcomes reported for CBT versus EPPIC TAU 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	Forest plot
Quality of life (SMD)	POWER 2003	K = 1, N = 42	-0.04 [-0.54, 0.47]	N/A	Very low[1,2,3]	Appendix 14b (5.1)
Suicide (number of participants; assuming drop	POWER	K = 1,	Not estimable	N/A	Very	Appendix

outs did not commit suicide) (RR)	2003	N = 56	[no events]		low[1,2,3]	14b (5.3)
Leaving the study early for any reason (RR)	POWER 2003	K = 1, N = 56	-2.02 [0.72, 5.66]	N/A	Very low[1,2,3]	Appendix 14b (5.2)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation and allocation concealment, only raters were blind, trial registration not found and missing data analysis not reported).
[2] Optimal information size (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 35: Summary evidence profile for outcomes reported for CBT versus EPPIC TAU 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**	**Forest plot**
Quality of life (SMD)	POWER 2003	K = 1, N = 33	0.03 [-0.66, 0.71]	N/A	Very low[1,2,3]	Appendix 14b (6.1)
Suicide (number of participants; assuming drop outs did not commit suicide) (RR)	POWER 2003	K = 1, N = 56	0.81 [0.05, 12.26]	N/A	Very low[1,2,3]	Appendix 14b (6.2)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation and allocation concealment, only raters were blind, trial registration not found and missing data analysis not reported).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of indirectness as participants were acutely suicidal

6.5.8 CBT (individual) plus clozapine versus clozapine in FEP participants who have not adequately responded to treatment

One RCT (N = 25) compared individual CBT plus clozapine versus clozapine alone, in children and young people experiencing a first episode of 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 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 36 and Table 37 for summary evidence profiles for individual CBT plus clozapine versus clozapine alone at 12 and 24 weeks respectively.

Table 36: Summary evidence profile for outcomes reported for CBT + clozapine versus clozapine in participants who 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	Forest plot
Symptoms: Positive (SMD)	EDWARDS 2012	K = 1, N = 25	0.19 [-0.60, 0.98]	N/A	Low[1, 2]	Appendix 14b (7.1)
Symptoms: Negative (SMD)	EDWARDS 2012	K = 1, N = 25	-0.30 [-1.09, 0.50]	N/A	Low[1, 2]	Appendix 14b (7.2)
Global State (Severity) (SMD)	EDWARDS 2012	K = 1, N = 25	0.00 [-0.79, 0.79]	N/A	Low[1, 2]	Appendix 14b (7.3)
Depression (SMD)	EDWARDS 2012	K = 1, N = 25	0.56 [-0.25, 1.37]	N/A	Low[1, 2]	Appendix 14b (7.4)
Social functioning (SMD)	EDWARDS 2012	K = 1, N = 25	0.18 [-0.61, 0.97]	N/A	Low[1, 2]	Appendix 14b (7.5)
Quality of life (SMD)	EDWARDS 2012	K = 1, N = 25	-0.04 [-0.83, 0.75]	N/A	Low[1, 2]	Appendix 14b (7.6)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation & 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, 64.3% of clozapine only group were male compared to 90.9% of clozapine+CBT group and the average daily dose of clozapine was 44.8 mg/day higher in the clozapine only group than the clozapine+CBT group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Table 37: Summary evidence profile for outcomes reported for CBT + clozapine versus clozapine in participants who 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	Forest plot
Symptoms: Positive (SMD)	EDWARDS 2012	K = 1, N = 25	-0.24 [-1.03, 0.55]	N/A	Low[1, 2]	Appendix 14b (8.1)
Symptoms: Negative (SMD)	EDWARDS 2012	K = 1, N = 25	-0.28 [-1.07, 0.51]	N/A	Low[1, 2]	Appendix 14b (8.2)
Global State (Severity) (SMD)	EDWARDS 2012	K = 1, N = 25	0.12 [-0.67, 0.91]	N/A	Low[1, 2]	Appendix 14b (8.3)
Depression (SMD)	EDWARDS 2012	K = 1, N = 25	0.62 [-0.19, 1.43]	N/A	Low[1, 2]	Appendix 14b (8.4)
Social functioning (SMD)	EDWARDS 2012	K = 1, N = 25	-0.15 [-0.94, 0.64]	N/A	Low[1, 2]	Appendix 14b (8.5)
Quality of life (SMD)	EDWARDS 2012	K = 1, N = 25	-0.56 [-1.36, 0.25]	N/A	Low[1, 2]	Appendix 14b (8.6)
Sensitivity analysis: Remission (number of participants: assuming dropouts did not achieve remission) (RR)	EDWARDS 2012	K = 1, N = 25	1.09 [0.51, 2.31]	**N/A**	Low[1, 2]	Appendix 14b (8.7)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including unclear sequence generation & 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, 64.3% of clozapine only group were male compared to 90.9% of clozapine+CBT group and the average daily dose of clozapine was 44.8 mg/day higher in the clozapine only group than the clozapine+CBT group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

6.5.9 Children and young people clinical evidence summary

There were no RCTs of CBT in children and young people aged 18 years and younger with psychosis or 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 TAU in the UK (JACKSON2009). Overall, the paucity and low to very low quality of evidence means no robust conclusions can be drawn.

6.5.10 Adult clinical evidence summary

The review in the adult guideline, *Schizophrenia* (NCCMH, 2010), contained 31 RCTs (N = 3052) comparing CBT to any control. 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). Consistent with the previous guideline, CBT was shown to be effective in reducing symptom severity as measured by total scores on items, 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 guideline, *Schizophrenia* (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: 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 the treatment arm rate of hospitalisation at 21.47% using a relative risk (RR) of 0.74. It is assumed that CBT consists 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 (HES) 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. The analysis also conducted one-way sensitivity analyses, such as substituting values of 95% CI of 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 (110.6 days average duration of hospitalisation was considered too long by the GDG members). The sensitivity analysis was undertaken using 95% CIs of RR. Under all these scenarios of one-way sensitivity analyses total net cost of providing CBT was estimated between -£2,277 (that is net saving) to £751 per person in 2006/07 prices.

The non-UK study BACH2002 was excluded from meta-analysis and TARRIER1998 was also excluded because it was carried out before the National Service Framework was implemented.

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 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 £751 per person of CBT.

The economic considerations from the adult guideline, *Schizophrenia* (NCCMH, 2010), should be interpreted with caution for children and young people with psychosis or schizophrenia. The pathways of treatment for children and young people with psychosis or schizophrenia 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/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 or 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 or schizophrenia. However, this is often a highly complex and co morbid group and thus, outcomes pertaining to anxiety, depression, psychosocial functioning and quality of life are also important. Owing to the heterogeneity of studies we were unable to meta-analyse any trials of CBT in this review. Evidence from individual trials indicates that CBT is no more effective than at active control at improving outcomes in young people with psychosis or schizophrenia. Conversely, evidence from the significantly larger adult data set suggests 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 guideline, *Schizophrenia* (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 or schizophrenia, and design problems in individual trials (for example, unclear methods of randomisation and allocation concealment, lack of blinding, small sample sizes), means that it is difficult to make robust conclusions regarding the efficacy of CBT, or the commonly used comparators (such as supportive counselling) in this population. While, there is no strong evidence to signify that we should treat children and young people with this condition any differently to 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 mean age of under 25). Particular care must be taken when drawing on the evidence reported in the adult guideline, *Schizophrenia* (NCCMH, 2010) and the GDG deemed consideration of the child or young person's cognitive development especially important when determining how to adapt CBT appropriately.

In summary, the GDG decided to recommend CBT as an adjunct to antipsychotic medication for children and young people with psychosis or schizophrenia, for both symptoms reduction and relapse prevention. However, the evidence base for this has been predominantly drawn from RCTs conducted in older adult populations. The evidence reviewed suggests that the benefits of CBT for psychosis and schizophrenia may well be less in younger patients generally seen in the first episode and early phase of illness than with older patients 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 or schizophrenia. Following this, a large multi centre 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 or schizophrenia, the GDG considered recommendations for CBT, counselling and supportive psychotherapy, adherence therapy and social skills training for adults in *Schizophrenia* (NICE, 2009a) and adapted them (see Table 38 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 2 the numbers refer to the recommendations in the NICE guideline.

Table 38: Adapted recommendations for the use of cognitive behavioural interventions in the treatment and management of children and young people with psychosis and schizophrenia

Original recommendation from *Schizophrenia*	**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	1.3.27 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	This recommendation was adapted 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

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.	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. * Treatment manuals that have evidence for their efficacy from clinical trials are preferred. If developed for adults, the manual should be adapted to suit the age and developmental level of the child or young person.	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.	**Treatment of subsequent acute episodes of psychosis or schizophrenia** 1.4.5 Offer CBT* 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. * CBT should be delivered as described in recommendation 1.3.27.	This recommendation was adapted 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.	1.4.8 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.	No significant adaptation required
1.3.4.5 Do not offer adherence therapy (as a specific intervention) to people with schizophrenia.	1.4.9 Do not offer adherence therapy (as a specific intervention) to children and young people with psychosis or schizophrenia.	No significant adaptation required
1.3.4.6 Do not routinely offer social skills training (as a specific intervention) to people with schizophrenia.	1.4.10 Do not routinely offer social skills training (as a specific intervention) to children and young people with psychosis or schizophrenia.	No significant adaptation required
	Early post-acute period	

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.	1.6.11 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 1.3.27.	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.	1.6.15 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.	No significant adaptation required

Additionally, in considering the evidence for antipsychotic medication in children and young people (see Chapter 7) and the treatment options for first episode psychosis, the GDG made two further recommendations, the first offering a choice between antipsychotic medication and individual CBT or family intervention, and the second advising children and young people and their parents or carers who wish to try individual CBT or family intervention alone of the lack of evidence that these interventions are effective in the acute phase without an antipsychotic.

6.5.13 Recommendations

6.5.14 Treatment options for first episode psychosis

6.5.14.1 For children and young people with first episode psychosis offer

- oral antipsychotic medication (see recommendations 7.27.2.1-7.27.3.110) and

- a psychological intervention; family intervention or individual CBT (delivered as set out in recommendations 6.8.4.1-6.8.6.2).

6.5.14.2 If the child or young person and their parents or carers wish to try a psychological intervention alone (family intervention or individual CBT), inform them that there is little evidence that psychological interventions are effective without antipsychotic medication. 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.

6.5.15 How to deliver psychological interventions

6.5.15.1 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[42] 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.[43]

6.5.16 Treatment of subsequent acute episodes

6.5.16.1 Offer CBT[44] 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.

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

[43] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

[44] CBT should be delivered as described in recommendation 6.5.15.1.

6.5.16.2 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.[45]

6.5.16.3 Do not offer adherence therapy (as a specific intervention) to children and young people with psychosis or schizophrenia. [46]

6.5.16.4 Do not routinely offer social skills training (as a specific intervention) to children and young people with psychosis or schizophrenia.[47]

6.5.17 Promoting recovery and providing possible future care

6.5.17.1 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 6.5.15.1.

6.5.18 Interventions for children and young people with psychosis or schizophrenia whose illness has not responded adequately to treatment

6.5.18.1 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, 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. [48]

[45] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[46] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[47] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[48] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

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, or
  - 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 in peer reviewed journal between 1996 and 2009. One study (LINZEN1996) 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 a shared, 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 39 for a summary of the study characteristics).

Table 39: Summary study characteristics for trials comparing family intervention

	CBT(individual) versus CBT(family)	**CBT (individual + family) versus EPPIC TAU**
Total no. of studies (N)	1 (N = 76)	1 (N = 82)
Study ID(s)	LINZEN1996*	GLEESON2009*
Diagnosis	Schizophrenic disorders in remission	First episode Psychosis in remission (Inc. BP)
Age	20.6	20.1
Sex (% male)	70	63
Ethnicity (% Caucasian)	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
*Extractable outcomes		

6.6.3 CBT (individual) versus CBT (family)

Table 40 provides a summary evidence profile for efficacy outcomes reported at treatment endpoint associated with individual CBT versus family CBT in the treatment of children and young people with psychosis and schizophrenia, in remission. At 1 year's post-randomisation 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).

Table 40: Summary evidence profile for outcomes reported for CBT (individual) versus CBT (family) at 52 weeks' post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Sensitivity analysis: Relapse (number of participants: assuming drop outs relapsed) (RR)	LINZEN1996	K = 1, N = 76	0.95 [0.34, 2.68]	N/A	Low[1,2]	Appendix14b (9.1)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[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] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

6.6.4 CBT (individual and family) versus EPPIC TAU

The summary evidence profile for outcomes reported for CBT (individual and family) versus EPPIC TAU are shown in Table 42.

Table 41: Summary evidence profile for outcomes reported for CBT (individual and family) versus EPPIC TAU at 30.33 weeks' post-treatment

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Symptoms: Total (SMD)	GLEESON2009	K = 1, N = 63	-0.08 [-0.57, 0.42]	N/A	Low [1,2]	Appendix14b (10.1)
Symptoms: Positive (SMD)	GLEESON2009	K = 1, N = 63	-0.28 [-0.78, 0.22]	N/A	Low [1,2]	Appendix14b (10.2)
Symptoms: Negative (SMD)	GLEESON2009	K = 1, N = 63	-0.03 [-0.52, 0.47]	N/A	Low [1,2]	Appendix14b (10.3)
Depression (SMD)	GLEESON2009	K = 1, N = 63	-0.24 [-0.73, 0.26]	N/A	Low [1,2]	Appendix14b (10.4)
Quality of life (SMD)	GLEESON2009	K = 1, N = 63	0.00 [-0.49, 0.49]	N/A	Low [1,2]	Appendix14b (10.5)
Social functioning (SMD)	GLEESON2009	K = 1, N = 63	0.06 [-0.43, 0.56]	N/A	Low [1,2]	Appendix14b (10.6)
Relapse (time in days)(SMD)	GLEESON2009	K = 1, N = 76	-3.26 [-3.96, -2.56]*	N/A	Low [1,2]	Appendix14b (10.7)
Sensitivity analysis: Relapse (number of participants: assuming drop outs relapsed) (RR)	GLEESON2009	K = 1, N = 82	0.45 [0.17, 1.19]	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
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours family therapy
[1] Serious risk of bias (only raters were blind and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

6.6.5 Children and young people clinical evidence summary

No RCTs of family intervention in children and young people aged 18 years and younger were reviewed. 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 TAU could extend time to relapse by approximately 1 month. Overall, the evidence base is drawn from small, non-UK studies with methodological limitations.

6.6.6 Adult clinical evidence summary

In 32 RCTs including 2,429 participants, there was robust and consistent evidence for the efficacy of family intervention (NCCMH, 2010). When compared with standard care (k = 19, N = 2118) or any other control, there was a reduction in the risk of relapse with numbers needed to treat (NNTs) of 4 (95% CIs 3.23 to 5.88) at the end of treatment and 6 (95% CIs 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 patient'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 for the update to explore the variation in terms of 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 interventions 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 interventions demonstrated some limited evidence to suggest that only the former may be efficacious in reducing hospital admission provides a summary evidence profile for efficacy outcomes reported at treatment endpoint associated with individual and family CBT for relapse prevention plus EPPIC TAU versus EPPIC TAU, in the treatment of children and young people with psychosis and schizophrenia, in remission. 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 38 participants in the treatment as usual group relapsed, compared with two of the 38 participants in the family group (see Appendix14b [10.8]), but this difference did not reach statistical significance (RR = 0.45, 0.17 to 1.19). However, time to relapse in the family group was significantly extended by 32.25 days (SMD = -3.26, -3.96 to-2.56).

Table 42: Summary evidence profile for outcomes reported for CBT (individual and family) versus EPPIC TAU at 30.33 weeks' post-treatment

Outcome or subgroup	Study ID	Number of studies/ participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Symptoms: Total (SMD)	GLEESON2009	K = 1, N = 63	-0.08 [-0.57, 0.42]	N/A	Low[1,2]	Appendix14b (10.1)
Symptoms: Positive (SMD)	GLEESON2009	K = 1, N = 63	-0.28 [-0.78, 0.22]	N/A	Low[1,2]	Appendix14b (10.2)
Symptoms: Negative (SMD)	GLEESON2009	K = 1, N = 63	-0.03 [-0.52, 0.47]	N/A	Low[1,2]	Appendix14b (10.3)
Depression (SMD)	GLEESON2009	K = 1, N = 63	-0.24 [-0.73, 0.26]	N/A	Low[1,2]	Appendix14b (10.4)
Quality of life (SMD)	GLEESON2009	K = 1, N = 63	0.00 [-0.49, 0.49]	N/A	Low[1,2]	Appendix14b (10.5)
Social functioning (SMD)	GLEESON2009	K = 1, N = 63	0.06 [-0.43, 0.56]	N/A	Low[1,2]	Appendix14b (10.6)
Relapse (time in days)(SMD)	GLEESON2009	K = 1, N = 76	-3.26 [-3.96, -2.56]*	N/A	Low[1,2]	Appendix14b (10.7)
Sensitivity analysis: Relapse (number of participants: assuming drop outs relapsed) (RR)	GLEESON2009	K = 1, N = 82	0.45 [0.17, 1.19]	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
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours family therapy
[1] Serious risk of bias (only raters were blind and missing data)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

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No RCTs of family intervention in children and young people aged 18 years and younger were reviewed. 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 TAU could extend time to relapse by approximately 1 month. Overall, the evidence base is drawn from small, non-UK studies with methodological limitations.

6.6.8 Adult clinical evidence summary

In 32 RCTs including 2,429 participants, there was robust and consistent evidence for the efficacy of family intervention (NCCMH, 2010). When compared with standard care (k = 19, N = 2118) or any other control, there was a reduction in the risk of relapse with numbers needed to treat (NNTs) of 4 (95% CIs 3.23 to 5.88) at the end of treatment and 6 (95% CIs 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 patient'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 for the update to explore the variation in terms of 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 interventions 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 interventions demonstrated some limited evidence to suggest that only the former may be efficacious in reducing hospital admission.

6.6.9 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 guideline *Schizophrenia* (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 relative risk (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) was used at of 50% 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 the duration of 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 (HES) 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 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 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 value of 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 CHRTTs, taking into account cost savings associated with reduced use of CHRTTs 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 the adult guideline, *Schizophrenia* (NCCMH, 2010), should be interpreted with caution for children and young people with psychosis or 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/assertive community provision, compared with those for adults. Nevertheless, the economic considerations from *Schizophrenia* (NCCMH, 2010) provide useful insights for children and young people with psychosis or schizophrenia.

6.6.10 From evidence to recommendations

The primary outcome of interest for family intervention is relapse and following this, symptom of psychosis, depression, anxiety, psycho social 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 or 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, was 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 guideline (*Schizophrenia*, 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 clinical and health economic evaluation of family intervention supports the incorporation and adaptation of conclusions and recommendations to 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). As a result, the GDG considered there to be no clear evidence to indicate that we should treat children and young people with psychosis and schizophrenia any differently to adults. The GDG however, 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 the use of family intervention for children and young people with psychosis or schizophrenia, particularly to prevent relapse and promote recovery. Nevertheless, further research through a large, multi centre RCT is necessary to establish the efficacy of family intervention in this population.

In the development of recommendations for the use of family intervention in children and young people with psychosis or 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 2 the numbers refer to the recommendations in the NICE guideline.

Table 43: Adapted recommendations for the use of family intervention in the treatment and management of children and young people with psychosis and schizophrenia

Original recommendation from *Schizophrenia*	**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.	1.3.26 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.	No significant adaptation required.
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.	**Treatment of subsequent acute episodes of psychosis or schizophrenia** 1.4.4 Offer family intervention* 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. * Family intervention should be delivered as described in recommendation 1.3.26.	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.	**Early post-acute period** 1.6.9 Offer family intervention to families of children and young people with psychosis or schizophrenia. Deliver family intervention as described in recommendation 1.3.26.	No significant adaptation required.
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.	1.6.10 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.	This recommendation was adapted 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.	1.6.15 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.	No significant adaptation required

In addition, the GDG, considering the evidence for antipsychotic medication in children and young people (see Chapter 7) and the treatment options for first episode psychosis made two further recommendations, the first offering a choice between antipsychotic medication and family intervention or individual CBT, and the second advising children and young people and their parents or carers who wish to try family intervention or individual CBT alone of the lack of evidence that these interventions are effective in the acute phase without an antipsychotic.

6.6.11 Recommendations

6.6.12 Treatment options for first episode psychosis

6.6.12.1 For children and young people with first episode psychosis offer

- oral antipsychotic medication (see recommendations 7.27.2.1-7.27.3.11) and
- a psychological intervention; family intervention or individual CBT (delivered as set out in recommendations 6.8.4.1-6.8.4.12).

6.6.12.2 If the child or young person and their parents or carers wish to try a psychological intervention alone (family intervention or individual CBT), inform them that there is little evidence that psychological interventions are effective without antipsychotic medication. 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.

6.6.12.3 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.[49]

6.6.13 Treatment of subsequent acute episodes

6.6.13.1 Offer family intervention[50] 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.

[49] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[50] Family intervention should be delivered as described in recommendation 6.6.12.3.

6.6.14 Promoting recovery and providing possible future care

6.6.14.1 Offer family intervention to families of children and young people with psychosis or schizophrenia. Deliver family intervention as described in recommendation 6.6.12.3.[51]

6.6.14.2 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. [52]

6.6.15 Interventions for children and young people with psychosis or schizophrenia whose illness has not responded adequately to treatment

6.6.15.1 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, 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.[53]

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 (http://www.eppic.org.au/). The core of the EPPIC clinical programme is the EPPIC Continuing Care Team which consists of consultant psychiatrists, qualified nurses,

[51] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[52] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[53] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

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, and include 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
- 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 well-being among family members and reducing the burden for carers.

The aims of EPPIC treatment as usual (TAU) 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, restore the normal developmental trajectory and psychosocial functioning
- 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 (EDWARDS2012, GLEESON2009, JACKSON2008, POWER2003) (N = 225) compared a CBT based psychological intervention plus EPPIC TAU with EPPIC TAU. 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 a very comprehensive treatment as usual (see Table 44 for a summary of the study characteristics).

6.7.3 Any psychological intervention in addition to EPPIC TAU versus EPPIC TAU

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 committed suicide was low and similar between groups

(RR = 2.06, 0.28 to 15.34), as was drop out (RR = 0.91, 0.38 to 2.19). Evidence from each reported outcome and overall quality of evidence are presented in Table 45

6.7.4 Children and young people 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-based services is a highly specialised treatment centre designed specifically for young people (15 to 25 year olds) experiencing a first episode of psychosis.

Table 44: Summary study characteristics for trials psychological interventions to EPPIC TAU

	CBT(individual) + EPPIC TAU versus EPPIC TAU	**CBT(individual) + EPPIC TAU versus EPPIC TAU in acutely suicidal participants**	**CBT (individual + family) + EPPIC TAU versus EPPIC TAU**	**CBT(individual) + clozapine + EPPIC TAU versus clozapine + EPPIC TAU**
Total no. of studies (N)	1 (N = 62)	1 (N = 56)	1 (N = 82)	1 (N = 25)1
Study ID(s)	JACKSON2008*	POWER2003*	GLEESON2009*	EDWARDS2012*
Diagnosis	First episode psychosis (Inc. BP)	Acutely suicidal first episode psychosis mixed (BP not specified)	First episode Psychosis in remission (Inc. BP)	First episode psychosis (Exc. BP) that had not adequately responded to treatment
Age	22.3	15-29	20.1	21.4
Sex (% male)	73	Not reported	63	71
Ethnicity (% Caucasian)	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

*Extractable outcomes

[1]EDWARDS2012 had 4 treatment arms: clozapine (CLZ), CLZ+CBT, thioridazine (TDZ), and TDZ+CBT (N = 48). However, two arms (TDZ and TDZ+CBT) contained a pharmacological intervention not included in the review protocol.

Table 45: Summary evidence profile for outcomes reported for any psychological intervention in addition to EPPIC TAU versus EPPIC TAU at post-treatment

Outcome or subgroup	Study ID	Number of studies / participants	Effect estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Symptoms: Positive (SMD)	EDWARDS2012 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)
Symptoms: Negative (SMD)	EDWARDS2012 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)	EDWARDS2012 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)	EDWARDS2012 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)	EDWARDS2012 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 drop outs did not commit 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
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*Favours family therapy
[1] Serious risk of bias (including unclear sequence generation & allocation concealment, unblinded, trial registration not found, missing data, 64.3% of clozapine only group were male compared with 90.9% of clozapine+CBT group and the average daily dose of clozapine was 44.8 mg/day).
[2] Optimal information size (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 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 *Schizophrenia* (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 two the numbers refer to the recommendations in the NICE guideline.

Table 46: Adapted recommendations for general principles for delivering psychological interventions in children and young people with psychosis or schizophrenia

Original recommendation from *Schizophrenia*	**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.	1.3.28 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.	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	1.3.29 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	No significant adaptation required

psychological interventions and equality of access across different ethnic groups.	access across different ethnic groups.	
1.3.4.9 Healthcare professionals providing psychological interventions should: • have an appropriate level of competence in delivering the intervention to people with schizophrenia • be regularly supervised during psychological therapy by a competent therapist and supervisor.	1.3.30 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 • be regularly supervised during psychological therapy by a competent therapist and supervisor.	No significant adaptation required
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.	1.3.31 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.	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. [1]	1.4.11 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.	No significant adaptation required.

In addition 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.

6.8.3 Recommendations

6.8.4 How to deliver psychological interventions

6.8.4.1 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.

6.8.5 Monitoring and reviewing psychological interventions

6.8.5.1 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. [54]

6.8.5.2 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. [55]

6.8.6 Competencies for delivering psychological interventions

6.8.6.1 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. [56]

6.8.6.2 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.[57]

6.8.7 Psychological and psychosocial interventions

6.8.7.1 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. [58]

6.9 RESEARCH RECOMMENDATIONS

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 13 for further details.)

[54] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[55] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[56] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[57] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[58] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

7 PHARMACOLOGICAL INTERVENTIONS

7.1 GENERAL INTRODUCTION

Antipsychotic medications have long been seen as playing an integral role in the treatment and management of 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 amongst adults. The starting point for this guideline was *Schizophrenia* (NCCMH, 2010), the updated NICE guideline on the treatment of schizophrenia in adults, 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 which appeared in the early 1950s. A steady stream of further drugs were developed during the following 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 – so-called 'first generation antipsychotics' (FGAs). The late twentieth 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 extrapyramidal side effects. Current evidence however, suggests that with the exception of clozapine in cases 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 medicines is in essence similar in adults and young people. However, where the impact may differ is that the young person is being exposed to these disturbances at a vulnerable phase of physical growth and development. Previously unexposed to antipsychotics, this young group may be particularly vulnerable to rapid weight gain (Alvarez-Jimenez *et al*., 2008) and adverse cardiometabolic disturbance (Correll *et al*., 2009; Foley & Morley, 2011). Combining these 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*., 2008) alongside evidence for rapid acquisition (within weeks) of weight gain and metabolic disturbances (Foley & Morley, 2011; Correll *et al*., 2009) 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 medicines 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 adolescents, will not have been granted a Marketing Authorisation (Product Licence) for use in children and adolescents 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).

SECTION 1: INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION

7.2 INTRODUCTION

Evidence published before the updated adult guideline *Schizophrenia* (NICE, 2009a) suggests that drug-naive 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 or schizophrenia. Lehman and colleagues (1998) have suggested that the maximum dose for drug-naive 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-naive adult patients.

7.3 CLINICAL REVIEW PROTOCOL FOR INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION IN CHILDREN AND YOUNG P PEOPLE WITH FIRST EPISODE PSYCHOSIS

A summary of the review protocol can be found in Table 47, including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline (further detail regarding the review protocol can be found in Appendix 8; and further information about the search strategy can be found in Appendix 9).

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	**RQB2** 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? **RQB3** Are children and young people more susceptible to side effects of antipsychotic medication, compared with adults (in particular, the metabolic, neurological and cognitive impairments)? **RQB5** Should the dose/duration (and where relevant frequency) be different compared with adult patients?
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding the pharmacological (antipsychotic) treatment and management of initial treatment in children and young people with psychosis or schizophrenia, including a review of NICE Clinical Guidance 82 for its relevancy to children and young people.

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 meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when only limited evidence for children and young people aged 18 and younger is available. Consideration will also be given to the specific needs of children and young people with schizophrenia and mild learning disability; and children and young people 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 or 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 or schizophrenia). • 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 events (including effects on metabolism; extrapyramidal side effects; hormonal changes; and , cardiotoxicity) • Remission

Electronic databases	1 and 3: Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic specific databases and grey literature (see Appendix 8) 2: Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic specific databases (see Appendix 8)
Date searched	SR: 1995 to May 2012; RCTs: inception of databases to May 2012
Study design	SR, 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 18 years. The review will seek to identify whether modifications in treatment and management of children aged 13 years and younger need to be made. • 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. Published data will not be included when evidence submitted is commercial in confidence.

7.4 STUDIES CONSIDERED[59]

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 people with first episode psychosis (ARANGO2009, BERGER2008; LIEBERMAN2003, MCEVOY2007 [McEvoy et al., 2007], ROBINSON2006, SCHOOLER2005, SIKICH208, SWADI2010, VANBRUGGEN2003). All included RCTs were published in peer-reviewed journals between 2003 and 2010. Additional unpublished data was also obtained from one study (ROBINSON2006). Only one study investigated antipsychotic medication use in FEP in children and young people aged 18 years and younger (ARANGO2009). We extrapolated data from eight remaining studies that provided relevant clinical data in FEP 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, SIKCIH2008, SCHOOLER2005, SWADI2010, VANBRUGGEN2003).

[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).

All studies reported at least one outcome in sufficient detail to allow for extraction and analysis. . In addition, 583 studies were considered irrelevant to the pharmacological treatment and management of psychosis or schizophrenia in children and young people and excluded from the review. Further information about both included and excluded studies can be found in Appendix 14.

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 to (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) (see Table 48 for a summary of the study characteristics). Forest plots and/or evidence profiles for each outcome can be found in Appendix 14 and Appendix 17, respectively.

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 = 6833)	K = 1 (N = 141)
Study ID(s)	ARANGO2009 [1] MCEVOY2007 [1]	MCEVOY2007 [1] SWADI2010 [1]	LIEBERMAN2003 [1]	SCHOOLER 2005 [1]	MCEVOY2007[1] ROBINSON2006[1] SIKICH2008[1,3] VANBRUGGEN2003[1]	BERGER2008 [1]
Diagnosis [2]	First episode psychosis	First episode psychosis	First episode psychosis	First episode psychosis	First episode psychosis (SIKICH2008: 93% First Episode Psychosis; VANBRUGGEN2003: 89% and 85% with First Episode Psychosis in the risperidone and olanzapine treated groups respectively)	First episode psychosis
Prior Antipsychotic Use (% naive prior to intervention) [2]	ARANGO2009: 50 MCEVOY2007: 96	MCEVOY2007: 96 SWADI2010: NR (participants who had earlier treatment with an atypical antipsychotic excluded)	26	47	MCEVOY2007: 96 ROBINSON2006: 78 SIKICH2008: 33 VANBRUGGEN2003: NR	0
Mean (range) Age (years) [2]	ARANGO2009: 16.0 (NR) MCEVOY2007: 24.5 (16.4 to 44.4)	MCEVOY2007: 24.5 (16.4 to 44.4) SWADI2010: NR (to be eligible for inclusion participants needed to be aged between 15 and 19 years)	23.8 (NR)	25.4 (NR)	MCEVOY2007: 24.5 (16.4 to 44.4) ROBINSON2006: 23.3 (NR) SIKICH2008: 13.8 (8.0 to 19.0) VANBRUGGEN2003: 20.8 (NR)	19.4 (NR)
Sex (% male) [2]	ARANGO2009: 78	MCEVOY2007: 73 SWADI2010: NR	82	71	MCEVOY2007: 73 ROBINSON2006: 70	68

	MCEVOY2007: 73				SIKICH2008: 65 VANBRUGGEN2003: 80	
Ethnicity (% Caucasian) [2]	ARANGO2009: 78	MCEVOY2007: 51 SWADI2010: NR	53	74	MCEVOY2007: 51 ROBINSON2006: 20 SIKICH2008: 64 VANBRUGGEN2003: NR	NR
Mean (range) medication dose (mg per day) [2]	ARANGO2009: *Olanzapine:* 12.1 (NR) *Quetiapine:* 438.8(NR) MCEVOY2007: *Olanzapine:* 11.7 (2.5 to 20.0) *Quetiapine:* 506.0 (100.0 to 800.0)	MCEVOY2007: *Risperidone:* 2.4 (0.5 to 4.0) *Quetiapine:* 506.0 (100.0 to 800.0) SWADI2010: *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 (NR) *Risperidone:* 3.3 (NR)	MCEVOY2007: *Risperidone:* 2.4 (0.5 to 4.0) *Olanzapine:* 11.7 (2.5 to 20.0) ROBINSON2006: *Risperidone:* 3.9 (1.0 to 6.0) *Olanzapine:* 11.8 (2.5 to 20.0) SIKICH2008: *Risperidone:* 2.8 (0.5 to 6.0) *Olanzapine:* 11.4 (2.5 to 20.0) mg per day) VANBRUGGEN2003: *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]	ARANGO2009: 26 MCEVOY2007: 52	MCEVOY2007: 52 SWADI2010: 6	104	206	MCEVOY2007: 52 ROBINSON2006: 156 SIKICH2008: 8 VANBRUGGEN2003: 6 to 1	12
Length of follow-up (weeks) [2]	ARANGO2009: 26 MCEVOY2007: 52	MCEVOY2007: 52 SWADI2010: 6	104	NR	MCEVOY2007: 52 ROBINSON2006: 156 SIKICH2008: 52 VANBRUGGEN2003: 6 to 10	12
Setting [2]	ARANGO2009: General Hospital MCEVOY2007: In- and outpatient clinics	MCEVOY2007: In- and outpatient clinics SWADI2010: Inpatient clinic	In- and outpatient clinics	NR	MCEVOY2007: In- and outpatient clinics ROBINSON2006: Inpatients and outpatients SIKICH2008: Inpatients and outpatients VANBRUGGEN2003: Inpatient	In- and outpatient specialist clinic
Country [2]	ARANGO2009: Spain MCEVOY2007: US and Canada	MCEVOY2007: US and Canada SWADI2010: New Zealand	North America and Western Europe	Eleven countries – details NR	MCEVOY2007: US and Canada ROBINSON2006: Denmark SIKICH2008: US VANBRUGGEN2003: The Netherlands	Australia

Funding [2]	ARANGO2009: AstraZeneca MCEVOY2007: AstraZeneca	MCEVOY2007: AstraZeneca SWADI2010: AstraZeneca	Lilly Research Laboratories	Johnson & Johnson	MCEVOY2007: AstraZeneca VANBRUGGEN2003: Eli Lily and non-industry sponsors SIKICH2008:Non-industry ROBINSON2006: Non-industry	AstraZeneca

Note.
NR = not reported.
[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 is reviewed in this guideline.

7.4.1 Clinical evidence for olanzapine versus quetiapine as initial treatment

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 naive 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. An overview of study characteristics can be found in Table 49 (includes study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 49 provides a summary evidence profile for efficacy outcomes reported associated with olanzapine versus quetiapine as initial treatment in children and young people with first episode psychosis. Both studies (N = 317) reported data for symptoms, depression and global state. ARANGO2009 report mean endpoint scores and MCEVOY2007 report mean change scores; however given the limited amount of data identified we included both studies in one analysis (sensitivity analysis is not considered appropriate in an analysis including only two studies). The only significant difference between groups was found for positive symptoms with olanzapine favoured over quetiapine (SMD = -0.42, -0.77 to -0.08). A small, significant difference between treatment groups, favouring olanzapine was found for quality of life (SMD = -0.18, -0.36 to -0.00).

Table 49: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	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 15 ci (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 15 ci (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 15 ci (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 15 ci (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 15 ci (1.5)

Mania (SMD)	ARANGO2009	K = 1; N = 60	0.10 [-0.45, 0.66]	N/A	Very low[1,2,3,5]	Appendix 15 ci (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 15 ci (1.7)

Note
ROB=risk of bias, RR = Relative risk; SMD = Standardised mean difference.
* Favours olanzapine
[1] Serious risk of bias (including sequence generation & allocation concealment; one open label trial (no blinding) or unclear blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry)

7.5 [2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.6 [3] Serious risk of reporting bias

7.7 [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).

Side effects

The summary evidence profile 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 can be found in Table 50 ARANGO2009 report mean endpoint scores and MCEVOY2007 report mean change scores; however given the limited amount of data identified we included both studies 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, 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, 0.59 to 1.53). In addition, 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, 0.61 to 1.54). We found a small, significant difference between treatment groups on mean change in high-density lipoprotein cholesterol, with olanzapine favoured over quetiapine (SMD = -0.48,-0.9 to -0.04). We found no significant differences on any other side effect outcome assessed in the study.

Table 50: Summary evidence profile 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)	Hetero-geneity	Quality	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 14 ci (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 14 ci (2.2)
Metabolic: BMI (SMD)	McEVOY2007	K = 1; N = 81	1.08 [0.61, 1.54]**	N/A	Very low[1,2,3]	Appendix 14 ci (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 14 ci (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 14 ci (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 14 ci (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 14 ci (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 14 ci (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 14 ci (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 14 ci (2.10)
Hormonal: Prolactin	McEVOY2007	K = 1; N = 81	0.17 [-0.27, 0.60]	N/A	Very low[1,2,3,4]	Appendix 14 ci (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 14 ci (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 14 ci (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 14 ci (2.14)

Note
ROB=risk of bias, RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
**Favours quetiapine
[1]Serious risk of bias (including: sequence generation & allocation concealment; one open label trial (no blinding) or unclear blinding; errors in reporting of number of included participants; errors in reporting of outcome data across publications; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry)
[2] Optimal information size (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).

7.7.1 Clinical evidence for risperidone versus quetiapine as initial treatment

Two studies (MCEVOY2007, SWADI2010) (N = 289) compared risperidone and quetiapine in children and young people with first episode psychosis, with the majority of the MCEVOY2007 trial participants antipsychotic naive at baseline (96%). SWADI2010 did not report antipsychotic use of trial participants prior to entering the study. The mean (range) age of participants in the MCEVOY2007 study was 24.5 (16.4 to 44.4) years. Mean age was not reported by SWADI2010, however to be eligible for the study participants had to be aged between 15 and 19 years. An overview of study characteristics can be found in Table 51 (included study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 52 provides a summary evidence profile for efficacy outcomes reported associated with risperidone versus quetiapine as initial treatment in children and young people with first episode psychosis. Data obtained from the MCEVOY2007 trial suggests a small, significant difference favouring risperidone over quetiapine on quality of life (SMD = -0.30, -0.60 to -0.00). We found no significant differences between treatment groups for any of the other measured efficacy outcomes in either study.

Table 51: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	Forest plot
Total Symptoms (SMD)	McEVOY2007	K = 1; N = 81	-0.28 [-0.72, 0.16]	N/A	Very low[1,2,3,4]	Appendix 14 ci (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 14 ci (3.2)
Positive Symptoms (SMD)	McEVOY2007	K = 1; N = 81	-0.39 [-0.83, 0.05]	N/A	Very low[1,2,3,4]	Appendix 14 ci (3.3)
Negative Symptoms (SMD)	McEVOY2007	K = 1; N = 81	-0.24 [-0.68, 0.20]	N/A	Very low[1,2,3,4]	Appendix 14 ci (3.4)

Global State (Severity) (SMD)	McEVOY2007	K = 1; N = 81	-0.14 [-0.58, 0.30]	N/A	Very low[1,2,3,4]	Appendix 15 ci (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 14 ci (3.6)
Depression (SMD)	McEVOY2007	K = 1; N = 81	0.38 [-0.07, 0.82]	N/A	Very low[1,2,3,4]	Appendix 14 ci (3.7)
Depression (RR: response)	SWADI2010	K = 1; N = 22	0.71 [0.33, 1.57]	N/A	Very low[1,2,3]	Appendix 14 ci (3.8)
Mania (RR: response)	SWADI2010	K = 1; N = 22	0.70 [0.43, 1.14]	N/A	Very low[1,2,3]	Appendix 14 ci (3.9)
Quality of Life (SMD)	McEVOY2007	K = 1; N = 81	-0.30 [-0.60, -0.00]*	N/A	Very l low[1,2,3,4]	Appendix 14 ci (3.10)

Note
ROB=risk of bias, RR = Relative risk; SMD = Standardised mean difference.
* Favours Risperidone
[1]Downgraded due to risk of bias (including: unclear sequence & allocation concealment; one open label trial (no blinding) or unclear blinding; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry; publication only reports dichotomous outcomes)
[2] Optimal information size (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

Side effects

We also found a small to moderate, significant differences between treatment groups, favouring risperidone over quetiapine on total cholesterol (SMD = -0.47, -0.91 to -0.03), fasting triglycerides (SMD = -0.56, -1.00 to -0.11) and systolic blood pressure (SMD = -0.60, -1.05 to -0.15). We found no other significant differences in side effect outcomes between treatment groups in these trials.

Table 52: Summary evidence profile 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**	**Studies/ number of participants**	**Effect Estimate (SMD or RR)**	Hetero-geneity	**Quality**	**Forest plot**
Metabolic: Weight (lbs) (SMD)	McEVOY2007	K = 1; N = 81	0.18 [-0.26, 0.62]	N/A	Very low [1,2,3,5]	Appendix 15 ci (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 15 ci (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 15 ci (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 15 ci (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 15 ci (4.5)
Metabolic: Fasting	McEVOY2	K = 1; N = 81	0.16 [-0.28,	N/A	Very low	Appendix

High-Density Lipoprotein Cholesterol mg per dl (SMD)	007		0.60]		[1,2,3,5]	15 ci (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 15 ci (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 15 ci (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 15 ci (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 15 ci (4.10)
Hormonal: Prolactin (RR)	SWADI2010	K = 1; N = 22	10.00 [1.53, 65.41]**	N/A	Very low [1,2,3]	Appendix 15 ci (4.11)
Neurological: AIMS (RR)	SWADI2010	K = 1; N = 22	3.00 [0.37, 24.58]	N/A	Very low [1,2,3]	Appendix 15 ci (4.12)
Neurological: SAS (RR)	SWADI2010	K = 1; N = 22	2.00 [0.66, 6.04]	N/A	Very low [1,2,3]	Appendix 15 ci (4.13)
Neurological: BARS (RR)	SWADI2010	K = 1; N = 22	1.00 [0.40, 2.50]	N/A	Very low [1,2,3]	Appendix 15 ci (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 15 ci (4.15)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*** Favours risperidone**
****Favours quetiapine**
[1]Serious risk of bias (including: unclear sequence & allocation concealment; one open label trial (no blinding) or unclear blinding; one analysis of a modified intent-to-treat population; incomplete list of outcomes reported on trial registry; publication only reports dichotomous outcomes)
[2]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias
[4] I^2 = ≥ 50%, p<.05
[5]Serious risk of indirectness (upper age range 44.4 years. May not be representative of children and young people).

7.7.2 Clinical evidence for olanzapine versus haloperidol as initial treatment

One study (LIEBERMAN2003) (N = 262) compared haloperidol and olanzapine in children and young people with first episode psychosis in whom 26% were antipsychotic naive at baseline, with a mean age of 23.8 years. An overview of study characteristics can be found in Table 53 (included study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 53 provides a summary evidence profile for efficacy outcomes reported associated with olanzapine versus haloperidol as initial treatment in children and young people with first episode psychosis. Total symptoms were significantly

different between groups at 12 weeks during treatment, with olanzapine favoured over haloperidol (SMD = -0.31, -0.56 to -0.06). This relative effect remained small but significant, and in the same direction for negative symptoms (SMD = -0.28, -0.53 to -0.03), but not for positive symptoms (SMD = -0.09,-0.34 to 0.16). Small, significant effects favouring olanzapine over haloperidol were also found for depression (SMD = -0.32, -0.57 to -0.07) and global state (SMD = -0.25, -0.50 to -0.01).

Table 53: Summary evidence profile for efficacy outcomes reported at 12 weeks treatment associated with olanzapine versus haloperidol 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	Forest plot
Total Symptoms (SMD)	LIEBERMAN2003	K = 1; N = 251	-0.31 [-0.56, -0.06]*	N/A	Very low[1,2,3,4]	Appendix 15 ci (5.1)
Positive Symptoms	LIEBERMAN2003	K = 1; N = 252	-0.09 [-0.34, 0.16]	N/A	Very low[1,2,3,4]	Appendix 15 ci (5.2)
Negative Symptoms	LIEBERMAN2003	K = 1; N = 252	-0.28 [-0.53, -0.03] *	N/A	Very low[1,2,3,4]	Appendix 15 ci (5.3)
Global State (Severity) (SMD)	LIEBERMAN2003	K = 1; N = 254	-0.25 [-0.50, -0.01] *	N/A	Very low[1,2,3,4]	Appendix 15 ci (5.4)
Depression (SMD)	LIEBERMAN2003	K = 1; N = 251	-0.32 [-0.57, -0.07]*	N/A	Very low[1,2,3,4]	Appendix 15 ci (5.5)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*** Favours olanzapine**
[1]Serious risk of bias (including: unclear sequence generation & allocation concealment; one open label trial, unclear blinding, not all outcomes reported; trial registration couldn't be found)
[2]Optimal information size (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 (inclusion upper age range was 40. May not be representative of children and young people)

Side effects

Table 54 provides a summary evidence profile for side effect outcomes reported associated with olanzapine versus haloperidol as initial treatment in children and young people with first episode psychosis. 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, -0.59 to -0.10). Data for this outcome was 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, 0.44 to 0.95) and significantly fewer haloperidol-treated participants left the study early for any reason compared with olanzapine-treated participants (RR = 1.95, 1.12 to 3.39).

Table 54: Summary evidence profile for side effect outcomes reported at treatment endpoint associated with olanzapine versus haloperidol 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	Forest plot
Metabolic: Weight kg (SMD)	LIEBERMAN2003	K = 1; N = 263	0.70 [0.44, 0.95]**	N/A	Very low[1,2,3,4]	Appendix 15 ci (6.1)
Hormonal: Prolactin[5] (RR)	LIEBERMAN2003	K = 1; N = 263	-0.34 [-0.59, -0.10]*	N/A	Very low[1,2,3,4]	Appendix 15 ci (6.2)
Leaving the Study Early for Any Reason (RR)	LIEBERMAN2003	K = 1; N = 253	1.95 [1.12, 3.39]**	N/A	Very low[1,2,3,4]	Appendix 15 ci (6.3)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours olanzapine
**Favours haloperidol
[1]Serious risk of bias (including: unclear sequence generation & allocation concealment; one open label trial, unclear blinding, not all outcomes reported; trial registration couldn't be found)
[2]Optimal information size (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 (inclusion upper age range was 40. May not be representative of children and young people)

7.7.3 Clinical evidence for haloperidol versus risperidone as initial treatment

One study (SCHOOLER2005) (N = 559) compared haloperidol and risperidone in children and young people with first episode psychosis, with whom 47% were antipsychotic naive at baseline with a mean age of 25.5 years. An overview of study characteristics can be found in Table 55 (included study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis) and detailed study characteristics can be found in Appendix 14.

Efficacy

SCHOOLER2005 assessed change in symptoms and global state (however time points were not clearly reported). We found no significant differences between treatment groups on either of these outcomes. Table 55 provides a summary evidence profile for efficacy outcomes reported associated with haloperidol versus risperidone as initial treatment in children and young people with first episode psychosis.

Table 55: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	SCHOOLER2005	K = 1; N = 528	-0.02 [-0.19, 0.15]	N/A	Very Low[1,2,3]	Appendix 15 ci (7.1)
Positive Symptoms	SCHOOLER2005	K = 1; N = 528	0.05 [-0.12, 0.22]	N/A	Very Low[1,2,3]	Appendix 15 ci (7.2)
Negative Symptoms	SCHOOLER2005	K = 1; N = 528	-0.12 [-0.29, 0.05]	N/A	Very Low[1,2,3]	Appendix 15 ci (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 15 ci (7.4)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (unclear blinding, unable to find trial registration; unclear at what time point data was taken; missing outcomes data)
[2] Serious risk of indirectness (48% population had bipolar disorder)
[3]Serious risk of reporting bias

Side effects

Table 56 provides a summary evidence profile for side effect outcomes reported associated with haloperidol versus risperidone as initial treatment in children and young people with first episode psychosis. A small, significant difference was found between treatment groups on prolactin level with haloperidol favoured over risperidone (SMD = 0.51, 0.33 to 0.69), however the time point at which this data was collected is unclear. No significant differences were found between the treatment groups on weight, or leaving the study early for any reason.

Table 56: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Metabolic: Weight (SMD)	SCHOOLER2005	K = 1; N = 415	0.01 [-0.19, 0.20]	N/A	Very Low[1,3,4]	Appendix 15 ci (8.1)
Hormonal: Prolactin (RR)	SCHOOLER2005	K = 1; N = 507	0.51 [0.33, 0.69]*	N/A	Very Low[1,3,4]	Appendix 15 ci (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 15 ci (8.3)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours haloperidol
[1]Serious risk of bias (unclear blinding, unable to find trial registration; unclear at what time point data was taken; missing outcomes data)
[2]Optimal information size (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

7.7.4 Clinical evidence for risperidone versus olanzapine as initial treatment

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. Where reported, prior antipsychotic use varied across trials with MCEVOY2007, ROBINSON2006 and SIKICH2008 reporting that 96.0%, 78.0% and 33.0% of their sample were antipsychotic naive at baseline respectively (VANBRUGGEN2003 do not report prior antipsychotic use in their trial). 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). An overview of study characteristics can be found in Table 57(included study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 57 provides a summary evidence profile for efficacy outcomes reported associated with risperidone versus olanzapine as initial treatment in children and young people with first episode psychosis. No significant differences between risperidone and olanzapine in symptoms, global state, depression, quality of life, response or remission were found.

Table 57: Summary evidence profile for efficacy outcomes reported associated with risperidone versus olanzapine 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	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 14 ci (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 14 ci (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 14 ci (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 14 ci (9.4)
Depression (SMD)	MCEVOY2007; VANBRUGGEN2003	K = 2; N = 116	-0.60 [-1.74, 0.53]	N/A	Very low[1,2,3]	Appendix 14 ci (9.5)
Quality of Life (SMD)	MCEVOY2007	K = 1; N = 74	-0.13 [-0.45, 0.19]		Very low[1,2,3]	Appendix 14 ci (9.6)

Response (RR)	ROBINSON	K = 1; N = 120	1.25 [0.84, 1.86]	N/A	Low[1,2]	Appendix 14 ci (9.7)
Remission (RR)	VANBRUGGEN2003	K = 1; N = 44	0.55 [0.17, 1.78]	N/A	Very low[1,2,3]	Appendix 14 ci (9.8)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1] Serious risk of bias (including serious or unclear blinding bias (including one open label trial); unable to extract all outcomes; trial registration couldn't be found; analysis included modified intent-to-treat 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)
[2]Optimal information size (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 40 years and may not therefore be representative of a CYP population)
[5] $I^2 \geq 50\%$, $p<.05$

Side effects

Table 58 summarises the evidence profile for side effects outcomes reported at treatment endpoint associated with risperidone versus olanzapine as initial treatment in children and young people with first episode psychosis. ROBINSON2006 reports mean endpoint scores and MCEVOY2007, SIKICH2008 and VANBRUGGEN2003 report mean change scores. Sensitivity analyses were conducted for outcomes measured using mean endpoint and mean changes 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, 0.47 to 0.98) and BMI increase was significantly greater in olanzapine-treated participants compared with risperidone-treated participants (SMD = -0.66, -0.98 to -0.33). In addition, risperidone was favoured over olanzapine on triglyceride level (SMD = -0.57, -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,-0.84 to -0.04) and a moderate effect seen for systolic blood pressure (SMD = -0.76, -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, 0.20 to 1.14) and a large effect favouring olanzapine for prolactin level (mg per dl) (SMD = 1.67, 1.22 to 2.11) was found.

Table 58: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Metabolic: Weight (SMD)	MCEVOY2007; VANBRUGGEN 2003	K = 2; N = 105	-0.40 [-1.49, 0.69]	(P = 0.01); I^2 = 85%	Very low[1,2,3,4.5]	Appendix 15 ci (10.1)
Metabolic: Weight	MCEVOY2007	K = 1; N =	0.68 [0.47,	N/A	Very	Appendix

(RR) (N pts with >7% gain)		74	098]*		low[1,2,3,4]	15 ci (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 15 ci (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 15 ci (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 15 ci (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 15 ci (10.6)
Metabolic: Fasting Triglycerides (SMD)	MCEVOY2007	K = 1; N = 74	-0.57 [-1.04, -0.11]*	N/A	Very low[1,2,3,4]	Appendix 15 ci (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 15 ci (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 15 ci (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 15 ci (10.10)
Neurological: AIMS (RR)	SIKICH2008	K = 1; N = 33	0.04 [-0.65, 0.73]	N/A	Very low[1,2,3]	Appendix 15 ci (10.11)
Neurological: SAS (RR)	ROBINSON2006; SIKICH2008; VANBRUGGEN 2003	K = 3; N = 168	0.34 [0.00, 0.67]	(P = 0.33); I^2 = 9%	Very low[1,2,3]	Appendix 15 ci (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 15 ci (10.13)
Neurological: BARS (RR)	SIKICH2008	K = 1; N = 33	0.36 [-0.34, 1.06]	N/A	Very low[1,2,3]	Appendix 15 ci (10.14)
Neurological: Parkinsonism (RR)	ROBINSON2006	K = 1; N = 112	0.56 [0.20, 1.55]	N/A	Very low[1,2,3]	Appendix 15 ci (10.15)
Neurological: Akathisia (RR)	VANBRUGGEN 2003	K = 1; N = 31	0.95 [0.34, 2.68]	N/A	Very low[1,2,3,4]	Appendix 15 ci (10.16)
Leaving the Study Early for Any Reason (RR)	MCEVOY2007; ROBINSON2006; VANBRUGGEN 2003	K = 1; N = 266	1.04 [0.89, 1.21]	(P = 0.68); I^2 = 0%	Very low[1,3,4]	Appendix 15 ci (10.17)

Note
ROB=risk of bias; RR = Relative risk; SMD = Standardised mean difference.
*favours risperidone
**favours olanzapine[1] Serious risk of bias (including serious or unclear blinding bias (including one open label trial); unable to extract all outcomes; trial registration couldn't be found; analysis included modified intent-to-treat 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)
[2]Optimal information size (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 40 years and may not therefore be representative of a CYP population)
[5] $I^2 \geq 50\%$, $p<.05$

7.7.5 Clinical evidence for antipsychotic medication administered at different doses as initial treatment

One study (BERGER2008) (N = 141) compared an antipsychotic 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. An overview of study characteristics can be found in Table 59 (included study information table for trials comparing antipsychotic medications in children and young people with first episode psychosis) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 59 summarises the evidence profile for efficacy outcomes 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. Extractable data were reported for the end of part one of the study (4 weeks) only. A small, significant difference favouring 400 mg per day over 200 mg per day was found for global state (SMD = 0.44, 0.02 to 0.85). No other significant differences between dosing schedules were found for the other efficacy outcomes reported.

Table 59: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	BERGER2008	K = 1; N = 91	0.35 [-0.06, 0.77]	N/A	Very low[1,2,3]	Appendix14 ci (11.1)
Positive Symptoms	BERGER2008	K = 1; N = 91	0.37 [-0.04, 0.79]	N/A	Very low[1,2,3]	Appendix14 ci (11.2)
Negative Symptoms	BERGER2008	K = 1; N = 91	0.32 [-0.10, 0.73]	N/A	Very low[1,2,3]	Appendix14 ci (11.3)
Global State (Severity) (SMD)	BERGER2008	K = 1; N = 91	0.44 [0.02, 0.85]*	N/A	Very low[1,2,3]	Appendix14 ci (11.4)
Depression (SMD)	BERGER2008	K = 1; N = 91	-0.08 [-0.49, 0.33]	N/A	Very low[1,2,3]	Appendix14 ci (11.5)
Mania	BERGER2008	K = 1; N = 91	0.34 [-0.07, 0.76]	N/A	Very low[1,2,3]	Appendix14 ci (11.6)
Psychosocial Functioning	BERGER2008	K = 1; N = 91	0.19 [-0.22, 0.60]	N/A	Very low[1,2,3]	Appendix14 ci (11.7)
Social Functioning	BERGER2008	K = 1; N = 91	-0.01 [-0.42, 0.40]	N/A	Very low[1,2,3]	Appendix14 ci (11.8)
Response (RR)	BERGER2008	K = 1; N = 141	1.39 [0.78, 2.49]	N/A	Very low[1,2,3]	Appendix14 ci (11.9)
Remission (RR)	BERGER2008	K = 1; N = 141	0.43 [0.16, 1.17]	N/A	Very low[1,2,3]	Appendix14 ci (11.10)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.

*Favours 400mg/day
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained; not all outcomes reported; not all data extractable)
[2]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

Side effects

Table 60 summarises the evidence profile 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. No significant differences were found between treatment groups on any of the side effect outcomes reported at 4 weeks' post-treatment.

Table 60: Summary evidence profile 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	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Metabolic: Weight (SMD)	BERGER2008	K = 1; N = 106	-0.04 [-0.54, 0.47]	N/A	Very low[1,2,3]	Appendix14ci (12.1)
Neurological: UKU	BERGER2008	K = 1; N = 91	-0.37 [-0.78, 0.04]	N/A	Very low[1,2,3]	Appendix14ci (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]	Appendix14ci (12.3)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
[1]Serious risk of bias (including blinding of participants and providers in part 2 not maintained; not all outcomes reported; not all data extractable)
[2]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[3]Serious risk of reporting bias

7.8 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 1674 participants with first episode psychosis, the evidence suggests minimal differences in efficacy between individual antipsychotic medications and antipsychotic doses examined. 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

quetiapine, haloperidol or 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 of included trials 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 was 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.

7.9 CLINICAL EVIDENCE SUMMARY FROM THE ADULT GUIDELINE FOR INITIAL TREATMENT WITH ANTIPSYCHOTIC MEDICATION

In 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 (NCCM, 2010). 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 SPC for each drug.

SECTION 2: ANTIPSYCHOTICS IN THE TREATMENT OF THE ACUTE EPISODE

7.10 INTRODUCTION

Antipsychotics in the treatment of the acute episode

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, 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 updated adult *Schizophrenia* guideline (NCCMH, 2010; which incorporated the recommendations from the NICE technology appraisal of SGAs [NICE, 2002]), particularly with regards 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).

7.11 CLINICAL REVIEW PROTOCOL FOR ANTIPSYCHOTICS IN THE TREATMENT OF THE ACUTE EPISODE IN CHILDREN AND YOUNG PEOPLE

The review protocol (see Table 61), including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Appendix 8 (further information about the search strategy can be found in Appendix 9).

Table 61: Clinical review protocol for the review of antipsychotics in the treatment of the acute episode in children and young people

Review questions	1. 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? 2. Are children and young people more susceptible to side effects of antipsychotic medication, compared with adults (in particular, the metabolic, neurological and cognitive impairments)? 3. Should the dose/duration (and where relevant frequency) be different compared with adult patients?
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding the pharmacological (antipsychotic) treatment and management of the acute episode in children and young people with psychosis or schizophrenia, including a review of NICE Clinical Guidance 82 for its relevancy to children and young people.
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 meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated if only limited evidence for children and young people aged 18 and younger is available. Consideration will also be given to the specific needs of children and young people with schizophrenia and a mild learning disability; and children and young people 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 or 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 or schizophrenia). • 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 events (including effects on metabolism; extrapyramidal side effects; hormonal changes; and , cardiotoxicity) • Remission
Electronic databases	4 and 6: Mainstream databases: Embase, MEDLINE, PreMEDLINE, 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 5: Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic specific databases: CDSR*, CENTRAL, DARE*
Date searched	SR: 1995 to May 2012; RCTs: inception of databases to May 2012
Study design	SR, 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 18 years. The review will seek to identify whether modifications in treatment and management of children aged 13 years and younger need to be made. • 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. Published data will not be included when evidence submitted is commercial in confidence.

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7.12 STUDIES CONSIDERED[60]

Thirteen RCTs (N = 1524) providing relevant clinical evidence met the eligibility criteria for the review of antipsychotic medication as treatment in the acute episode (AZD1441C00112, FINDLING2008A, HAAS2009, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011, PALLIERE-MARTINOT1995, POOL1976, MOZES2006, SIKICH2004, JENSEN2008, XIONG2004/KENNEDY2012, YAO2003/KENNEDY2012). Two of these studies were not published in English and were identified via an included systematic review of antipsychotic medication for childhood-onset schizophrenia (KENNEDY2012). The remaining twelve included RCTs were published in peer-reviewed journals between 1976 and 2012. Additional unpublished data was also obtained from one placebo controlled trial of quetiapine (AZD1441C00112). 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 or schizophrenia aged 18 years and younger (AZD1441C00112, FINDLING2008A, HAAS2009, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011, POOL1976, MOZES2006, JENSEN2008 XIONG2004/KENNEDY2012, YAO2003/KENNEDY2012). We extrapolated data from two remaining studies providing relevant clinical evidence in populations of young people experiencing an acute episode of psychosis or schizophrenia, that included children and young people aged over and under 18 years, but with an overall mean age 25 years and younger (PALLIERE-MARTINOT1995, SIKICH2004). In addition, 583 studies were considered irrelevant to the pharmacological treatment and management of psychosis or schizophrenia in children and young people and excluded from the review. Further information about both included and excluded studies can be found in Appendix 14.

There were a total of 22 evaluations across three comparison groups: antipsychotic medication versus placebo; antipsychotic medication in head-to-head trials; and antipsychotic medications at different doses. Section 2 has been sub divided according to these comparison groups: antipsychotic medications versus placebo (Section 7.9.1); antipsychotic medications in head-to-head trials (Section 7.9.2); and antipsychotic medications administered at different doses (Section 7.9.3). Study characteristics for all included studies within each comparison group can be found within each section (Table 62, Table 69 and Table 80 respectively). Forest plots and/or evidence profiles for each outcome can be found in Appendix 14 and Appendix 17, respectively.

[60] 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).

7.12.1 Antipsychotic medication versus placebo

Table 62 provides the study characteristics for seven included RCTs (N = 1067) providing relevant clinical evidence for antipsychotic medication compared with placebo in the treatment of the acute episode (AstraZenecaD1441C0012, FINDLING2008A, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011, PALLIERE-MARTINOT1995, POOL1976). 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 (AstraZenecaD1441C0012); quetiapine 800 mg per day (AstraZenecaD1441C0012); 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 50-100 mg per day (PALLIERE-MARTINOT1995); and haloperidol 11.9 mg per day (POOL1976). To assess the efficacy of antipsychotics versus placebo, we used the lower and upper dose ranges identified by the POMH Topic 10 benchmarking exercise of antipsychotic prescribing in children and young people in practice [POMH-UK 2012], to categorised doses administered in the included trials as either 'lower' or 'higher' doses of medication. We compared 'lower dose' antipsychotic medication with placebo and 'higher dose' antipsychotic to 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: Included 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 or 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(s)	AstraZenecaD1441C00112	FINDLING2008A	HAAS2009B	KRYZHANOVSKAYA2009B	SINGH2011	PALLIERE-MARTINOT1995	POOL1976
Diagnosis	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenic disorder	Schizophrenia
Prior antipsychotic use (% naive prior to intervention)	NR	51.7	NR	56.5	36% and 60% atypical and typical, respectively	NR	NR
Mean (range) Age (years)	15.4 (13.0 to 17.0)	15.5 (NR)	15.6 (13.0 to 17.0)	16.2 (NR)	15.4 (NR)	20.0 (NR)	15.5 (NR)
Sex (% male)	59	57	64	70	59	NR	95
Ethnicity (% Caucasian)	61	37	53	72	68	NR	NR
Mean (range) medication dose (mg per day)	'Lower dose': 400.0 (NR) 'Higher dose': 800.0 (NR)	'Lower dose': 10.0 (2.0 to 10.0) 'Higher dose': 30.0 (2.0 to 30.0)	'Lower dose': (NR) 1.0 to 3.0 'Higher dose': (NR) 4.0 to 6.0	'Lower dose': 11.1 (2.5 to 20.0)	'Lower dose': 1.5 (NR) 'Higher dose': 3.0 (3.0 to 6.0) (Additional dose arm: 6.0 (6.0 to 12.0))	'Lower dose': NR (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	In- and outpatients	In- and outpatients	In- and outpatients	In- and outpatients	In- and outpatients	In- and outpatients	Adolescent Hospital
Country	43 international sites, including the US and Asia	US, Europe, South America, Asia, the Caribbean, and 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

7.12.1.1 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 (AstraZenecaD1441C0012, FINDLING2008A, HAAS2009B, KRYZHANOVSKAYA2009B, SINGH2011, PALLIERE-MARTINOT1995). Antipsychotic medications and respective mean (range) doses included were: quetiapine 400 mg per day (NR); aripiprazole 10 mg per day (2 to 10); risperidone (mean not reported) 1-3 mg per day; olanzapine 11.1 mg per day (2.5 to 20.0); paliperidone 1.5 mg per day (NR); 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 (AstraZenecaD1441C0012, 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 (PALLIERE-MARTINOT1995). The median of the mean ages is 15.5 years. An overview of study characteristics can be found in Table 63 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 13.

Efficacy

Table 63 provides a summary evidence profile 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 or schizophrenia. KRYZHANOVSKAYA2009B and PALLIERE-MARTINOT1995 report mean endpoint scores, while all remaining studies report 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, -0.52 to -0.13), negative symptoms (SMD = -0.33, -0.50 to -0.16) and global state (SMD = -0.38, -0.58 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 = -0.30, -0.59 to -0.01), however when mean endpoint scores were removed (KRYZHANOVSKAYA2009B; PALLIERE-MARTINOT1995) in a sensitivity analysis, the effect did not remain significant (SMD = -0.26, -0.56 to 0.05) (see Table 63). 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 psychosocial functioning (SMD = -0.29,-0.52 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).

Table 63: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B; SINGH2011	K=4; N=516	-0.32 [-0.52, -0.13]*	(P = 0.31); I^2 = 16%	Low[1,2]	Appendix 14cii (1.1)
Sensitivity analysis: Total Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; SINGH2011	K = 3; N = 409	-0.25 [-0.45, -0.06]*	(P = 0.66); I^2 = 0%	Low[1,2]	Appendix 14 cii (1.2)
Positive Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B; HAAS2009B; PALLIERE-MARTINOT1995; SINGH2011	K=6; N=634	-0.30 [-0.59, -0.01] *	(P < 0.0001); I^2 = 82%	Very low[1,2,4]	Appendix 14cii (1.3)
Sensitivity analysis: Positive Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	K = 4; N = 506	-0.26 [-0.56, 0.05]	(P = 0.0007); I^2 = 82%	Very low[1,2,4]	Appendix 14 cii (1.4)
Negative Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B; HAAS2009B; PALLIERE-MARTINOT1995; SINGH2011	K=6; N=634	-0.33 [-0.50, -0.16] *	(P = 0.33); I^2 = 13%	Very low[1,2,4]	Appendix 14cii (1.5)
Sensitivity analysis: Negative Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	K = 4; N = 507	-0.31 [-0.52, -0.09]*	(P = 0.22); I^2 = 31%	Low[1,2]	Appendix14 cii (1.6)
Global State (Severity) (SMD)	AstraZenecaD1441C0012; FINDLING2008A; KRYZHANOVSKAYA2009B	K=3; N=400	-0.38 [-0.58, -0.18] *	(P = 0.44); I^2 = 0%	Low[1,2]	Appendix 14cii (1.7)

Sensitivity analysis: Global State (Severity) (SMD)	AstraZenecaD1441C0012; FINDLING2008A	K = 2; N = 193	-0.31 [-0.54, -0.08]	(P = 0.90); I^2 = 0%	Very Low[1,2,3]	Appendix 14 cii (1.8)
Depression (SMD)	AstraZenecaD1441C0012; PALLIERE-MARTINOT1995; SINGH2011	K=2; N=202	-0.20 [-0.46, 0.07]	(P = 0.63); I^2 = 0%	Very low[1,2,3]	Appendix 14cii (1.9)
Sensitivity analysis: Depression (SMD)	AstraZenecaD1441C0012; SINGH2011	K = 2; N = 202	-0.16 [-0.44, 0.12]	(P = 0.63); I^2 = 0%	Very low[1,2,3]	Appendix 14 cii (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 14cii (1.11)
Psychosocial Functioning (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	K=4; N=535	-0.29 [-0.52, -0.06]*	(P = 0.15); I^2 = 43%	Low[1,2]	Appendix 14cii (1.12)
Response (RR)	AstraZenecaD1441C0012	K=1; N=98	1.43 [0.95, 2.17]	N/A	Very low[1,2,3]	Appendix 14cii (1.13)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours 'lower dose'
[1] Serious risk of bias (including unclear blinding procedures, reports LOCF analysis but the number of participants included results suggests available case analysis, participants excluded if they had a previous non-response to study treatment, some outcomes not reported; treatment exposure (time) differ between groups,
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[4] $I^2 \geq 50\%$, $p<.05$

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 assessed according to individual antipsychotic and respective dose. Table 64 provides a summary evidence profile for side effect outcomes reported at treatment endpoint associated with the 'lower' doses of antipsychotic medications versus placebo in the treatment of the acute episode in children and young people with psychosis or schizophrenia. Three out of four studies found a significant difference between treatment groups, favouring placebo on weight gain (FINDLING2008A, KRYZHANOVSKAYA2009B, AZD1441C0012). The largest effect found was between olanzapine and placebo (SMD = 1.33, 0.88 to 1.77). Similarly, significant differences, favouring placebo were found between treatment groups on BMI increase with the largest effect found between olanzapine and placebo (SMD = 1.31, 0.87 to 1.75). For other metabolic outcomes small to moderate significant effects favouring placebo compared with aripiprazole 10 mg per day on fasting serum glucose level (SMD = 0.38, 0.03 to 0.74); quetiapine 400 mg per day on fasting low-density lipoprotein cholesterol levels (SMD = 0.58, 0.22 to 0.93) and total cholesterol (SMD = 0.58, 0.22 to 0.94); and olanzapine on fasting triglycerides (SMD = 0.54, 0.05 to 1.02). Placebo was also favoured over quetiapine 400 mg per day on systolic and diastolic blood pressure (SMD = 0.40, 0.07 to 0.73 for both outcomes) and standing pulse (SMD = 0.67, 0.33 to 1.00). Large differential effects between placebo and olanzapine (11.1 mg per day) and risperidone (1-3 mg per day) were found for prolactin level increase (SMD = 0.71, 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, 0.36 to 0.87). No further significant differences were found for any other side effect outcomes measured.

Table 64: Summary evidence profile for side effect outcomes reported at treatment endpoint associated with a 'lower dose' antipsychotic medications versus placebo in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	Study ID	Antipsychotic (dose)	Number of studies / participants	Effect Estimate (SMD or RR)	Heterog eneity	Quality	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 14cii (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 14cii (2.1)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=146	0.75 [0.41, 1.08] **	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (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 14cii (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 14cii (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 14cii (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 14cii (2.3)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=135	0.14 [-0.20, 0.48]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.4)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=125	0.58 [0.22, 0.94] **	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.5)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=125	0.04 [-0.31, 0.39]	N/A	Very low[1,2,3]	Appendix 14cii (2.5)

Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg/dl (SMD)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=125	0.58 [0.22, 0.93] **	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.7)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=125	0.36 [0.00, 0.71]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (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 14cii (2.8)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=129	-0.28 [-0.63, 0.06]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.8)
Cardio: QT Interval (RR) (Incidence of prolonged QT)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	3.08 [0.13, 74.43]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.9)
Cardio: Systolic BP (SMD)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=146	0.40 [0.07, 0.73] **	N/A	Very low[1,2,3]	Appendix 14cii (2.10)
Cardio: Diastolic BP (SMD)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=146	0.40 [0.07, 0.73] **	N/A	Very low[1,2,3]	Appendix 14cii (2.11)
Cardio: Tachycardia (RR)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	9.24 [0.51, 168.69]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.12)
	HAAS2009B	Risperidone (1-3 mg per day)	K=1; N=109	0.98 [0.21, 4.65]	N/A	Very low[1,2,3]	Appendix 14cii (2.12)
Cardio: Standing Pulse	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=146	0.67 [0.33, 1.00] **	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (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 14cii (2.14)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=125	0.33 [-0.02, 0.68]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.14)
	HAAS2009B	Risperidone (1-3 mg per day)	K=1; N=109	1.05 [0.65, 1.45]**	N/A	Very low[1,2,3]	Appendix 14cii (2.14)
Hormonal: Insulin	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=122	0.28 [-0.08, 0.63]	N/A	Very low[1,2,3]	Appendix 14cii (2.15)
Neurological: Extrapyramidal Side Effects (RR)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	3.08 [0.13, 74.43]	N/A	very low[1,2,3]	Appendix 14cii (2.16)
Neurological: AIMS	HAAS2009B	Risperidone (1-3 mg per day)	K=1; N=109	0.23 [-0.15, 0.61]	N/A	Very low[1,2,3]	Appendix 14cii (2.16)
Neurological: SAS	HAAS2009B	Risperidone (1-3 mg per day)	K=1; N=109	0.00 [-0.38, 0.38]	N/A	Very low[1,2,3]	Appendix 14cii (2.17)
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 14cii (2.18)
Neurological: Tremor (RR)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	1.54 [0.27, 8.96]	N/A	Very low[1,2,3]	Appendix 14cii (2.19)
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 14cii (2.20)
	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	1.54 [0.27, 8.96]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (2.21)
Neurological: Dyskinesia (RR)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	5.14 [0.25, 105.17]	N/A	Very low[1,2,3]	Appendix 14cii (2.22)
Neurological: Extrapyramidal Disorder (RR)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	3.08 [0.13, 74.43]	N/A	Very low[1,2,3]	Appendix 14cii (2.23)
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 14cii (2.24)

	HAAS2009B	Risperidone (1-3 mg per day)	K=1; N=109	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14cii (2.24)
Leaving the Study Early for Any Reason (RR)	AstraZenecaD1441C0012	Quetiapine (400 mg per day)	K=1; N=148	0.62 [0.37, 1.04]	N/A	Very low[1,2,3]	Appendix 14cii (2.25)
	FINDLING2008A	Aripiprazole (10 mg per day)	K=1; N=200	1.60 [0.76, 3.35]	N/A	Very low[1,2,3]	Appendix 14cii (2.25)
	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 14cii (2.25)
	PALLIERE-MARTINOT1995	Amisulpride (50-100 mg per day)	K=1; N=17	1.11 [0.45, 2.78]	N/A	Very low[1,2,3]	Appendix 14cii (2.25)
	HAAS2009B	Risperidone (1-3 mg per day)	K=1; N=109	0.55 [0.28, 1.07]	N/A	Very low[1,2,3]	Appendix 14cii (2.25)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours 'lower dose'
** Favours placebo
[1] Serious 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 (time) differ between groups in one study)
[2] Serious risk of publication bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

7.12.1.2 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 (AstraZenecaD1441C0012, FINDLING2008A, HAAS2009B, SINGH2011, POOL1976). Antipsychotic medications and respective mean (range) doses included were: quetiapine 800.0 mg per day (NR); aripiprazole 30 mg per day (2.0-30.0); risperidone (mean not reported) 4.0-6.0 mg per day; paliperidone 3.0-6.0 mg per day (NR); and haloperidol 11.9 (2.0-12.0) mg per day. All studies were conducted in children and young people aged 18 years and younger with a median of the mean of 15.5 years. An overview of study characteristics can be found in Table 65(included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14

Efficacy

Table 65 provides a summary evidence profile 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 or schizophrenia. Small to moderate, significant effects were found between a 'higher dose' or antipsychotic and placebo on total symptoms (SMD = -0.48,-0.68 to -0.28), positive symptoms (SMD = -0.48, -0.66 to -0.30), negative symptoms (SMD = -0.29, -0.51 to -0.07), global state (SMD = -0.43, -0.66 to -0.20), quality of life (SMD = -0.42, -0.83 to -0.01), and psychosocial functioning (SMD = -0.49, -0.66 to -0.31). No significant differences between treatment groups were found on depression or number of participants considered to have responded (measured using the CGI). SINGH2011 also report data for a 3rd dose of paliperidone (6.0 to 12.0 mg per day) versus placebo .

Table 66 presents the summary evidence profile for efficacy outcomes reported at treatment endpoint associated with this additional (high) dose of paliperidone). A small, significant difference favouring 6.0-12.0 mg per day over placebo was found for negative symptoms (SMD = -0.40, -0.8 to -0.01), but no significant differences between 6.0-12.0 mg per day of paliperidone and placebo were found (see Table 66).

Table 65: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; SINGH2011	K=3; N=402	-0.48 [-0.68, -0.28] *	(P = 0.90); I² = 0%	Low[1,2]	Appendix 14cii (3.1)
Positive Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	K=4; N=496	-0.48 [-0.66, -0.30] *	(P = 0.88); I² = 0%	Low[1,2]	Appendix 14cii (3.2)
Negative Symptoms (SMD)	AstraZenecaD1441C0012; FINDLING2008A; HAAS2009B; SINGH2011	K=4; N=495	-0.29 [-0.51, -0.07] *	(P = 0.22); I² = 32%	Low[1,2]	Appendix 14cii (3.3)
Global State (Severity) (SMD)	AstraZenecaD1441C0012; FINDLING2008A	K=2; N=292	-0.43 [-0.66, -0.20] *	(P = 0.74); I² = 0%	Very low[1,2,3]	Appendix 14cii (3.4)
Depression (SMD)	AstraZenecaD1441C0012; SINGH2011	K=2; N=197	-0.28 [-0.56, 0.00]	(P = 0.94); I² = 0%	Very low[1,2,3]	Appendix 14cii (3.5)
Quality of Life (SMD)	FINDLING2008A	K=1; N=195	-0.42 [-0.83, -0.01] *	N/A	Very low[1,2,3]	Appendix 14cii (3.6)
Psychosocial Functioning (SMD)	AstraZenecaD1441C0012; FINDLING2008A	K=4; N=522	-0.49 [-0.66, -0.31]*	(P = 0.63); I² = 0%	Low[1,2]	Appendix 14cii (3.7)
Response (RR)	AstraZenecaD1441C0012	K=1; N=98	1.35 [0.88, 2.05]	N/A	Very low[1,2,3]	Appendix 14cii (3.8)

Note
ROB= Risk of bias; RR = Relative risk; SMD = Standardised mean difference.
* Favours 'higher dose'
[1] Serious risk of bias (including unclear blinding procedures, reports LOCF analysis but the number of participants included results suggests available case analysis, participants excluded if they had a previous non-response to study treatment, some outcomes not reported; treatment exposure (time) differ between groups, patients who failed to complete four 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)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Table 66: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	SINGH2011	K=1; N=98	-0.32 [-0.72, 0.08]	N/A	Very low[1,2,3]	Appendix 14cii (4.1)
Positive Symptoms (SMD)	SINGH2011	K=1; N=98	-0.27 [-0.67, 0.13]	N/A	Very low[1,2,3]	Appendix 14cii (4.2)
Negative Symptoms (SMD)	SINGH2011	K=1; N=98	-0.41 [-0.80, -0.01]*	N/A	Very low[1,2,3]	Appendix 14cii (4.3)
Depression (SMD)	SINGH2011	K=1; N=98	-0.24 [-0.63, 0.16]	N/A	Very low[1,2,3]	Appendix 14cii (4.4)
Psychosocial Functioning (SMD)	SINGH2011	K=1; N=98	-0.28 [-0.68, 0.12]	N/A	Very low[1,2,3]	Appendix 14cii (4.5)

Note
ROB=risk of bias
*favours 6 to 12 mg per day paliperidone
[1] Serious risk of bias (including some outcomes not reported; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Side effects

Table 67 provides a summary evidence profile 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 or schizophrenia. Three trials assessing weight gain, found small to moderate, significant effects favouring placebo quetiapine 800.00 mg per day (SMD = 0.58, 0.25 to 0.91); aripiprazole 30.0 mg per day (SMD = 0.41, 0.12 to 0.69); and paliperidone 3.0-6.0 mg per day (SMD = 0.57, 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, 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, 0.25 to 0.98) and low-density lipoprotein cholesterol level (SMD = 0.41, 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, 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, 0.02 to 0.73) and a large effect favouring placebo was found for risperidone 4.0-6.0 mg per day (SMD = 1.38, 0.95 to 1.81). Participants treated with placebo scored significantly better than patients treated with risperidone 4.0-6.0 mg per day on the SAS (SMD = 0.45, 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, 2.05 to 9.58). A significant effect was also found favouring placebo over haloperidol 11.9 mg per day on extra-pyramidal side effects (RR = 17.28, 2.50 to 119.55) however confidence intervals are wide. Significantly fewer people treated with quetiapine 800.0 mg per day dropped out compared with placebo-treated participants (SMD = 0.47, 0.27 to 0.84). SINGH2011 also report data for a third dose of paliperidone (6 to 12 mg per day) versus placebo (see Table 68 for the summary evidence profile for side effect outcomes reported at treatment endpoint associated with this additional (high) dose of paliperidone). A moderate and significant difference favouring placebo versus 6.0-12.0 mg per day of paliperidone was found for weight increase (SMD = 0.72, 0.31 to 1.13), but no further significant differences were found on the other side effects measured.

Table 67: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Antipsychotic (dose)	Number of studies / participants	Effect Estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Metabolic: Weight (SMD)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=146	0.58 [0.25, 0.91] **	N/A	Very low[1,2,3]	Appendix 14cii (5.1)
	INDLING2008A	Aripiprazole (30mg per day)	K=1; N=195	0.41 [0.12, 0.69] **	N/A	Very low[1,2,3]	Appendix 14cii (5.1)
	SINGH2011	Paliperidone (3-6mg per day)	K=1; N=100	0.57 [0.17, 0.97] **	N/A	Very low[1,2,3]	Appendix 14cii (5.1)
Metabolic: BMI (SMD)	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=195	0.33 [0.05, 0.61] **	N/A	Very low[1,2,3]	Appendix 14cii (5.2)
Metabolic: Fasting Serum Glucose Level mg per dl (SMD)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=137	0.03 [-0.30, 0.37]	N/A	Very low[1,2,3]	Appendix 14cii (5.3)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=120	0.17 [-0.19, 0.53]	N/A	Very low[1,2,3]	Appendix 14cii (5.3)
Metabolic: Fasting Total Cholesterol mg per dl (SMD)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=119	0.12 [-0.24, 0.48]	N/A	Very low[1,2,3]	Appendix 14cii (5.4)
	INDLING2008A	Aripiprazole (30mg per day)	K=1; N=194	0.11 [-0.17, 0.39]	N/A	Very low[1,2,3]	Appendix 14cii (5.4)
Metabolic: Fasting High-Density Lipoprotein Cholesterol mg per dl (SMD)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=123	-0.16 [-0.51, 0.20]	N/A	Very low[1,2,3]	Appendix 14cii (5.5)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=85	0.38 [-0.05, 0.81]	N/A	Very low[1,2,3]	Appendix 14cii (5.5)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg per dl (SMD)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=123	K=1; N=123	N/A	Very low[1,2,3]	Appendix 14cii (5.6)
Metabolic: Fasting Triglycerides	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=123	0.61 [0.25, 0.98] **	N/A	Very low[1,2,3]	Appendix 14cii (5.7)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=85	0.11 [-0.32, 0.53]	N/A	Very low[1,2,3]	Appendix 14cii (5.7)
Cardio: QT Interval (SMD)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=129	0.37 [0.03, 0.72] **	N/A	Very low[1,2,3]	Appendix 14cii (5.8)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=198	0.21 [-0.08, 0.49]	N/A	Very low[1,2,3]	Appendix 14cii (5.8)
Cardio: QT Interval (RR) (Incidence of prolonged QT)	AstraZenecaD1441 C0012	Quetiapine (400mg per day)	K=1; N=149	3.04 [0.13, 73.44]	N/A	Very low[1,2,3]	Appendix 14cii (5.9)

	SINGH2011	Paliperidone (3-6mg per day)	K=1; N=99	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14cii (5.9)
Cardio: Systolic BP (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=147	0.13 [-0.19, 0.46]	N/A	Very low[1,2,3]	Appendix 14cii (5.10)
Cardio: Diastolic BP (SMD)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=147	0.25 [-0.07, 0.58]	N/A	Very low[1,2,3]	Appendix 14cii (5.10)
Cardio: Tachycardia (RR)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=149	13.17 [0.76, 229.73]	N/A	Very low[1,2,3]	Appendix 14cii (5.12)
	HAAS2009B	Risperidone (4-6mg per day)	K=1; N=105	0.71 [0.12, 4.05]	N/A	Very low[1,2,3]	Appendix 14cii (5.12)
	SINGH2011	Paliperidone (3-6mg per day)	K=1; N=99	7.43 [0.39, 140.15]	N/A	Very low[1,2,3]	Appendix 14cii (5.12)
Cardio: Standing Pulse	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=147	0.31 [-0.02, 0.63]	N/A	Very low[1,2,3]	Appendix 14cii (5.13)
Hormonal: Prolactin	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=123	0.37 [0.02, 0.73] **	N/A	Very low[1,2,3]	Appendix 14cii (5.14)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=188	-0.26 [-0.55, 0.03]	N/A	Very low[1,2,3]	Appendix 14cii (5.14)
	HAAS2009B	Risperidone (4-6mg per day)	K=1; N=105	1.38 [0.95, 1.81] **	N/A	Very low[1,2,3]	Appendix 14cii (5.14)
	SINGH2011	Paliperidone (3-6mg per day)	K=1; N=83	0.09 [-0.34, 0.52]	N/A	Very low[1,2,3]	Appendix 14cii (5.14)
Hormonal: Insulin	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=119	0.12 [-0.24, 0.48]	N/A	Very low[1,2,3]	Appendix 14cii (5.15)
Neurological: Extrapyramidal Side Effects (RR)	POOL1976	Haloperidol (11.9mg per day)	K=1; N=59	17.28 [2.50, 119.55]**	N/A	Very low[1,2,3]	Appendix 14cii (5.16)
Neurological: AIMS	HAAS2009B	Risperidone (4-6mg per day)	K=1; N=105	0.35 [-0.03, 0.74] **	N/A	Very low[1,2,3]	Appendix 14cii (5.17)
Neurological: SAS	HAAS2009B	Risperidone (4-6mg per day)	K=1; N=105	0.45 [0.06, 0.84] **	N/A	Very low[1,2,3]	Appendix 14cii (5.18)
Neurological: Parkinsonism (RR)	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=200	4.43 [2.05, 9.58]**	N/A	Very low[1,2,3]	Appendix 14cii (5.19)
Neurological: Tremor (RR)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=149	1.52 [0.26, 8.84]	N/A	Very low[1,2,3]	Appendix 14cii (5.20)
Neurological: Akathisia (RR)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=149	1.52 [0.26, 8.84]	N/A	Very low[1,2,3]	Appendix 14cii (5.21)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=200	2.00 [0.78, 5.12]	N/A	Very low[1,2,3]	Appendix 14cii (5.21)
Neurological: Dystonia	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=200	5.00 [0.24, 102.85]	N/A	Very low[1,2,3]	Appendix 14cii (5.22)

(RR)							
Neurological: Dyskinesia (RR)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=149	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14cii (5.23)
Neurological: Extrapyramidal Disorder (RR)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=149	3.04 [0.13, 73.44]	N/A	Very low[1,2,3]	Appendix 14cii (5.24)
Mortality (RR)	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=200	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14cii (5.25)
	HAAS2009B	Risperidone (4-6mg per day)	K=1; N=105	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14cii (5.25)
Leaving the Study Early for Any Reason (RR)	AstraZenecaD1441C0012	Quetiapine (400mg per day)	K=1; N=149	0.47 [0.27, 0.84]*	N/A	Very low[1,2,3]	Appendix 14cii (5.26)
	FINDLING2008A	Aripiprazole (30mg per day)	K=1; N=202	1.76 [0.86, 3.63]	N/A	Very low[1,2,3]	Appendix 14cii (5.26)

Note
ROB=risk of bias
* Favours 'Higher dose'
**Favours placebo
[1] Serious risk of bias (including unclear blinding procedures, reports LOCF analysis but the number of participants included results suggests available case analysis, participants excluded if they had a previous non-response to study treatment, some outcomes not reported; treatment exposure (time) differ between groups, patients who failed to complete four 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)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Table 68: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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 14cii (6.1)
Cardio: QT Interval	SINGH2011	K=1; N=98	1.00 [0.00, 0.00]	N/A	Very low[1,2,3]	Appendix 14cii (6.2)
Cardio: Tachycardia (RR)	SINGH2011	K=1; N=98	9.75 [0.54, 176.36]	N/A	Very low[1,2,3]	Appendix 14cii (6.3)
Hormonal: Prolactin	SINGH2011	K=1; N=83	-0.10 [-0.53, 0.33]	N/A	Very low[1,2,3]	Appendix 14cii (6.4)

Note
ROB=risk of bias
*favours placebo
[1] Serious risk of bias (including some outcomes not reported; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

7.12.2 Antipsychotic medications in head-to-head trials

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). All studies were conducted in children and young people experiencing an acute episode of psychosis or 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 we could not included the risperidone arm of this three-arm trial, however we were able to extract and analyze data for the olanzapine and quetiapine arms. SIKICH2004 also conducted a three-arm trial and there were therefore a total of five comparisons: two studies comparing risperidone with to olanzapine (MOZES2006; SIKICH2004); one study comparing olanzapine with quetiapine (JENSEN2008); two studies comparing risperidone with haloperidol (SIKICH2004, YAO2003/KENNEDY2012); one study comparing olanzapine with haloperidol (SIKCIH2004); and one study comparing risperidone with chlorpromazine (XIONG2004/KENNEDY2012).

Table 69: Included Study Information table for trials comparing an antipsychotic medication in head-to-head trials for the treatment of an acute episode in children and young people with psychosis or 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(s)	MOZES2006[2] SIKICH2004[2]	SIKICH2004[2] YAO2003/KENNEDY2012[2]	XIONG2004/KENNEDY2012[2]	JENSEN2008[2]	SIKICH2004[2]
Diagnosis [1]	MOZES2006: Schizophrenic disorder SIKICH2004: Psychosis, including schizophrenia spectrum disorders and affective disorders	SIKICH2004: Psychosis, including schizophrenia spectrum disorders and affective disorders YAO2003/KENNEDY2012: Childhood onset schizophrenia	Childhood-onset schizophrenia	Schizophrenic disorder	Psychosis, including schizophrenia spectrum disorders and affective disorders
Prior Antipsychotic Use (% naive prior to intervention) [1]	MOZES2006: NR SIKICH2004: 24.0	SIKICH2004: 24.0 YAO2003/KENNEDY2012: NR	NR	76.7	24.0
Mean (range) Age (years) [1]	MOZES2006: 11.1 (9.0 to 14.0) SIKICH2004: 14.8 (NR)	SIKICH2004: 14.8 (NR) YAO2003/KENNEDY2012: 11 (NR)	13.0 (7.0 to 16.0)	15.2 (10.0 to 18.0)	14.8 (NR)
Sex (% male) [1]	MOZES2006: 40.0 SIKICH2004: 60.0	SIKICH2004: 60 YAO2003/KENNEDY2012: 56%	57	66.7	60.0
Ethnicity (% Caucasian) [1]	MOZES2006: NR SIKICH2004: 60.0	SIKICH2004: 60 YAO2003/KENNEDY2012: NR	NR	60.0	60.0
Mean (range) medication dose (mg per day) [1]	MOZES2006: *Risperidone:* 1.62(0.25 to 4.5) *Olanzapine:* 8.18 (2.5 to 20) SIKICH2004: *Risperidone:* 4.0 (0.5 to 6.0) *Olanzapine:* 12.3 (2.5 to 20)	SIKICH2004: *Risperidone:* 4.0 (0.5 to 6.0) *Haloperidol:* 5.0 (1 to 8) YAO2003/KENNEDY2012: *Risperidone:* NR (0.25 to 3.0) *Haloperidol:* NR (0.5 to 12)	*Risperidone:* NR (0.5 to 5.0) *Chlorpromazine:* NR (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)	MOZES2006: 12	SIKICH2004: 8	8	12	8

[1]	SIKICH2004: 8	YAO2003/KENNEDY2012: 6			
Length of follow-up (weeks) [1]	MOZES2006: 12 SIKICH2004: 8	SIKICH2004: 8 YAO2003/KENNEDY2012: 6	8	12	8
Setting [1]	MOZES2006: Inpatient SIKICH2004: Inpatient and outpatient	Inpatient and outpatient	Inpatient	Inpatient and outpatient	Inpatient and outpatient
Country [1]	MOZES2006: Israel SIKICH2004: US	SIKICH2004: US YAO2003/KENNEDY2012: China	China	US	US
Funding [1]	MOZES2006: NR SIKICH2004: Eli Lily, Janssen and non-industry sponsors	SIKICH2004: Eli Lily, Janssen and non-industry sponsors YAO2003/KENNEDY2012: NR	NR	AstraZeneca	Eli Lily, Janssen and non-industry sponsors

Note.
NR = not reported
[1] Extractable outcomes.
[2] Data is reported for the population characteristics of each study, not the population characteristics of each treatment group

7.12.2.1 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 or schizophrenia. The median of the mean ages across studies is 12.9 years. An overview of study characteristics can be found in Table 70 (included study information table for trials comparing an antipsychotic with placebo in the treatment of an acute episode in children and young people with psychosis or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 70 provides a summary evidence profile 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 or schizophrenia. No significant differences between treatment groups were found for any efficacy outcome measured.

Table 70: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	MOZES2006; SIKICH2004	K=2; N=60	0.25 [-0.53, 1.04]	(P = 0.13); I^2 = 56%	Very low[1,2,3,4]	Appendix 14cii (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 14cii (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 14cii (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 14cii (7.4)
Psychosocial Functioning (SMD)	MOZES2006	K=1; N=15	0.25 [-0.54, 1.04]	N/A	Very low[1,2,3]	Appendix 14cii (7.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including open label trial, minimal information regarding eligibility criteria; trial registration cannot be found; missing outcomes data)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met
[4] $I^2 \geq 50\%$, $p<.05$

Side effects

Table 71 provides a summary evidence profile 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 or schizophrenia.

Significantly fewer participants treated with olanzapine 11.1 mg per day left the study early for any reason, compared with to placebo-treated participants (RR = 3.90, 1.25 to 12.17), however the sample size is extremely small and confidence intervals 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.

Table 71: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	Study ID	Number of studies / participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	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 14cii (8.1)
Metabolic: BMI (SMD)	SIKICH2004	K=1; N=35	-0.09 [-0.75, 0.58]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (8.3)
Neurological: SAS (SMD)	SIKICH2004	K=1; N=35	0.09 [-0.58, 0.75]	N/A	Very low[1,2,3]	Appendix 14cii (8.4)
Neurological: Extrapyramidal symptoms (SAS) (RR)	MOZES2006	K=1; N=25	0.95 [0.50, 1.80]	N/A	Very low[1,2,3]	Appendix 14cii (8.5)
Neurological: BARS	MOZES2006	K=1; N=25	3.25 [0.39, 27.15]	N/A	Very low[1,2,3]	Appendix 14cii (8.6)
Neurological: Tremor (RR)	MOZES2006	K=1; N=15	1.38 [0.71, 2.71]	N/A	Very low[1,2,3]	Appendix 14cii (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 14cii (8.8)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
[1] Serious risk of bias (including open label trial, minimal information regarding eligibility criteria; trial registration cannot be found; missing outcomes data)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

7.12.2.2 Clinical evidence for risperidone versus haloperidol for treatment of the acute episode

Two studies (SIKCIH2004; YAO2003/KENNEDY2012) (N = 77) compared risperidone and haloperidol in children and young people with psychosis or schizophrenia with a median of mean ages of 12.9 years. An overview of study characteristics can be found in Table 72 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 72 provides a summary evidence profile 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 or schizophrenia. No significant differences between treatment groups were found.

Table 72: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	**STUDY ID**	**Number of studies / participants**	**Effect Estimate (SMD or RR)**	**Heterogeneity**	**Quality**	**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 15 cii (9.1)
Positive Symptoms (SMD)	SIKICH2004	K = 1; N = 34	-0.25 [-0.93, 0.43]	N/A	Very low[1,2,3]	Appendix 15 cii (9.2)
Negative Symptoms (SMD)	SIKICH2004	K = 1; N = 34	-0.11 [-0.79, 0.57]	N/A	Very low[1,2,3]	Appendix 15 cii (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 15 cii (9.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including inadequate allocation concealment, unclear blinding procedures, trial registration could not be found)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012

Side effects

Table 73 provides a summary evidence profile 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 or schizophrenia. YAO2003/KENNEDY2012 found a significant risk reduction of experiencing an extra-pyramidal side effect, favouring risperidone over haloperidol (RR = 0.12 [0.04, 0.37], however the sample size in this trial was very small. No other significant differences between risperidone and haloperidol were found.

Table 73: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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 15 cii (10.1)
Metabolic: BMI (SMD)	SIKICH2004	K = 1; N = 34	-0.55 [-1.24, 0.14]	N/A	Very low[1,2,3]	Appendix 15 cii (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 15 cii (10.3)
Neurological: Extrapyramidal Side effects (RR)	YAO2003/ KENNEDY2012	K = 1; N = 42	0.12 [0.04, 0.37]*	N/A	Low[1,3,4]	Appendix 15 cii (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 15 cii (10.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* favours risperidone
[1] Serious risk of bias (including inadequate allocation concealment, unclear sequence generation and blinding procedures, trial registration could not be found; missing outcomes data)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012

7.12.2.3 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 or schizophrenia with a mean age of 13 years. An overview of study characteristics can be found in Table 74 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 74 provides a summary evidence profile 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 or schizophrenia. No significant differences between groups were found.

Table 74: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	XIONG2004/ KENNEDY2012	K = 1; N = 60	-0.29 [-0.80, 0.22]	N/A	Low[1,2,3,4]	Appendix 15 cii (11.1)
Note ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference [1] Serious risk of bias (including open label trial, unable to extract all outcomes) [2] Serious risk of reporting bias [3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. [4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012						

Side effects

Table 75 provides a summary evidence profile 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 or schizophrenia. No significant differences between groups were found.

Table 75: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Tremor (RR)	XIONG2004/ KENNEDY2012	K = 1; N = 60	0.50 [0.05, 5.22]	N/A	Low[1,2,3,4]	Appendix 15 cii (12.1)
Note ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference [1] Serious risk of bias (including unclear sequence generation, allocation concealment and blinding procedures) [2] Serious risk of reporting bias [3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met. [4] Sequence generation, allocation concealment, analysis and selective outcome reporting not reported by KENNEDY2012						

7.12.2.4 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 or schizophrenia, with a mean age of 15.2 years. An overview of study characteristics can be found in Table 76(included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

JENSEN2008 measured response using the PANSS. We found no significant difference between treatment groups at 12 weeks. Table 76 provides a summary evidence profile 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 or schizophrenia.

Table 76: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	Forest plot
Response (RR)	JENSEN2008	K = 1; N = 20	0.60 [0.19, 1.86]	N/A	Very low[1,2,3]	Appendix 15 cii (13.1)
Note ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference [1] Serious risk of bias (including open label trial, unable to extract all outcomes) [2] Serious risk of reporting bias [3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.						

Side effects

Table 77 provides a summary evidence profile 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 or schizophrenia. No significant differences between treatment groups were found on side effects assessed.

Table 77: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Number of studies / participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	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 15 cii (14.1)
Metabolic: BMI (SMD)	JENSEN2008	K = 1; N = 20	0.51 [-0.38, 1.40]	N/A	Very low[1,2,3]	Appendix 15 cii (14.2)
Neurological: SAS	JENSEN2008	K = 1; N = 20	-0.43 [-1.32, 0.46]	N/A	Very low[1,2,3]	Appendix 15 cii (14.3)
Neurological: Akathisia (RR)	JENSEN2008	K = 1; N = 20	2.00 [0.21, 18.69]	N/A	Very low[1,2,3]	Appendix 15 cii (14.4)
Leaving the Study Early for	JENSEN2008	K = 1; N = 20	1.00 [0.34, 2.93]	N/A	Very low[1,2,3]	Appendix 15 cii (14.5)

Any Reason (RR)						

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including open label trial, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.12.2.5 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 3-arm trial (also including risperidone) in children and young people with psychosis or schizophrenia with a mean age of 14.8 years. An overview of study characteristics can be found in Table 78 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 78 provides a summary evidence profile 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 or schizophrenia. No significant differences between treatment groups on efficacy outcomes were found.

Table 78: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Number of studies / participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	SIKICH2004	K = 1; N = 31	-0.68 [-1.41, 0.05]	N/A	Very low[1,2,3]	Appendix 15 cii (15.1)
Positive Symptoms (SMD)	SIKICH2004	K = 1; N = 31	-0.58 [-1.30, 0.14]	N/A	Very low[1,2,3]	Appendix 15 cii (15.2)
Negative Symptoms (SMD)	SIKICH2004	K = 1; N = 31	0.00 [-0.70, 0.70]	N/A	Very low[1,2,3]	Appendix 15 cii (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 15 cii (15.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including inadequate allocation concealment, unclear blinding procedures, trial registration could not be found)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400

participants) not met.

Side effects

Table 79 provides a summary evidence profile 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 or schizophrenia. A small, significant difference, favouring olanzapine over haloperidol was found for SAS scores (SMD = -0.73, -1.46 to -0.00). No further significant differences were found on any other side effect outcome assessed.

Table 79: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Number of studies / participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	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 15 cii (16.1)
Metabolic: BMI (SMD)	SIKICH2004	K = 1; N = 31	-0.21 [-0.92, 0.50]	N/A	Very low[1,2,3]	Appendix 15 cii (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 15 cii (16.3)
Neurological: SAS (SMD)	SIKICH2004	K = 1; N = 31	-0.73 [-1.46, -0.00]*	N/A	Very low[1,2,3]	Appendix 15 cii (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 15 cii (16.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
[1] Serious risk of bias (including inadequate allocation concealment, unclear blinding procedures, trial registration could not be found)
[2] Serious risk of reporting bias
[3]Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.12.3 Antipsychotic medications administered at different doses

Five RCTs (N = 861) providing relevant clinical evidence for antipsychotic medication administered at different doses for the treatment of the acute episode were identified (AZD144C00112; FINDLING2008A; HAAS2009; HAAS2009B; SINGH2011) (see Table 80). All studies were conducted in children and young people experiencing an acute episode of psychosis or schizophrenia aged 18 years and younger and reported at least one outcome in sufficient detail to allow for

extraction and analysis. There were a total of seven comparisons: quetiapine 400.0 mg per day versus quetiapine 800.0 mg per day (AZD144C00112), aripiprazole 10.0 mg per day versus aripiprazole 30.0 mg per day (FINDLING2008A), risperidone 1.0-3.0 mg per day versus risperidone 4.0-6.0 mg per day (HAAS2009B), risperidone 0.15-0.6 mg per day versus risperidone 1.5-6.0 mg per day (HAAS2009), paliperidone 1.5 mg per day versus paliperidone 3.0-6.0 mg per day (SINGH2011), paliperidone 1.5 mg per day versus paliperidone 6-12 mg per day (SINGH2011), and paliperidone 3.0-6.0 mg per day versus paliperidone 6.0-12.0 mg per day (SINGH2011).

Table 80: Included 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 or schizophrenia

Medication dose (mg per day)	**Quetiapine 400.0 mg per day versus 800.0 mg per day**	**Aripiprazole 10.0 mg per day versus 30.0 mg per day**	**Risperidone 1.0-3.0 mg per day versus 4.0-6.0 mg per day**	**Risperidone 0.15-0.6 mg per day versus 1.5-6.0 mg per day**	**Paliperidone 1.5 mg per day versus 3.0-6.0 mg per day versus 6.0-12.0 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(s)	AstraZenecaD1441C00112	FINDLING2008A	HAAS2009B	HAAS2009	SINGH2011
Diagnosis	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia	Schizophrenia
Prior Antipsychotic Use (% naive prior to intervention)	NR	51.7	NR	NR	36% and 60% atypical and typical, respectively
Mean (range) Age (years)	15.4 (13.0 to 17.0)	15.5 (NR)	15.6 (13.0 to 17.0)	15.6 (13.0 to 17.0)	15.4 (NR)
Sex (% male)	59	57	64	56	59
Ethnicity (% Caucasian)	61	37	53	85	68
Treatment length (weeks)	6	6	6	8	6
Length of follow-up (weeks)	6	6	6	8	6
Setting	In- and outpatients	In- and outpatients	In- and outpatients	In- and outpatients	In- and outpatients
Country	43 international sites, including the US and Asia	US, Europe, South America, Asia, the Caribbean, and 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

7.12.3.1 Clinical evidence for quetiapine 400 mg per day versus quetiapine 800 mg per day for treatment of the acute episode

One trial (AZD1441C00112) (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 (range) age of 15.4 (13 to 17) years was identified. An overview of study characteristics can be found in Table 81 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 81 provides a summary evidence profile for efficacy outcomes reported at treatment endpoint associated with quetiapine 400.0 mg per day versus quetiapine 800.0 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. No significant differences in efficacy outcomes were found between the two different doses administered.

Side effects

Table 82 provides a summary evidence profile for side effect outcomes reported at treatment endpoint associated with quetiapine 400.0 mg per day versus quetiapine 800.0 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. No significant differences in side effects were found between the two different doses administered.

Table 81: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	**STUDY ID**	**Studies/number of participants**	**Effect Estimate (SMD or RR)**	**Heterogeneity**	**Quality**	**Forest plot**
Total Symptoms (SMD)	AstraZenecaD1441C0012	K = 1; N = 109	0.07 [-0.31, 0.44]	N/A	Very low	Appendix 14d cii (16.1)
Positive Symptoms (SMD)	AstraZenecaD1441C0012	K = 1; N = 109	0.16 [-0.22, 0.53]	N/A	Very low	Appendix 14d cii (16.2)
Negative Symptoms (SMD)	AstraZenecaD1441C0012	K = 1; N = 109	-0.03 [-0.40, 0.35]	N/A	Very low	Appendix 14d cii (16.3)
Global State (Severity) (SMD)	AstraZenecaD1441C0012	K = 1; N = 110	0.14 [-0.23, 0.51]	N/A	Very low	Appendix 14d cii (16.4)
Depression (SMD)	AstraZenecaD1441C0012	K = 1; N = 109	0.09 [-0.29, 0.46]	N/A	Very low	Appendix 14d cii (16.5)
Psychosocial Functioning (SMD)	AstraZenecaD1441C0012	K = 1; N = 128	0.15 [-0.19, 0.50]	N/A	Very low	Appendix 14d cii (16.6)
Response (RR)	AstraZenecaD1441C0012	K = 1; N = 110	1.06 [0.78, 1.46]	N/A	Very low	Appendix 14d cii (16.7)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, participants and providers blind, but unclear if raters blind; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 82: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Metabolic: Weight kg (SMD)	AstraZenecaD1441C0012	K = 1; N = 105	-0.05 [-0.37, 0.28]	N/A	Very low[1,2,3]	Appendix 14d cii (17.1)
Metabolic: Fasting Serum Glucose Level mg per dl (SMD)	AstraZenecaD1441C0012	K = 1; N = 138	0.12 [-0.21, 0.46]	N/A	Very low[1,2,3]	Appendix 14d cii (17.3)
Metabolic: Fasting Total Cholesterol mg per dl	AstraZenecaD1441C0012	K = 1; N = 121	0.01 [-0.34, 0.37]	N/A	Very low[1,2,3]	Appendix 14d cii (17.4)
Metabolic: Fasting High-Density Lipoprotein Cholesterol mg per dl (SMD)	AstraZenecaD1441C0012	K = 1; N = 125	0.04 [-0.31, 0.39]	N/A	Very low[1,2,3]	Appendix 14d cii (17.5)
Metabolic: Fasting Low-Density Lipoprotein Cholesterol mg per dl (SMD)	AstraZenecaD1441C0012	K = 1; N = 122	0.17 [-0.18, 0.53]	N/A	Very low[1,2,3]	Appendix 14d cii (17.6)
Metabolic: Fasting Triglycerides	AstraZenecaD1441C0012	K = 1; N = 122	-0.10 [-0.46, 0.25]	N/A	Very low[1,2,3]	Appendix 14d cii (17.7)
Cardio: QT Interval (SMD)	AstraZenecaD1441C0012	K = 1; N = 128	0.29 [-0.06, 0.64]	N/A	Very low[1,2,3]	Appendix 14d cii (17.8)
Cardio: QT Interval (RR) (Prolonged QT interval)	AstraZenecaD1441C0012	K = 1; N = 147	1.01 [0.06, 15.90]	N/A	Very low[1,2,3]	Appendix 14d cii (17.9)
Cardio: Systolic BP (SMD)	AstraZenecaD1441C0012	K = 1; N = 147	0.26 [-0.07, 0.58]		Very low[1,2,3]	Appendix 14d cii (17.10)
Cardio: Diastolic BP (SMD)	AstraZenecaD1441C0012	K = 1; N = 147	0.10 [-0.22, 0.43]		Very low[1,2,3]	Appendix 14d cii (17.11)
Cardio: Tachycardia (RR)	AstraZenecaD1441C0012	K = 1; N = 147	0.68 [0.20, 2.30]		Very low[1,2,3]	Appendix 14d cii (17.12)
Cardio: Standing Pulse (SMD)	AstraZenecaD1441C0012	K = 1; N = 147	0.27 [-0.06, 0.59]		Very low[1,2,3]	Appendix 14d cii (17.13)
Hormonal: Prolactin (SMD)	AstraZenecaD1441C0012	K = 1; N = 123	-0.12 [-0.48, 0.23]		Very	Appendix 14d cii (17.14)

					low[1,2,3]	
Hormonal: Insulin (SMD)	AstraZenecaD1441C0012	K = 1; N = 121	0.17 [-0.19, 0.52]		Very low[1,2,3]	Appendix 14d cii (17.16)
Neurological: Akathisia (RR)	AstraZenecaD1441C0012	K = 1; N = 147	1.01 [0.21, 4.86]		Very low[1,2,3]	Appendix 14d cii (17.19)
Neurological: Extrapyramidal Disorder (RR)	AstraZenecaD1441C0012	K = 1; N = 148	1.03 [0.07, 16.12]		Very low[1,2,3]	Appendix 14d cii (17.20)
Leaving the Study Early for Any Reason (RR)	AstraZenecaD1441C0012	K = 1; N = 147	1.33 [0.70, 2.53]		Very low[1,2,3]	Appendix 14d cii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, participants and providers blind, but unclear if raters blind; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.12.3.2 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 (range) age of 15.5 (NR) years. An overview of study characteristics can be found in Table 83(included study information table for trials comparing antipsychotic medication administered at different doses in the treatment of an acute episode in children and young people with psychosis or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 83 provides a summary evidence profile 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 or schizophrenia. The only significant differences between the two doses of aripiprazole administered was on quality of life and favored 30 mg per day over 10 mg per day (SMD = 0.63, 0.42 to 0.84).

Table 83: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	FINDLING2008A	K = 1; N = 198	0.13 [-0.15, 0.41]	N/A	Very low[1,2,3]	Appendix 14d cii (16.1)
Global State (Severity) (SMD)	FINDLING2008A	K = 1; N = 196	0.10 [-0.18, 0.38]	N/A	Very low[1,2,3]	Appendix 14d cii (16.4)
Quality of Life (SMD)	FINDLING2008A	K = 1; N = 196	0.63 [0.42, 0.84]*	N/A	Very low[1,2,3]	Appendix 14d cii (16.8)
Psychosocial Functioning (SMD)	FINDLING2008A	K = 1; N = 198	0.01 [-0.27, 0.29]	N/A	Very low[1,2,3]	Appendix 14d cii (16.6)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours Aripiprazole 30mg per day
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Side effects

Table 84 provides a summary evidence profile 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 or schizophrenia. A significant differences 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, 0.28 to 0.84). No other significant differences between doses for side effect outcomes were found.

Table 84: Summary evidence profile 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 or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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 14d cii (17.1)
Metabolic: BMI (SMD)	FINDLING2008A	K = 1; N = 196	0.00 [-0.28, 0.28]	N/A	Very low[1,2,3]	Appendix 14d cii (17.2)
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 14d cii (17.3)
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 14d cii (17.4)
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 14d cii (17.5)
Metabolic: Fasting Triglycerides	FINDLING2008A	K = 1; N = 87	-0.08 [-0.50, 0.35]	N/A	Very low[1,2,3]	Appendix 14d cii (17.7)
Cardio: QT Interval (SMD)	FINDLING2008A	K = 1; N = 196	0.28 [-0.00, 0.56]	N/A	Very low[1,2,3]	Appendix 14d cii (17.8)
Hormonal: Prolactin	FINDLING2008A	K = 1; N = 190	0.13 [-0.16, 0.41]	N/A	Very low[1,2,3]	Appendix 14d cii (17.14)
Neurological: Parkinsonism (RR)	FINDLING2008A	K = 1; N = 200	0.48 [0.28, 0.84]*	N/A	Very low[1,2,3]	Appendix 14d cii (17.23)
Neurological: Akathisia (RR)	FINDLING2008A	K = 1; N = 200	0.50 [0.20, 1.28]	N/A	Very low[1,2,3]	Appendix 14d cii (17.19)
Neurological: Dystonia (RR)	FINDLING2008A	K = 1; N = 200	2.00 [0.37, 10.67]	N/A	Very low[1,2,3]	Appendix 14d cii (17.22)
Mortality (RR)	FINDLING2008A	K = 1; N = 200	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14d cii (17.26)
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 14d cii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours Aripiprazole 10mg per day
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design; study reports LOCF analysis, but the number of participants included in reports results suggests available case was used)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.12.3.3 Clinical evidence for risperidone 1-3 mg per day versus risperidone 4-6 mg per day for treatment of the acute episode

One trial (HAAS2009) (N = 106) assessing risperidone at different doses (1-3 mg per day versus 4-6 mg per day) in children and young people with psychosis or schizophrenia with a mean (range) age of 15.6 (13 to 17) years was identified. An overview of study characteristics can be found in Table 85 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 85 provides a summary evidence profile for efficacy outcomes reported at treatment endpoint associated with risperidone 1-3 mg per day versus risperidone 4-6 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. No significant differences in efficacy outcomes were found between the two different doses administered.

Table 85: Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with risperidone 1-3 mg per day versus risperidone 4-6 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Positive Symptoms (SMD)	HAAS2009B	K = 1; N = 104	0.03 [-0.35, 0.42]	N/A	Very low[1,2,3]	Appendix 14d cii (16.2)
Negative Symptoms (SMD)	HAAS2009B	K = 1; N = 104	-0.09 [-0.47, 0.30]	N/A	Very low[1,2,3]	Appendix 14d cii (16.3)
Psychosocial Functioning (SMD)	HAAS2009B	K = 1; N = 99	-0.12 [-0.51, 0.28]	N/A	Very low[1,2,3]	Appendix 14d cii (16.6)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Side effects

Table 86 provides a summary evidence profile for side effect outcomes reported at treatment endpoint associated with risperidone 1-3 mg per day versus risperidone 4-

6 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. Small, significant differences, favoring 1-3 mg per day risperidone over 4-6 mg per day risperidone were found for weight (SMD = -0.44, -0.69 to -0.19), prolactin level (SMD = -0.41, -0.79 to -0.02) and SAS scores (SMD = -0.39, -0.78 to -0.01). No other significant effects were found for side effect outcomes reported.

Table 86: Summary evidence profile for side effect outcomes reported at treatment endpoint associated with risperidone 1-3 mg per day versus risperidone 4-6 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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 14d cii (17.1)
Cardio: Tachycardia (RR)	HAAS2009B	K = 1; N = 106	1.39 [0.24, 7.99]	N/A	Very low[1,2,3]	Appendix 14d cii (17.12)
Hormonal: Prolactin (SMD)	HAAS2009B	K = 1; N = 106	-0.41 [-0.79, -0.02]*	N/A	Very low[1,2,3]	Appendix 14d cii (17.14)
Neurological: AIMS (SMD)	HAAS2009B	K = 1; N = 109	0.23 [-0.15, 0.61]	N/A	Very low[1,2,3]	Appendix 14d cii (17.17)
Neurological: SAS (SMD)	HAAS2009B	K = 1; N = 106	-0.39 [-0.78, -0.01]*	N/A	Very low[1,2,3]	Appendix 14d cii (17.18)
Neurological: Extrapyramidal Disorder (RR)	HAAS2009B	K = 1; N = 106	0.58 [0.20, 1.66]	N/A	Very low[1,2,3]	Appendix 14d cii (17.19)
Neurological: Extrapyramidal Symptoms (RR)	HAAS2009B	K = 1; N = 106	0.83 [0.50, 1.39]	N/A	Very low[1,2,3]	Appendix 14d cii (17.21)
Mortality (RR)	HAAS2009B	K = 1; N = 106	Not estimable (no events in either group)	N/A	Very low[1,2,3]	Appendix 14d cii (17.27)
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 14d cii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 1-3 mg per day
[1] Serious risk of bias (including unclear sequence generation, unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design, missing outcomes data)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.12.3.4 Clinical evidence for risperidone 0.15-0.6 mg per day versus risperidone 1.5-6.0 mg per day for treatment of the acute episode

One trial (HAAS2009) (N = 257) assessing risperidone at 0.15-0.6 mg per day versus 1.5-6.0 mg per day in children and young people with schizophrenia with a mean (range) age of 15.6 (13 to 17) years was identified. An overview of study characteristics can be found in Table 87 (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 87 provides a summary evidence profile for efficacy outcomes reported at treatment endpoint associated with risperidone 0.15-0.6 mg per day versus risperidone 1.5-6.0 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. Small significant differences, favoring 1.5-6.0 mg per day over 0.15-0.6 mg per day were found on all efficacy outcomes measured, including total symptoms (SMD = 0.34, 0.09 to 0.59), positive symptoms
(SMD = 0.42, 0.17 to 0.67), negative symptoms (SMD = 0.42, 0.17 to 0.67) and global sate (SMD = 0.41, 0.16 to 0.66).

Table 87: Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with risperidone 0.15-0.6 mg per day versus risperidone 1.5-6.0 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Total Symptoms (SMD)	HAAS2009	K = 1; N = 256	0.34 [0.09, 0.59]*	N/A	Very low[1,2,3]	Appendix 14d cii (16.1)
Positive Symptoms (SMD)	HAAS2009	K = 1; N = 256	0.42 [0.17, 0.67] *	N/A	Very low[1,2,3]	Appendix 14d cii (16.2)
Negative Symptoms (SMD)	HAAS2009	K = 1; N = 256	0.42 [0.17, 0.67] *	N/A	Very low[1,2,3]	Appendix 14d cii (16.3)
Global State (Severity) (SMD)	HAAS2009	K = 1; N = 256	0.41 [0.16, 0.66] *	N/A	Very low[1,2,3]	Appendix 14d cii (16.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
*Favours 1.5-6.0 mg per day
[1] Serious risk of bias (including unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met

Side effects

Table 88 provides a summary evidence profile for side effect outcomes reported at treatment endpoint associated with risperidone 0.15-0.6 mg per day versus risperidone 1.5-6.0 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. Small significant differences were found, favouring 0.15-0.6 mg per day over 1.5-6.0 mg per day on elevated prolactin level (RR: 0.74, 0.58 to 0.96), number of participants experiencing an extrapyramidal symptom (RR = 0.30, 0.17 to 0.53), dystonia (RR = 0.33, 0.15 to 0.71) and tremor (RR = 0.29, 0.10 to 0.87).

Table 88: Summary evidence profile for side effect outcomes reported at treatment endpoint associated with risperidone 0.15-0.6 mg per day versus risperidone 1.5-6.0 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	STUDY ID	Studies/number of participants	Effect Estimate (SMD or RR)		Quality	Forest plot
Hormonal: Prolactin Level (RR)	HAAS2009	K = 1; N = 257	0.74 [0.58, 0.96]*		Very low[1,2,3]	Appendix 14d cii (17.15)
Neurological: Extrapyramidal Symptoms (RR)	HAAS2009	K = 1; N = 157	0.30 [0.17, 0.53]*		Very low[1,2,3]	Appendix 14d cii (17.21)
Neurological: Symptoms of Parkinsonism (RR)	HAAS2009	K = 1; N = 157	0.09 [0.00, 1.54]		Very low[1,2,3]	Appendix 14d cii (17.24)
Neurological: Tremor (RR)	HAAS2009	K = 1; N = 157	0.29 [0.10, 0.87]*		Very low[1,2,3]	Appendix 14d cii (17.26)
Neurological: Dystonia (RR)	HAAS2009 B	K = 1; N = 157	0.33 [0.15, 0.71]*		Very low[1,2,3]	Appendix 14d cii (17.22)
Neurological: Dyskinesia (RR)	HAAS2009	K = 1; N = 157	0.27 [0.06, 1.28]		Very low[1,2,3]	Appendix 14d cii (17.25)
Leaving the Study Early for Any Reason (RR)	HAAS2009	K = 1; N = 157	1.35 [0.95, 1.93]		Very low[1,2,3]	Appendix 14d cii (17.28)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 0.15-0.6 mg per day
[1] Serious risk of bias (including unclear allocation concealment, unclear whether participants, providers or raters were blinded in the double-blind design, unable to extract all outcomes)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.12.3.5 Clinical evidence for paliperidone 1.5 mg per day versus paliperidone 3-6 mg per day versus paliperidone 6-12 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 3-6 mg per day versus 6-12 mg per day) in children and young people with schizophrenia was identified. The mean (range) age of the sample was 15.4 (NR) years. An overview of study characteristics can be found in Table 89 included 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 or schizophrenia and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 89 provides a summary evidence profile for efficacy outcomes reported at treatment endpoint associated with paliperidone 1.5 mg per day versus paliperidone 3-6 mg per day versus paliperidone 6-12 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. Small, significant differences were found, favoring 3-6 mg per day versus 1.5 mg per day on total symptoms (SMD = 0.48, 0.09 to 0.88), positive symptoms (SMD = 0.48, 0.08 and 0.87) and psychosocial functioning (SMD = 0.76, 0.36 to 1.16), but no other differences between the three different doses of paliperidone were found.

Table 89: Summary evidence profile for efficacy outcomes reported at treatment endpoint associated with paliperidone 1.5 mg per day versus paliperidone 3-6 mg per day versus paliperidone 6-12 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	STUDY ID	Dose comparison	Studies/number of participants	Effect Estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Total Symptoms (SMD)	SINGH 2011	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 14d cii (16.1)
		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 14d cii (19.1)
		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 14d cii (18.1)
Positive Symptoms (SMD)	SINGH 2011	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 14d cii (16.2)
		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 14d cii (19.2)
		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 14d cii (18.2)
Negative Symptoms (SMD)	SINGH 2011	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 14d cii (16.3)
		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 14d cii (19.3)
		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 14d cii (18.3)
Depression (SMD)	SINGH 2011	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 14d cii (16.5)
		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 14d cii (19.4)
		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 14d cii (18.4)
Psychosocial Functioning (SMD)	SINGH 2011	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 14d cii (16.6)
		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 14d cii (19.5)
		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 14d cii (18.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 3-6mg per day
[1] Serious risk of bias (including some outcomes not reported; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Side effects

Error! Reference source not found. provides a summary evidence profile for side effect outcomes reported at treatment endpoint associated with paliperidone 1.5 mg per day versus paliperidone 3-6 mg per day versus paliperidone 6-12 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia. Small to moderate, significant differences were found for weight, favoring 1.5 mg per day over 3-6 mg per day (SMD = -0.43, -0.83 to -0.04) and 1.5 mg per day over 6-12 mg per day (SMD = -0.59, -0.99 to -0.19); and for prolactin level favouring 1.5 mg per day over 3-6 mg per day (SMD = -0.62, -1.03 to -0.20) and 1.5 mg per day over 6-12 mg per day (SMD = -0.53, -0.94 to -0.11).

Table 90: Summary evidence profile for side effect outcomes reported at treatment endpoint associated with paliperidone 1.5 mg per day versus paliperidone 3-6 mg per day versus paliperidone 6-12 mg per day in the treatment of the acute episode in children and young people with psychosis or schizophrenia

Outcome or Subgroup	**STUDY ID**	Dose comparison	**Number of studies / participants**	**Effect Estimate (SMD or RR)**	**Heterogeneity**	**Quality**	**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 14d cii (17.1)
		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 14d cii (21.1)
		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 14d cii (20.1)
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 14d cii (17.9)
		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 14d cii (21.2)
		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 14d cii (20.2)
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 14d cii (17.12)
		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 14d cii (21.3)
		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 14d cii (20.3)
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 14d cii (17.14)
		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 14d cii (21.4)
		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 14d cii (20.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours 1.5 mg per day
[1] Serious risk of bias (including missing outcomes data; each treatment group exposed to treatment for different lengths of time)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.13 CLINICAL EVIDENCE SUMMARY FOR TREATMENT OF THE ACUTE EPISODE

In 13 RCTs, with a total of 1,524 participants experiencing an acute episode of psychosis or schizophrenia, the evidence suggests there are small differences in efficacy favouring antipsychotic medication over placebo, including symptoms, global state and psychosocial functioning. We found no evidence for differences in efficacy between antipsychotics and only minimal differences in efficacy between different doses of the same antipsychotic medication. Placebo was consistently favoured over an antipsychotic on weight 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 or 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 or schizophrenia.

7.14 CLINICAL EVIDENCE SUMMARY FROM THE ADULT GUIDELINE FOR TREATMENT OF THE ACUTE EPISODE

In 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. Metabolic and neurological side effects were consistent with those reported in the SPC for each drug (NCCMH, 2010).

SECTION 3: ANTIPSYCHOTICS IN CHILDREN AND YOUNG PEOPLE WHO HAVE NOT RESPONDED ADEQUATELY TO PHARMACOLOGICAL TREATMENT

7.15 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 strategy 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, 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 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 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, 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. An adequate trial will involve titrating the dosage to achieve a target plasma level, usually considered to be above 350 mg per l, 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 NICE, 2009a, 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). Secondly, 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). Thirdly, 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).

7.16 CLINICAL REVIEW PROTOCOL FOR CHILDREN AND YOUNG PEOPLE WHO HAVE NOT RESPONDED ADEQUATELY TO PHARMACOLOGICAL TREATMENT

The review protocol (see Table 91), including the review questions, information about the databases searched, and the eligibility criteria used for this section of the guideline, can be found in Appendix 8 (further information about the search strategy can be found in Appendix 9).

Table 91: Clinical review protocol for the review of antipsychotics in the treatment of the acute episode in children and young people

Review questions	1. 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 who have not responded adequately to pharmacological treatment? 2. Are children and young people who have not responded adequately to pharmacological treatment, more susceptible to side effects of antipsychotic medication, compared with adults (in particular, the metabolic, neurological and cognitive impairments)? 3. For children and young people who have 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? 4. Does the most appropriate treatment strategy in cases where antipsychotic medication is effective but not tolerated, differ between children and young people with schizophrenia compared with adults with schizophrenia?

Objectives	To provide evidence based recommendations, via GDG-consensus, regarding the pharmacological (antipsychotic) treatment and management of children and young people with psychosis or schizophrenia who have not responded adequately to pharmacological treatment, including a review of NICE Clinical Guidance 82 for its relevancy to children and young people.
Population	**Inclusion** Children and young people (aged 18 years and younger) with psychosis or schizophrenia, who have not responded adequately to pharmacological treatment. Consideration will be given to studies in which the study sample consists of children and young people meeting the above criteria AND with a mean age of 25 years and younger. Consideration will also be given to the specific needs of children and young people with schizophrenia and a mild learning disability; and children and young people 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 or 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 or schizophrenia). • 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
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 events (including effects on metabolism; extrapyramidal side effects; hormonal changes; and , cardiotoxicity) • Remission
Electronic databases	1, 3 and 4:

	Mainstream databases: Embase, MEDLINE, PreMEDLINE, 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 2: Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic specific databases: CDSR*, CENTRAL, DARE*
Date searched	SR: 1995 to May 2012; RCTs: inception of databases to May 2012
Study design	SR, 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 18 years. The review will seek to identify whether modifications in treatment and management of children aged 13 years and younger need to be made. • 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. Published data will not be included when evidence submitted is commercial in confidence.

7.17 STUDIES CONSIDERED[61]

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 or schizophrenia who have not responded adequately to pharmacological treatment (KUMRA1996; KUMRA2008A; SHAW2006). 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 or schizophrenia in

[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).

children and young people and excluded from the review. Further information about both included and excluded studies can be found in Appendix 14.

All included RCTs compared clozapine with another antipsychotic medication: clozapine versus haloperidol (KUMRA1996) or clozapine versus olanzapine (KUMRA2008A; SHAW2006). Study characteristics for these studies can be found in Table 92.

Table 92: Study information table for trials comparing clozapine with another antipsychotic in children and young people with psychosis or 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(s)	KUMRA2008A SHAW2006	KUMRA1996
Diagnosis	KUMRA2008A: Schizophrenic disorder SHAW2006: Schizophrenia	Schizophrenia
Definition of inadequate response	KUMRA2008A: 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 SHAW2006: Failure to respond to 2 antipsychotic medications (typical or atypical, not including clozapine or olanzapine) used at adequate doses (>100- mg chlorpromazine equivalents) and for adequate duration (>4 weeks unless terminated owing to intolerable adverse effects). Failure was defined as insufficient response with persistence of symptoms significantly impairing the child's functioning according to child, parental, medical, and school reports or intolerable adverse effects.	NR
Mean (range) Age (years)	KUMRA2008A: 15.6 (NR) SHAW2006: 12.3 (7.0 to 16.0)	14.1 (NR)
Sex (% male)	KUMRA2008A: 54 SHAW2006: 60	52
Ethnicity (% Caucasian)	KUMRA2008A: 21 SHAW2006: 56	NR
Mean (range) medication dose (mg per day)	KUMRA2008A: *Clozapine:* 403.1 (25.0 to 900.0) *Olanzapine:* 26.2 (5.0 to 30.0) SHAW2006: *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)	KUMRA2008A: 12 SHAW2006: 8	6
Length of follow-up (weeks)	KUMRA2008A: 12 SHAW2006: 8	104
Setting	KUMRA2008A: In- and outpatient	Participants were

	SHAW2006: Inpatient	identified though national recruitment via professional and patient advocacy organizations
Country	KUMRA2008A: US SHAW2006: US	US
Funding	KUMRA2008A: NR SHAW2006: NR	NR
Note. NR = not reported. [1] Extractable outcomes.		

7.17.1 Clozapine versus another antipsychotic drug in children and young people with psychosis or 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). Of the two trials reporting a definition of inadequate response, both excluded participants who had previously inadequately responded to the Table 93 study treatments. An overview of study characteristics can be found in (included 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 or schizophrenia) and detailed study characteristics can be found in Appendix 14.

Efficacy

Table 93 provides a summary evidence profile for efficacy outcomes reported associated with clozapine versus another antipsychotic in children and young people. 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 between participants treated with clozapine and participants treated with another antipsychotic (olanzapine or haloperidol) on total symptoms (SMD = 0.50, 0.06 to 0.94), positive symptoms (SMD = 0.71, 0.27 to 1.16) and negative symptoms (SMD = 0.53, 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, 0.07 to 1.38). A small significant difference was found for global state, with clozapine favoured over another antipsychotic (SMD = 0.51, 0.01 to 1.01), however no significant differences was found between clozapine and another treatment for psychosocial functioning.

Table 93: Summary evidence profile for efficacy outcomes reported associated with clozapine versus another antipsychotic in children and young people at treatment endpoint

Outcome or Subgroup	STUDY ID	Number of studies/ participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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[1,2,4]	Appendix 15 ciii (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[1,2,4]	Appendix 15 ciii (1.2)
Positive Symptoms (SMD)	KUMRA1996; KUMRA2008A; SHAW2006	K = 3; N = 85	0.71 [0.27, 1.16] *	(P = 0.49); I^2 = 0%	Very Low[1,2,4]	Appendix 15 ciii (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[1,2,4]*	Appendix 15 ciii (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[1,2,4]	Appendix 15 ciii (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[1,2,4]*	Appendix 15 ciii (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[1,2,4]	Appendix 15 ciii (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 15 ciii (1.8)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours clozapine
[1]Downgraded due to risk of bias (including: method of allocation concealment unclear, blinding of raters unclear; ITT method of analysis unclear or available case analysis used, eligibility criteria states that patients must be not be treatment refractory to treatment of study meds, not all data reported sufficiently to allow for extraction and analysis and trial registration could not be found)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] $I^2 \geq 50\%$, $p<.05$

Side effects

Table 94 provides a summary evidence profile for side effect outcomes reported associated with clozapine versus another antipsychotic in children and young people. A moderate significant difference was found favouring olanzapine over clozapine for fasting serum glucose level (SMD = -0.79, -1.45 to -0.12). A significant difference favouring clozapine over haloperidol was found for the number of people experiencing tachycardia (RR = 4.80, 1.30 to 17.66), but no difference was found between haloperidol and clozapine on this outcome (RR = 0.18, 0.01 to 3.41). No other significant differences were found between clozapine and another antipsychotic on side effect outcomes reported.

Table 94: Summary evidence profile for side effect outcomes reported associated with clozapine versus another antipsychotic in children and young people at treatment endpoint

Outcome or subgroup	STUDY ID	Studies/ number of participants	Effect Estimate (SMD or RR)	Hetero-geneity	Quality	Forest plot
Metabolic: Weight kg (SMD)	SHAW2006	K = 1; N = 25	-0.04 [-0.82, 0.75]	N/A	Low[1,2]	Appendix14 ciii (2.1)
Metabolic: BMI (SMD)	SHAW2006; KUMRA2008A	K = 2; N = 63	0.03 [-0.47, 0.52]	(P = 0.70); I^2 = 0%	Low[1,2]	Appendix14 ciii (2.2)
Metabolic: Fasting Serum Glucose Level mg per dl (SMD)	KUMRA2008A	K = 1; N = 38	-0.79 [-1.45, -0.12]*	N/A	Low[1,2]	Appendix14 ciii (2.3)
Metabolic: Fasting Total Cholesterol mg per dl (SMD)	KUMRA2008A	K = 1; N = 38	0.31 [-0.34, 0.95]	N/A	Low[1,2]	Appendix14 ciii (2.4)
Metabolic: Fasting Triglycerides mg per dl (SMD)	KUMRA2008A	K = 1; N = 38	-0.28 [-0.92, 0.37]	N/A	Low[1,2]	Appendix14 ciii (2.5)
Cardio: Tachycardia (RR)	KUMRA1996	K = 1; N = 21	0.18 [0.01, 3.41]	N/A	Low[1,2]	Appendix14 ciii (2.6)
	SHAW2006	K = 1; N = 22	4.80 [1.30, 17.66]**	N/A	Low[1,2]	Appendix14 ciii (2.6)
Neurological: AIMS (SMD)	KUMRA1996	K = 1; N = 21	0.02 [-0.83, 0.88]	N/A	Low[1,2]	Appendix14 ciii (2.7)
Neurological: SAS (SMD)	KUMRA1996	K = 1; N = 21	0.66 [-0.23, 1.54]	N/A	Low[1,2]	Appendix14 ciii (2.8)
Leaving the Study Early for Any Reason (RR)	KUMRA1996; KUMRA2008A; SHAW2006	K = 1; N = 21	1.15 [0.43, 3.03]	(P = 0.35); I^2 = 6%	Low[1,2]	Appendix14 ciii (2.9)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
* Favours olanzapine
** Favours clozapine
[1]Downgraded due to risk of bias (including: method of allocation concealment unclear, blinding of raters unclear; ITT method of analysis unclear or available case analysis used, eligibility criteria states that patients must be not be treatment refractory to treatment of study meds, not all data reported sufficiently to allow for extraction and analysis and trial registration could not be found)
[2] Serious risk of reporting bias
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

7.18 CLINICAL EVIDENCE SUMMARY FOR CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS OR 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) with only one moderate differential effect in side effects found for fasting serum glucose level, favouring olanzapine over clozapine. However, the paucity of data and very low quality of the evidence means it is difficult to draw robust conclusions regarding relative efficacy and safety of antipsychotics in the treatment children and young people who have not adequately responded to treatment.

7.19 CLINICAL EVIDENCE SUMMARY FROM THE ADULT GUIDELINE IN PEOPLE WHOSE ILLNESS HAS NOT RESPONDED ADEQUATELY TO TREATMENT

In 18 RCTs including 2,554 participants whose illness had not responded adequately to treatment, clozapine had the most consistent evidence for efficacy over the FGAs included in the trials (NCCMH, 2010). Further evidence is required to establish equivalence between clozapine and any other SGA, and to establish 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.

SECTION 4: SIDE EFFECTS OF ANITPSYCHOTIC MEDICATION

7.20 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. Our review identified only three RCTs with a total of 95 participants aged 18 years and younger reporting side-effect data of 12 weeks or more (MOZES2006; JENSEN 2008; ARANGO2009). Detailed review of these studies, including information regarding study characteristics and analyses, has been provided in Sections 1 and 2 of this chapter. A summary of the RCT evidence of side effects associated with antipsychotic medication at 12 weeks or more is provided below. Forest plots and evidence profiles for each outcome can be found in Appendix 14 and Appendix 17, respectively.

7.20.1 Summary of RCT evidence of side effects associated with antipsychotic medication at 12 weeks or more

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 participants up over 12 (MOZES2006, JENSEN2008) or 26 weeks (ARANGO2009). No significant differences were found between any of the treatment groups across trials.

The scarcity of RCTs and extremely small sample sizes results in a limited evidence base from which clinical implications remain undetermined. 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 a search for observational study data associated with side effects occurring at 12 weeks or more.

7.21 OBSERVATIONAL STUDY DATA

The review focused on observational studies which included children and young people aged 18 years and younger with a diagnosis of psychosis or schizophrenia. Studies needed to report side-effect outcomes (metabolic, neurological [extrapyramidal], cardiotoxicity, hormonal) at 12 weeks or more to be included in the review. The following antipsychotic medications licensed for use in the UK for the treatment of children and young people with psychosis or schizophrenia were considered:

- amisulpride
- aripiprazole
- benperidol

- chlorpromazine hydrochloride
- clozapine
- flupentixol
- haloperidol
- levomepromazine
- olanzapine
- pericyazine
- pimozide
- prochlorperazine
- promazine hydrochloride
- quetiapine
- risperidone
- sulpiride
- trifluoperazine
- zuclopenthixol
- zuclopenthixol acetate.

We excluded studies including samples consisting of individuals with a formal diagnosis of any other psychiatric disorder (in whom different dosing schedules are administered) where results pertaining to participants with psychosis could not be extracted and reviewed.

7.22 STUDIES CONSIDERED

Seven observational studies, with a total of 470 children and young people aged 18 years and younger with psychosis or schizophrenia were identified that reported side effect outcome data at 12 weeks or more for four antipsychotics: quetiapine (K = 3; N = 246: AZD1441C00150; CASTRO-FORNILES2008; SCHIMMELMAN2007), risperidone (K = 2; N = 57: CASTRO-FORNILES2008; CROCQ2007), olanzapine (K = 5; N = 155: CASTRO-FORNILES2008, CROCQ2007, DITTMANN2008, ROSS2003) and clozapine (K = 1; N = 12: KUMRA1997). Data could be extracted and analysed in RevMan for two studies (CASTRO-FORNILES2008, CROCQ2007), whilst the remaining five studies are reported narratively (see Table 95 for a summary of study characteristics). In addition, 303 studies were excluded from the analysis. Further information about both included and excluded studies can be found in Appendix 14.

All included participants had psychosis or schizophrenia. The AZD1441C00150 trial included 54% bipolar disorder participants; however the data reviewed here pertains to the participants with schizophrenia only. Where reported the majority of participants were antipsychotic naive (apart from participants in the DITTMANN2008 trial in which 38% participants were antipsychotic naive), male, and Caucasian (except in the study conducted by KUMRA1997 in which 44% of the sample were Caucasian). 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 (ROSS2007). Two studies followed participants post-treatment: at 52 weeks (CASTRO-FORNILES2008) and 104 to 208

weeks (KUMRA1998). Participants were recruited from inpatient (CASTRO-FORNILES2008, SCHIMMELMAN2007, CROCQ2007) and outpatient settings (CASTRO-FORNILES2008, DITTMANN2008). KUMRA1998 recruited participants via professional and patient advocacy organisations. ROSS2007 did not report the study setting. All studies that reported sponsorship were industry funded.

Table 95: Study information table for observational studies investigating side effects of antipsychotic medication in children and young people with psychosis or 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(s)	(1) AZD1441C00150[1,2] (2) CASTRO-FORNILES2008[1,3] (3) SCHIMMELMAN2007[1]	(1) CASTRO-FORNILES2008[1,3] (2) CROCQ2007[1]	(1) CASTRO-FORNILES2008[1,3] (2) CROCQ2007[1] (3) DITTMANN2008[1,4] (4) ROSS2003[1]	KUMRA1997[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 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 (% naive prior to intervention)	(1) NR (2) 51 (3) 77	(1) 51 (2) 75	(1) 51 (2) 75 (3) 38 (4) 58	0
Mean (range) age (years)	(1) 14.4 (NR) (2) 15.5 (9.0-17.0) (3) 15.9 (12.0-17.9)	(1) 15.5 (range 9.0 to 17.0) (2) 15.2 (NR)	(1) 15.5 (9.0-17.0) (2) 15.2 (NR) (3) 15.5 (12.0-19.0)	14.2 (6.0-18.0)

			(4) 10.5 (6.0-15.0)	
% Male	(1) 60 (2) 67 SCHIMMELMAN2007: 68	(1) 67 (2) 58	(1) 67 (2) 58 (3) 71 ROSS2003: 74	56
% Caucasian	(1) 71 (2) 86 SCHIMMELMAN2007: 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 (NR) (3) 594.9 (50.0-800.0)	(1) 3.3 (NR) (2) 2.8 (NR)	(1) 11.6 (NR) (2) Standard Oral Tablets: 16.6 (NR) Orally Disintegrating tablets: 18.0 (NR) (3) 14.0 (10.0-20.0) (4) 7.7 (2.5-17.5)	176.0 (25.0-525.0)[6]
Treatment length (weeks)	(1) 26 (2) 26 (3) 12	(1) 26 CROCQ2007: 12	(1) 26 (2) 12 (3) 24 (4) 52	Unclear
Follow-up (weeks)	(1) 26 (2) 52 (3) 12	(1) 52 CROCQ2007: 12	(1) 52 (2) 12 (3) 24 (4) 52	104-208
Setting	(1) NR (2) In- and outpatient psychiatric units SCHIMMELMAN2007: 98% hospitalised	(1) In- and outpatient psychiatric units (2) Inpatient hospital	(1) In- and outpatient psychiatric units (2) Inpatient hospital (3) Inpatients during Phase I (6 weeks); outpatients during Phase II (18 weeks) (4) NR	NR (recruited via professional and patient advocacy organisations)
Country	(1) US (2) Spain (3) Germany	(1) Spain CROCQ2007: France	(1) Spain (2) France (3) Germany ROSS2003: US	US
Funding	(1) AstraZeneca (2) Non-industry funded (3) AstraZeneca	(1) NR (2) NR	(1) NR (2) NR (3) Lilly Deutschland (4) Veterans' Administration Research	NR

			Services; Public Health Service; Eli Lilly	

Note.
[1] Data is reported for the population characteristics of each study, not the population characteristics of each treatment group
[2] This trial also included bipolar patients with no psychotic symptoms and therefore we only extract and review data pertaining to those participants with schizophrenia.
[3] Data for the three most used antipsychotics during the first 6 months of follow-up is extracted and reviewed
[4] Error in reporting of 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 has been reviewed
[6] Reported for the sixth week of treatment

7.22.1 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-FORNILES2008; SCHIMMELMAN2007; CROCQ2007; DITTMANN2008; ROSS2003). Data could be extracted and analyzed in RevMan for two included studies (CASTRO-FORNILES2008; CROCQ2007) and Table 96 provides a summary of reported results. At 12 weeks or more, large, significant effects were found on weight and BMI, favouring both quetiapine (weight: SMD = -0.96, -1.73 to -0.18) and risperidone (weight: SMD = 1.75, 0.30 to 3.21; BMI: SMD = 2.17, 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, 0.36 to 1.69; BMI: SMD = 0.93, 0.27 to 1.59). Olanzapine administered as an orally disintegrating tablet resulted in significant less weight gain (SMD = -1.62, -2.54 to -0.69) and BMI increase (SMD = -1.06, -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.

Table 97 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 is significantly greater than patients treated with risperidone or quetiapine. Similarly significant BMI increases have been 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 have not been reported.

Table 96: Summary evidence profile for extractable metabolic side effect outcomes in children and young people

Outcome or subgroup	STUDY ID	Comparison	Studies/ number of participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest plot
Metabolic: Weight change kg (SMD)	CASTRO-FORNILES2008[1]	Quetiapine versus risperidone	K = 1; N = 46	-0.02 [-0.64, 0.60]	N/A	Very low[3,4,5]	Appendix 14 civ (1.1)
	CASTRO-FORNILES2008[1]	Quetiapine versus olanzapine	K = 1; N = 29	-0.96 [-1.73, -0.18]*	N/A	Very low[3,4,5]	Appendix 14 civ (1.2)
	CASTRO-FORNILES2008[1] CROCQ2007[2]	Olanzapine (SOT) versus risperidone	K = 2; N = 81	1.75 [0.30, 3.21]**	N/A	Very low[3,4,5]	Appendix14 civ (1.3)
	CROCQ2007[2]	Olanzapine (ODT) versus risperidone	K = ; N = 42	1.02 [0.36, 1.69]**	N/A	Very low[3,4,5]	Appendix 14 civ (1.4)
	CROCQ2007[2]	Olanzapine (SOT) versus olanzapine (ODT)	K = ; N = 26	-1.62 [-2.54, -0.69]***	N/A	Very low[3,4,5]	Appendix 14 civ (1.5)
Metabolic: BMI change (SMD)	CROCQ2007[2]	Olanzapine (SOT) versus risperidone	K = 1; N = 36	2.17 [1.27, 3.08]**	N/A	Very low[3,4,5]	Appendix 14 civ (2.1)
	CROCQ2007[2]	Olanzapine (ODT) versus risperidone	K = ; N = 42	0.93 [0.27, 1.59]**	N/A	Very low[3,4,5]	Appendix 14 civ (2.2)
	CROCQ2007[2]	Olanzapine (SOT) versus olanzapine (ODT)	K = 1; N = 26	-1.06 [-1.91, -0.21]***	N/A	Very low[3,4,5]	Appendix 14 civ (2.3)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
ODT: Orally disintegrating tablet
SOT: Standard oral tablet
*Favours quetiapine
**Favours risperidone
*** Favours olanzapine (ODT)
[1]26 weeks' treatment
[2]12 weeks' treatment
[3] Serious risk of bias (including: observational study)
[4] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Serious risk of reporting bias

Table 97: Summary of results for effect of antipsychotic medication on weight (kg) and BMI (kg per m^2)

K = 5 **N = 283**			
TP	**Study ID**	**Intervention**	**Results**
12 weeks	CROCQ2007	Olanzapine	Mean (SD) weight (kg) and BMI (kg per m^2) increased for all treatment groups at 12 weeks: *Weight* *BMI* Olanzapine SOT (n = 10): 8.9 (5.1) [3] 1.9 (0.6) [3] Olanzapine ODT (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] Significance (p) of difference between OLZ ODT and risperidone; and between OLZ ODT and OLZ SOT, respectively: [1] p = 0.002; p < 0.001. [2] p = 0.003; p = 0.001. [3]Significance in differences unclear/not reported
	ROSS2003	Olanzapine	Mean weight (kg) increases were significant (p<0.001) at each time point from baseline to 12 weeks (measure of variance not reported): 3 weeks: 1.6 6 weeks: 3.8 13 weeks: 4.2
	SCHIMMELMAN2007	Quetiapine	Mean (SD) weight (kg) and BMI (kg/m^2) 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/m^2)*: 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 time (3, 6, 13, 26 weeks) point from baseline; but did not significantly change from 6 months to 1 year (mean changes not reported).
	CASTRO-FORNILES2008	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 events who gained weight at 26 weeks was 30.2%. Of those patients with possible olanzapine related treatment emergent adverse events (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. OLZ ODT = olanzapine disintegrating tablet; OLZ SOT = olanzapine standard oral tablet			

Fasting serum glucose level

One study included 161 participants in an analysis of fasting serum glucose level associated with treatment for quetiapine at 26 weeks (ADZ144100150). Table 98 provides a summary of reported results. Fasting serum glucose level increased, however the significance of this increase is not reported.

Table 98: Summary of results for effect of antipsychotic medication on fasting serum glucose level (mg per dl)

K = 1 **N = 161**			
TP	**Study ID**	**Intervention**	**Results**
26 weeks	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was 5.2931(25.1642) (p value not reported)

Total cholesterol

Two studies with a total of 217 participants assessed total cholesterol level in participants treated with quetiapine for 12 or 26 weeks (SCHIMMELMAN2007; ADZ144100150 respectively). Studies reported inconsistent findings: SCHIMMELMAN2007 reported a non-significant increase in patients treated with quetiapine at 12 weeks; and ADZ144100150 reporting a decrease (significance not reported) at 26 weeks. Table 99 provides a summary of reported results.

Table 99: Summary of results for effect of antipsychotic medication on total cholesterol level (mg per dl)

K = 2 N = 217			
TP	**Study ID**	**Intervention**	**Results**
12 weeks	SCHIMMELMAN2007	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	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was -0.1750 (23.5883) (p value not reported)

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 (ADZ144100150). Table 100 provides a summary of reported results. High-density lipoprotein cholesterol level decreased, however the significance of this decrease is not reported.

Table 100: Summary of results for effect of antipsychotic medication on high-density lipoprotein cholesterol level (mg per dl)

K = 1 N = 161			
TP	**Study ID**	**Intervention**	**Results**
26 weeks	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was -0.5940 (8.6012) (p value not reported)

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 (ADZ144100150). Table 101 provides a summary of reported results. Low-density lipoprotein cholesterol level decreased, however the significance of this decrease is not reported.

Table 101: Summary of results for effect of antipsychotic medication on low-density lipoprotein cholesterol level (mg per dl)

K = 1 **N = 161**			
TP	**Study ID**	**Intervention**	**Results**
26 weeks	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was -0.1750 (23.5883) (p value not reported)

Metabolic: triglycerides

One included study with a total of 161 participants assessed triglycerides in participants treated with quetiapine treated for 26 weeks (ADZ144100150). Table 102 provides a summary of reported results. Triglycerides decreased, however the significance of this decrease is not reported.

Table 102: Summary of results for effect of antipsychotic medication on triglycerides (mg per dl)

K = 1 N = 161			
TP	**Study ID**	**Intervention**	**Results**
26 weeks	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was -0.1148 (68.0005) (p value not reported)

7.22.2 Neurological side effects

Extra-pyramidal side effects scales

Four studies with a total of 310 participants used a standard scale to assess extra-pyramidal side effects (SCHIMMELMAN2007, ADZ144100150, CASTRO-FORNIELES2007, ROSS2003): Abnormal Involuntary Movement Scale (AIMS), Simpson Angus extra-pyramidal Side effects Scale (SAS), Barnes Akathisia Scale Side effects Scale (BARS) or the Udvalg for Kliniske Undersogelser Neurologic Subscale (UKU). Data could be extracted and analyzed in RevMan for one study (CASTRO-FORNILES2008) and Table 103 provides a summary of reported results. At 26 weeks no significant between group differences in neurological side effects were found.

Table 104 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% of participants worsened (significance not reported) (ADZ144100150). No significant differences were observed in participants treated with quetiapine at 12 weeks, or olanzapine at 52 weeks on the SAS (SCHIMMELMAN2007 and ROSS2033 respectively); and at 26 weeks the majority of participants treated with quetiapine included in the ADZ144100150 trial showed no change in scores (significance not reported). An improvement was observed in 15.5% participants and a worsening in 8.6% participants (ADZ144100150). A significant decrease (improvement) was observed in quetiapine treated participants at 12 weeks on the BARS (p = 0.001) (SCIMMELMAN2007); and an improvement in BARS scores was observed in 6.9% of patients and worsening in 2.3% (significance not reported) at 26 weeks (ADZ144100150). 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 neurological side effects subscale was significantly different between risperidone and olanzapine treated participants, with risperidone favoured over olanzapine (p = 0.022) at 26 weeks.

Table 103: Summary evidence profile for extractable neurological side effect outcomes in children and young people

Outcome or subgroup	STUDY ID	Comparison	Studies/ number of participants	Effect Estimate (SMD or RR)	Hetero geneity	Quality	Forest plot
Neurological: UKU (SMD)	CASTRO-FORNILES 2008[1]	Quetiapine versus risperidone	K = 1; N = 46	-0.28 [-0.90, 0.34]	N/A	Very low[2,3,4]	Appendix 14 civ (3.1)
	CASTRO-FORNILES 2008[1]	Quetiapine versus olanzapine	K = 1; N = 29	0.11 [-0.62, 0.84]	N/A	Very low[2,3,4]	Appendix 14 civ (3.2)
	CASTRO-FORNILES 2008[1]	Olanzapine (SOT) versus risperidone	K = 1; N = 45	-0.39 [-1.03, 0.25]	N/A	Very low[2,3,4]	Appendix 14 civ (3.3)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] 26 weeks' treatment
[2] Serious risk of bias (including: observational)
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Serious risk of reporting bias

Table 104: Summary of results for effect of antipsychotic medication on extra-pyramidal side effect scales

K = 2, N = 310			
TP	**Study ID**	**Intervention**	**Results**
12 weeks	SCHIMMELMAN 2007	Quetiapine	AIMS: NU SAS: A non-significant decrease in mean (SD) SAS scores was observed: 2.4(4.4) at baseline to 1.4 (2.6) at 12 weeks. BARS: A significant decrease in mean (SD) BAS scores was observed: 1.1 (1.7) at baseline to 0.5 (1.4) at 12 weeks (p = 0.001) UKU: NU
26 weeks	ADZ144100150	Quetiapine	AIMS: 86.3% of participants showed no change on the AIMS; 8.6% showed an improvement (defined as ≤-1change in AIMS-7 total score); and 5.1% worsened (defined as ≥1change in AIMS-7 total score) (p value not reported). SAS: 75% of participants showed no change on the SAS; 15.5% showed an improvement (defined as ≤-1change in SAS total score); and 8.6% worsened (defined as ≥1change in SAS total score) (p value not reported). BARS: 90.8% of participants showed no change on the BAS; 6.9% showed an improvement (defined as ≤-1change in BAS global score); and 2.3% worsened (defined as ≥1change in BAS global score) (p value not reported) UKU: NU
	CASTRO-FORNILES2008	Risperidone Olanzapine Quetiapine	AIMS: NU SAS: NU BARS: NU UKU: The only UKU subscale with significant differences between drugs was the neurological side effects scale, 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: AIMS scores all remained at or close to the minimum values, with no significant differences over the year. SAS: SAS scores all remained at or close to the minimum values, with no significant differences over the year. BARS: BAS scores all remained at or close to the minimum values, with no significant differences over the year UKU: NU
Note. NU = measure not used			

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. Table 105 provides a summary of reported results. Mild tardive dyskinesia was observed in one participant.

Table 105: Summary of results for effect of antipsychotic medication on tardive dyskinesia

K = 1, N = 12			
TP	**Study ID**	**Intervention**	**Results**
104-208	KUMRA1997	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 TD.

7.22.3 Hormonal side effects

Prolactin level (mg per dl)

Three included studies with a total of 313 participants assessed prolactin level in participants treated with quetiapine or olanzapine for 12 (SCHIMMELMAN2007) or 26 weeks (ADZ144100150, DITTMAN2007). Table 106 provides a summary of reported results. A non-significant decrease was observed at 12 weeks in participants treated with quetiapine (SCHIMMELMAN2007), however in a separate study an increase was observed at 26 weeks (ADZ144100150) (significance not reported). In a study of olanzapine 22.9% patients with possible olanzapine related emergent AEs had increased prolactin levels at 26 weeks.

Table 106: Summary of results for effect of antipsychotic medication on prolactin level (mg per dl)

K = 3, N = 313			
TP	**Study ID**	**Intervention**	**Results**
12 weeks	SCHIMMELMAN2007	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	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was 0.4516 (13.8392) (p value not reported)
	DITTMANN2008	Olanzapine	The % of patients with reported treatment emergent adverse events with increased prolactin level at 26 weeks was 25%. Of those participants with possible olanzapine related treatment emergent adverse events (as judged by a clinician) 22.9% had increased prolactin at 26 weeks.

Thyroid stimulating hormone

Two included studies with a total of 213 participants assessed thyroid stimulating hormone in participants treated with quetiapine for 12 (SCHIMMELMAN2007) or 26 weeks (ADZ144100150). Table 107 provides a summary of reported results. Quetiapine significantly increased thyroid stimulating hormone at 12 weeks (p = 0.014) (SCHIMMELMAN2007); and at 26 weeks (significance not reported) (ADZ144100150).

Table 107: Summary of results for effect of antipsychotic medication on thyroid stimulating hormone (mg per dl)

K = 2, N = 213			
TP	**Study ID**	**Intervention**	**Results**
12 weeks	SCHIMMELMAN2007	Quetiapine	A significant increase in mean (SD) TSH was observed: 1.8 (0.7) at baseline to 2.4 (1.5) at 12 weeks (p = 0.014).
26 weeks	ADZ144100150	Quetiapine	Mean (SD) change at 26 weeks from baseline was 0.3223 (1.2095) (p value not reported)

7.22.4 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 (SCHIMMELMAN2007) or 26 weeks (ADZ144100150). Table 108 provides a summary of reported results. 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 108: Summary of results for effect of antipsychotic medication on blood pressure (mm Hg)

K = 2, N = 231			
TP	**Study ID**	**Intervention**	**Results**
12 weeks	SCHIMMELMAN2007	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	ADZ144100150	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 (ADZ144100150). Table 109 provides a summary of reported results. Direction of mean change in QTc interval depended on the clinical correction used.

Table 109: Summary of results for effect of antipsychotic medication on blood pressure (mm Hg)

K = 1, N = 118			
TP	**Study ID**	**Intervention**	**Results**
26 weeks	ADZ144100150	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).

7.22.5 Leaving the study early for any reason

The percentage of participants leaving the study early for any reason was reported by four studies and ranged between 26% at 52 weeks for olanzapine treated participants and 62% at 24 weeks for olanzapine treated participants (AZD1441C00150, DITTMANN2008, KUMRA1998, ROSS2003) (see Table 110).

Table 110: Dropout rates (%): leaving the study early for any reason

	Treatment					
Study ID	**Follow-up (weeks)**	**Olanzapine**	**Quetiapine**	**Risperidone**	**Clozapine**	**Haloperidol**
AZD1441C00150	26	-	38	-	-	-
CASTRO-FORNILES2008	52	NR	NR	NR	-	-
CROCQ2007	12	NR	-	NR	-	-
DITTMANN2008	24	62	-	-	-	-
KUMRA1997	108-204	NR	-	-	NR	NR
ROSS2003	52	26	-	-	-	-
SCHIMMELMANN2007	12	-	48	-	-	-
Note. - = not applicable NR = not reported						

7.23 CLINICAL EVIDENCE SUMMARY FOR SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATION AT 12 WEEKS OR MORE

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 or 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 have been observed at 12, 26 and 52 weeks. Dropout rates across observational studies were insufficiently reported. Very few studies, all of which are very low quality mean it is difficult to draw robust conclusions regarding the long-term harm caused by antipsychotic medication in this age group.

7.24 CLINICAL EVIDENCE SUMMARY FROM THE ADULT GUIDELINE

Pooling 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 (NCCMH, 2010). 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.

7.25 HEALTH ECONOMIC EVIDENCE

The systematic search of the economic literature undertaken for the guideline did not identify any eligible studies on pharmacological interventions. The NICE guideline *Schizophrenia* in adults (NCCMH, 2010) developed a decision-analytic model to assess the relative cost effectiveness of pharmacological interventions. The model 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 was from the perspective of the public and social sector. National UK costs were used in 2007 prices.

The results were presented as estimated incremental cost-effectiveness ratios (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 is increased to £30,000/QALY, paliperidone is 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 (CEAC) 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 or schizophrenia. The pathways of treatment for children and young people with psychosis or schizophrenia 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/assertive community provision, compared with adults. Nevertheless, the economic considerations from *Schizophrenia* (NCCMH, 2010) provide useful insights for the treatment of psychosis and schizophrenia in children and young people.

7.26 FROM EVIDENCE TO RECOMMENDATIONS

Symptom reduction is one of the primary efficacy outcomes of interest for antipsychotic medication targeting psychosis or schizophrenia. As symptoms are almost always accompanied by considerable distress; and because the onset of schizophrenia during childhood disrupts social and cognitive development; psycho-social 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 *Schizophrenia* (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.

Adverse effects, including extrapyramidal side effects; 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; and lower doses were favoured over higher doses, indicating the importance of starting on a low dose of medication. The significant side effects associated with antipsychotic medication observed in short term trials (4 to 12 weeks) suggests the need to begin monitoring side effects immediately upon administration; and data from the few longer term RCTs and observational study data suggests that the side effects observed need to be routinely monitored thereafter and throughout the period 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 were concerned that the evidence perhaps signalled that side effects such as weight gain and diabetes may 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 or schizophrenia. The GDG therefore considered the decision-analytic model developed for the adult guideline, *Schizophrenia* (NCCMH, 2010), which assessed the relative cost effectiveness of pharmacological interventions for schizophrenia in adults. The deterministic analysis presented estimated ICERs (incremental cost-effectiveness ratios) 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 as compared with the other alternatives included in the model. The GDG agreed that any economic considerations for children and young people with psychosis or schizophrenia that used data from the adult guideline should be interpreted carefully due to differences in pathways of treatment. However, it was also agreed that this data may also provide useful insights for children and young people with psychosis or 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 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 adolescents, have not been granted a Marketing Authorisation (Product Licence) for use in children and adolescents 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 or schizophrenia, as well as evidence from the adult 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 the adult guideline which supports the specific recommendation of clozapine for people whose illness does not respond adequately to other antipsychotic medications. In addition, evidence from the adult 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 agreed that treatment with an antipsychotic in a child or young person with psychosis or schizophrenia should be considered an explicit individual therapeutic trial.

The GDG highlighted the following key points to be considered before initiating antipsychotic medication. Firstly, 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 side effects is required. 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.

Secondly, 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 Children's BNF range on the understanding that many antipsychotic drugs have not been recommended for use in children and adolescents and the BNF for adults may need to be considered. It was also agreed that monitoring of side effects should begin with a baseline assessment and be routinely monitored throughout the course of treatment. A clinical and research recommendation has been made to allow for the possibility that children and young people and their parents may prefer to attempt initial treatment without an antipsychotic, although this should only be for a relatively short period if no improvement is in evidence.

In the development of recommendations for the pharmacological treatment and management of children and young people, the GDG considered the underlying evidence and recommendations in the adult guideline, *Schizophrenia* (NCCMH, 2010; NICE, 2009a) and adapted them (see Table 111) based on the methodological principles outlined in Chapter 3. Some recommendations, however, required no adaptation. 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 2 the numbers refer to the recommendations in the NICE guideline.

Table 111: Adapted and incorporated recommendations from *Schizophrenia* (NICE, 2009a) for the pharmacological treatment and management of children and young people with psychosis or schizophrenia

Original recommendation from *Schizophrenia*	**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.	1.3.15 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 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.	This recommendation was adapted 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 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	1.3.16 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, 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.	This recommendation was adapted based on GDG expert opinion to take account of special considerations when prescribing antipsychotic medication in children and young people. A new recommendation was developed for monitoring side effects. 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 of

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. • Carry out a trial of the medication at optimum dosage for 4–6 weeks.	• 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.	the medication, 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 NHS 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 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.
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.	1.3.18 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.	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.	1.3.19 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	This recommendation was adapted because of the GDG's concerns for the potential of illicit drugs to exacerbate psychotic symptoms in children and young people.

	psychological interventions and the potential of illicit drugs to exacerbate psychotic symptoms.	
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.	1.3.20 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 1.3.16. 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.	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').	1.3.21 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').	N/A
1.2.4.8 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).	1.3.22 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication).	N/A
1.2.4.9 If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.	1.3.23 If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary.	N/A
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.	**Treatment of subsequent acute episodes of psychosis or schizophrenia** 1.4.1 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 1.3.14–1.3.23). Take into account the clinical response to and side effects associated with current and previous medication, and monitor as described in recommendation 1.3.17	No significant adaptation required.
1.3.3.1 Occasionally people with schizophrenia pose an immediate risk to themselves	**Rapid tranquillisation** 1.4.25 Occasionally children and young people with psychosis or schizophrenia	This recommendation was adapted based on GDG expert opinion to account for special

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).	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.	considerations regarding the use of rapid tranquillisation in children and young people.
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.	1.4.26 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.	No significant adaptation required
1.3.3.5 Follow the recommendations in 'Self-harm' (NICE clinical guideline 16) when managing acts of self-harm in people with schizophrenia.	1.4.27 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.	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.	**Early post-acute period** 1.5.2 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.	No significant adaptation required
1.3.5.4 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse.	1.5.3 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse.	N/A
1.3.5.5 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.	1.5.4 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years.	N/A
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** 1.6.13 The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 1.3.14–1.3.23).	No significant adaptation required
1.4.4.2 Do not use targeted,	1.6.14 Do not use targeted,	No significant adaptation

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.	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. *Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.	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.	**Interventions for children and young people with psychosis or schizophrenia whose illness has not responded adequately to treatment** 1.6.16 Offer clozapine to children and young people whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs.	This recommendation was adapted 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 that given the questionable status of these classes and the lack of evidence about these classes in the context of inadequate response to treatment would be better to not specify what class of antipsychotic should be included in the definition of inadequate response. The last sentence is therefore omitted.
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.	1.6.17 For children and young people whose illness has not responded adequately to clozapine at an optimised dose, consider a multidisciplinary review, and recommendation 1.6.15 (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.	No significant adaptation required.

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In addition, the GDG, based on consensus and expert opinion, developed a number of other recommendations on joint decision-making and providing information about potential benefits and side effects of antipsychotics. The GDG was particularly concerned that professionals should undertake baseline physical investigations of weight and height, pulse and blood pressure, fasting blood glucose glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels, and any movement disorder. The GDG emphasised that these should continue to be monitored regularly and systematically throughout treatment, as well as efficacy, adherence and physical health.

The GDG was also concerned about the use of rapid tranquillisation in children and young people and wished to make clear that healthcare professionals should be trained and competent in undertaking this procedure in children and young people.

Finally, recommendations from NICE technology appraisal guidance 213 on 'Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years' were incorporated, as set out in the scope (see Appendix 1).

7.27 RECOMMENDATIONS

7.27.1 Treatment options for first episode psychosis

7.27.1.1 For children and young people with first episode psychosis offer

- oral antipsychotic medication (see recommendations 7.27.2.1-7.27.3.11) and
- a psychological intervention; family intervention or individual CBT (delivered as set out in recommendations 6.8.4.1-6.8.4.12).

7.27.2 Choice of antipsychotic medication

7.27.2.1 The choice of antipsychotic medication 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).

7.27.3 How to use oral antipsychotic medication[62]

7.27.3.1 Before starting antipsychotic medication, undertake and record the following baseline investigations:

- weight and height (both plotted on a growth chart)
- waist and hip circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity.

7.27.3.2 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 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. [63]

7.27.3.3 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, 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.

[62] At the time of consultation (August 2012), 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 for further information.

[63] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

- 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. [64]

7.27.3.4 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 thereafter (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 thereafter
- fasting blood glucose, HbA_{1c}, blood lipid and prolactin levels at 12 weeks and then every 6 months thereafter
- adherence
- physical health.

The secondary care team should maintain responsibility for physical monitoring of antipsychotic medication for at least the first 12 months or until the child or young person's condition has stabilised. Thereafter, the responsibility for physical monitoring may be transferred to primary care under shared care arrangements.

7.27.3.5 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. [65]

7.27.3.6 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

[64] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[65] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

psychological interventions and the potential of illicit drugs to exacerbate psychotic symptoms. [66]

7.27.3.7 'As required' (p.r.n.) prescriptions of antipsychotic medication should be made as described in recommendation 7.27.3.3. 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. [67]

7.27.3.8 Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation').[68]

7.27.3.9 Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). [69]

7.27.3.10 If prescribing chlorpromazine[70], warn of its potential to cause skin photosensitivity. Advise using sunscreen if necessary. [71]

7.27.3.11 Review antipsychotic medication annually, including observed benefits and any side effects.

[66] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[67] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[68] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[69] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[70] At the time of consultation (August 2012), chlorpromazine 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 for further information..
[71] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

7.27.4 Treatment of subsequent acute episodes of psychosis or schizophrenia[72]

7.27.4.1 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 7.27.2.1- 0). Take into account the clinical response to and side effects associated with current and previous medication, and monitor as described in recommendation 7.27.3.4.

7.27.4.2 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).]

7.27.4.3 People aged 15 to 17 years currently receiving aripiprazole for the treatment of schizophrenia who do not meet the criteria specified in 7.27.4.2 should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinician and the person with schizophrenia, and if appropriate, their parents or carers. [This recommendation is from 'Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years' (NICE technology appraisal guidance 213).]

7.27.5 Rapid tranquillisation and restraint

7.27.5.1 Healthcare professionals undertaking rapid tranquillisation 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.

7.27.5.2 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

[72] At the time of consultation (August 2012), 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 for further information.

antipsychotic medication before, because of the increased risk of acute dystonic reactions in that age group. [73]

7.27.5.3 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.[74]

7.27.5.4 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.[75]

7.27.6 Early post-acute period

7.27.6.1 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. [76]

7.27.6.2 If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. [77]

7.27.6.3 After withdrawal from antipsychotic medication, continue monitoring for signs and symptoms of relapse for at least 2 years. [78]

7.27.7 Promoting recovery and providing possible future care

7.27.7.1 The choice of drug should be influenced by the same criteria recommended for starting treatment (see recommendations 7.27.2.1- 7.27.3.110).

7.27.7.2 Do not use targeted, intermittent dosage maintenance strategies[79] 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. [80]

[73] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[74] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[75] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[76] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[77] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[78] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[79] Defined as the use of antipsychotic medication only during periods of incipient relapse or symptom exacerbation rather than continuously.
[80] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

7.27.8 Interventions for children and young people with psychosis or schizophrenia whose illness has not responded adequately to treatment

7.27.8.1 Offer clozapine[81] to children and young people whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. [82]

7.27.8.2 For children and young people whose illness has not responded adequately to clozapine[83] at an optimised dose, consider a multidisciplinary review, and recommendation 6.5.18.1 (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. [84]

7.28 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 13 for further details.)

[81] At the time of consultation (August 2012), 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 for further information.
[82] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[83] At the time of consultation (August 2012), 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 for further information.
[84] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

8 COGNITION, EMPLOYMENT AND EDUCATION IN CHILDREN AND YOUNG PEOPLE WITH PSYCHOSIS AND SCHIZOPHRENIA

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.

The symptoms of psychosis and schizophrenia, as well as antipsychotic medication used in the treatment and management of the disorder, can interfere with a child or young person's ability to continue attending and engaging with their education, training or employment. In the longer term, psychosis or schizophrenia and its pharmacological treatment can interfere with a child or young person's cognitive function. Some therapies have attempted to improve cognitive function, such as cognitive remediation therapy (CRT), and have been used to enhance engagement with, and performance in, education and work[1].

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 or schizophrenia. Nevertheless, once a person has an established psychosis, including schizophrenia, they are often not in education and 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 or 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 amongst people with schizophrenia, especially at times of high unemployment. Vocational rehabilitation programmes have been developed, such as pre-vocational training or supported employment, aimed to encourage, support and prepare young people for re-entry to education or employment. However good practice has developed from consensus opinion about what works (Bertolote & McGorry, 2008; Killackey *et al*., 2010). This chapter therefore reviews the evidence for cognitive remediation 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 112 (further detail on the review protocol can be found in Appendix 8 and further information about the search strategy can be found in Appendix 9).

Table 112: Clinical review protocol for the review of cognition, employment and education in children and young people with psychosis and schizophrenia

Review question	RQC1 For children and young people with psychosis and schizophrenia: • Are there any psychological or psychosocial interventions (cognitive remediation) that enhance cognition and/or improve engagement with education/occupational activities?
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding interventions that may enhance cognition of 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. Data from studies in which the study sample consists of children and young people meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger 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 schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. Exclusion**:** Individuals with a formal diagnosis of bipolar disorder.
Intervention(s)	• Cognitive remediation therapy • Psychoeducation • Social skills training
Comparison	Alternative management strategies • Treatment as usual (TAU) • Wait-list • 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	Mainstream databases: Embase, MEDLINE, PreMEDLINE, PsycINFO Topic specific databases and grey literature (see Appendix 8):

Date searched	SR: 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 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 aged 13 years or younger need to be made

8.3 STUDIES CONSIDERED[85]

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; URBAN2012). URBAN2012 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, WYKES2007, KILLACKEY2008). In all other respects, these studies met the eligibility criteria for this review and so were included and data extrapolated. This provided a total of five RCTs (N = 197) providing relevant clinical evidence and meting the eligibility criteria for 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 (UELAND2004, EACK2009, KILLACKEY2008) and additional unpublished data were obtained for a further study (URBEN2012). No RCTs investigating educational or service level interventions were identified. Further information regarding included studies can be found in Appendix 14.

8.4 COGNITIVE REMEDIATION THERAPY

8.4.1 Introduction

Definition

Cognitive remediation was defined as:

[85] 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).

- an identified procedure that is specifically focused on basic cognitive processes, such as attention, working memory, or 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 cognitive remediation therapy (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 cognitive remediation therapy (focussed computer-based CRT) versus psychoeducation (UELAND2004); one RCT of CRT versus treatment as usual in the UK (WYKES2007); and one RCT of CRT (focussed computer assisted CRT) to computer games (URBEN2012) (see Table 113 for a summary of the study characteristics). EACK2009 described its experimental and control interventions as 'cognitive enhancement therapy (CET)' and 'enrichment supportive therapy (EST)' but we considered the procedures and intentions of these treatments as sufficiently similar 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 for psychosis. Forest plots and/or evidence profiles for each outcome can be found in Appendix 14 and Appendix 17, respectively.

Table 113: Summary study characteristics for trials comparing cognitive remediation therapy

	Cognitive enhancement therapy (CRT and group group-based social cognition therapy) versus psychoeducation	**CRT versus psychoeducation**	**CRT versus TAU**	**CRT versus computer games**
Total no. of studies (N)	1 (N = 58)	1 (N = 26)	1(N = 40)	1 (N = 32)
Study ID(s)	EACK2009*	UELAND2004 (UELAND2005)*	WYKES2007	URBEN2012*
Diagnosis	Schizophrenic disorder (stable)	Psychosis mixed (including BP)	Schizophrenic disorder	Psychosis (n = 21) or at high risk of psychosis (n = 11)
Mean Age (yrs)	25.9	15.3	18.2	15.5
Sex (% male)	69	54	65	64
Ethnicity (% Caucasian)	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
*Extractable outcomes				

8.4.3 Cognitive enhancement therapy versus psychoeducation

Table 114 provides a summary evidence profile for outcomes reported for cognitive enhancement therapy (CET) versus psychoeducation (EACK2009) at 104 weeks' post-treatment. The sample included young people with a mean age of 25.9 and CET 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 CET were found for total psychotic symptoms (SMD -0.72, -1.25 to -0.19), negative symptoms (SMD = -0.96, to -1.51, -0.41), psychosocial functioning (SMD = -0.86, -1.41, to -0.32) and social cognition (SMD = -1.20, -1.76 to -0.64). Furthermore, at 2 years' post-treatment significantly more participants receiving CET (13 out of 31) than EST (four out of 27) were actively engaged in paid, competitive employment (assuming dropouts did not gain employment, RR = 2.83, 1.05 to 7.65; see Appendix 14d (3.6)). No significant effect was found for leaving the study early for any reason (Table 114).

Table 114: Summary evidence profile for outcomes reported for cognitive enhancement therapy versus psychoeducation at 104 weeks' post-treatment

Outcome or Subgroup	Study ID	Number of studies/ participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest Plot
Symptoms: Total (SMD)	EACK2009	K = 1, N = 58	-0.72 [-1.25, -0.19]*	N/A	Low[1, 2]	Appendix 14d (3.2)
Symptoms: Negative(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 (3.15)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
*Favours CRT
[1]Serious risk of bias (including unblind and missing data).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

8.4.4 Cognitive remediation therapy versus psychoeducation

Table 115 and Table 116 provide summary evidence profiles for outcomes reported 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 (Table 115) or 1 year's follow-up (Table 116). Data pertaining to participant discontinuation were not reported.

Table 115: Summary evidence profile 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	Forest Plot
Symptoms: Total (SMD)	UELAND2004	K = 1, N = 24	-0.40 [-1.22, 0.42]	N/A	Low[1,2]	Appendix 14d (1.1)
Symptoms: Positive (SMD)	UELAND2004	K = 1, N = 24	-0.35 [-1.17, 0.47]	N/A	Low[1,2]	Appendix 14d (1.2)
Symptoms: Negative (SMD)	UELAND2004	K = 1, N = 24	-0.66 [-1.50, 0.17]	N/A	Low[1,2]	Appendix 14d (1.3)
Psychosocial functioning (SMD)	UELAND2004	K = 1, N = 25	-0.15 [-0.94, 0.64]	N/A	Low[1,2]	Appendix 14d (1.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1]Serious risk of bias (including unblind, trial registration not found and drop out not reported by group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

Table 116: Summary evidence profile 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)	Heterogeneity	Quality	Forest Plot
Symptoms: Total (SMD)	UELAND2004	K = 1, N = 25	-0.19 [--0.98, 0.60]	N/A	Low[1, 2]	Appendix 14d (2.1)
Symptoms: Positive (SMD)	UELAND2004	K = 1, N = 25	-0.33 [-1.13, 0.47]	N/A	Low[1, 2]	Appendix 14d (2.2)
Symptoms: Negative (SMD)	UELAND2004	K = 1, N = 25	-0.17 [-0.96, 0.62]	N/A	Low[1, 2]	Appendix 14d (2.3)
Psychosocial functioning(SMD)	UELAND2004	K = 1, N = 26	-0.46 [-1.24, 0.32]	N/A	Low[1, 2]	Appendix 14d (2.4)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1]Serious risk of bias (including unblind, trial registration not found and drop out not reported by group).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

8.4.5 Cognitive remediation therapy versus treatment as usual

One study compared cognitive remediation therapy to treatment as usual (TAU) 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 report 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, 0.75 to 1.40) and this remained at 26 weeks' follow-up (RR = 0.97, 0.69 to 1.35). Evidence from each reported outcome and the overall quality of the evidence are presented in Table 117 and Table 118.

Table 117: Summary evidence profile for outcomes reported for CRT versus TAU at 14 weeks' post-treatment

Outcome or Subgroup	Study ID	Number of studies/ participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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 ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference [1]Serious risk of bias (including sequence generation unclear and unblind). [2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.						

Table 118: Summary evidence profile for outcomes reported for CRT versus TAU at 26 weeks' follow-up

Outcome or Subgroup	Study ID	Number of studies/ participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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 ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference 1Serious risk of bias (including sequence generation unclear and unblind). 2 Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.						

8.4.6 Cognitive remediation therapy versus computer games

One study compared computer assisted CRT to a set of computer games that required 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 cognitive remediation therapy 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 drop out (RR = 1.17, 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 is presented in Table 119 and Table 120.

Table 119: Summary evidence profile for outcomes reported for CRT versus Computer Games (CG) at 8 weeks' post-treatment

Outcome or Subgroup	Study ID	Number of studies/ participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	Forest Plot
Symptoms: Total (SMD)	URBEN 2012	K = 1, N = 28	0.26 [-0.49, 1.00]	N/A	Very low[1, 2, 3]	Appendix 14d (6.1)
Symptoms: Positive (SMD)	URBEN 2012	K = 1, N = 28	0.35 [-0.39, 1.10]	N/A	Very low[1, 2, 3]	Appendix 14d (6.2)
Symptoms: Negative (SMD)	URBEN 2012	K = 1, N = 28	0.29 [-0.46, 1.04]	N/A	Very low[1, 2, 3]	Appendix 14d (6.3)
Symptoms: General (SMD)	URBEN 2012	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)	URBEN 2012	K = 1, N = 28	0.21 [-0.53, 0.96]	N/A	Very low[1, 2, 3]	Appendix 14d (6.5)
Social Functioning	URBEN 2012	K = 1, N = 28	0.31 [-0.44, 1.06]	N/A	Very low[1, 2, 3]	Appendix 14d (6.6)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including sequence generation and allocation concealment unclear, only raters blind and trial registration not found).
[2] Optimal information size (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 120: Summary evidence profile for outcomes reported for CRT versus CG at 26 weeks' follow-up

Outcome or Subgroup	Study ID	Number of studies/ participants	Effect Estimate (SMD or RR)	Heterogeneity	Quality	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
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
[1] Serious risk of bias (including sequence generation and allocation concealment unclear, only raters blind and trial registration not found).
[2] Optimal information size (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).

8.4.7 Children and young people clinical evidence summary

In four RCTs, with a total of 156 participants with schizophrenia and psychosis the evidence for cognitive remediation therapy is limited. One small RCT of 'cognitive enhancement therapy' (CET), which consisted of computer-based CRT and group-based social cognition therapy, found moderate effects favouring CET over psychoeducation on symptoms, psychosocial functioning and social cognition. In addition, participants in the CET 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 suggests that in this age group the remediation programme does not add any benefits 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.

8.4.8 Adult clinical evidence summary

In the six RCTs (out of 17 included in the meta-analysis) that reported cognitive outcomes at follow-up, there was limited evidence that cognitive remediation produced sustained benefits in terms of cognition. However, these effects were driven primarily by two studies (HOGARTY2004, PENADES2006); 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 cognitive remediation when compared with standard care may improve social functioning. However, this effect was driven by a range of studies conducted by Velligan and colleagues (VELLIGAN2000, 2002, 2008A, 2008B), in which the intervention was more comprehensive than typical cognitive remediation 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 cognitive remediation 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. Thus, 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 immediately in competitive employment. 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 an Early Psychosis Prevention and Intervention Centre (EPPIC TAU) to EPPIC TAU. IPS was defined by 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 may involve participation in the vocationally oriented groups within the group programme (see Table 121 for a summary of the study characteristics). Forest plots and/or evidence profiles for each outcome can be found in Appendix 14 and Appendix 17, respectively.

Table 121: Summary study characteristics for trials comparing individual placement and support to EPPIC TAU

	IPS versus EPPIC TAU
Total no. of studies (N)	1 (N = 41)
Study ID(s)	KILLACKEY2008*
Diagnosis	First episode schizophrenic disorder
Mean Age (yrs)	Mean: 21.4
Sex (% male)	81
Ethnicity (% Caucasian)	Not reported
Treatment length (weeks)	26
Length of follow-up (weeks)	N/A
Setting	Specialist centre
Country	Australia
*Extractable outcomes	

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 TAU group (2 out of 21) had found a job, enrolled in a course or done both (RR = 6.83, 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, -1.99 to 1.02) but not significantly more hours per week (SMD = -0.71, -2.22 to 0.81). Finally, one participant in the IPS group compared with five participants in the EPPIC TAU group dropped out; however, this difference was not statistically significant (RR = 0.21, 0.03 to 1.64; see Appendix 14d (8.5)). Evidence from each reported outcome and overall quality of evidence are presented in Table 122.

Table 122: Summary evidence profile for outcomes reported for IPS versus EPPIC TAU at 26 weeks' post-treatment

Outcome or Subgroup	**Study ID**	**Number of studies/ participants**	**Effect Estimate (SMD or RR)**	**Hetero geneity**	**Quality**	**Forest Plot**
Sensitivity analysis: Employment/ enrolled on a course (assuming dropouts did not gain employment; RR)	KILLAC KEY2008	K = 1, N = 41	6.83 [1.76, 26.51]*	N/A	Low[1, 2]	Appendix 14d (8.1)
Number of weeks worked (SMD)	KILLAC KEY2008	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)	KILLAC KEY2008	K = 1, N = 15	-0.71 [-2.22, 0.81]	N/A	Low[1, 2]	Appendix 14d (8.4)
Leaving the study early for any reason (RR)	KILLAC KEY2008	K = 1, N = 41	0.21 [0.03, 1.64]*	N/A	Low[1, 2]	Appendix 14d (8.5)

Note
ROB = Risk of bias; RR = Relative risk; SMD = Standardised mean difference
*Favours IPS.
[1] Serious risk of bias (including unblind and more people in the TAU group were in marital or marital-like relationships. This would tend to bias the study against finding success for the vocational intervention, as people in marital relationships tend to function better socially and in employment).
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

8.5.4 Children and young people clinical evidence summary

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.

8.5.5 Adult clinical evidence summary

The GDG selected a Cochrane review (Crowther *et al.*, 2001) of 18 RCTs, updated with two new RCTs (MUESER [Hartford; Mueser *et al.*, 2004], LEHMAN [Baltimore; Lehman *et al.*, 2002][86]), for further systematic review and meta-analysis. There is 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.

8.6 EDUCATION

8.6.1 Introduction

'Enjoying and achieving', 'making a positive contribution' and 'economic well-being' 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 within compulsory school age should receive appropriate education (Department for Education and Skills, 2001). Children suffering with an early onset psychosis may be considered to have special education needs and require individual educational planning to meet their needs. Request for assessment of special educational needs is a lengthy process and 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 evidence about a child's change in educational performance secondary to the illness for the educational authority to make a decision to assess a child. However the diagnosis and liaison with the child's

[86] Unpublished data only.

school and education authority where the young person resides should occur to ensure a plan is put in place to meet that young person's educational needs. Baseline assessments can be useful so a 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

The paucity and low quality of the evidence in children and young people and in adults with psychosis and schizophrenia makes it difficult to draw any conclusions and therefore to make any recommendations for cognitive remediation therapy.

There is some low quality evidence that supported employment has a beneficial effect in helping young people aged under 25 to gain employment or to enrol on a course; but this evidence alone is insufficient to make a recommendation. However, evidence from *Schizophrenia* (NCCMH, 2010) suggests that supported employment in the US is clearly superior to pre-vocational training programmes; and on the balance of this evidence the GDG decided to adapt the recommendations in *Schizophrenia* (NICE, 2009a) regarding supported employment and related good practice points (see Table 123) 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'. See Table 123 for the original and adapted recommendations, and the reasons for adaptation. In column 2 the numbers refer to the recommendation numbers in the NICE guideline.

The GDG also consulted a special advisor 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 in this area, 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. In cases of 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. Additionally, liaison between Mental Health Services, the school and parents or carers is required to assess the child's or young person's special educational needs. 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. For young

people above compulsory school age with psychosis or schizophrenia who wish to return to work or gain employment, supported employment programmes and other occupational activities should be provided. Access to local employment and educational opportunities may be enhanced through mental health services and local stakeholders, including those representing BME groups, working in partnership. 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. Daytime activities of young people with psychosis or schizophrenia should be routinely recorded in their care plans, including educational and occupational outcomes.

Table 123: Recommendations from *Schizophrenia* (NICE, 2009a) for inclusion

Original recommendation from Schizophrenia	**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.	1.6.20 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.	This recommendation was adapted 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 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.	1.6.21 Mental health services should work in partnership with local stakeholders, including those representing black and minority ethnic groups, to enable children and 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.	No significant adaptation required
1.4.7.3 Routinely record the daytime activities of people with schizophrenia in their care plans, including occupational outcomes.	1.6.22 Routinely record the daytime activities of young people with psychosis or schizophrenia in their care plans, including educational and occupational outcomes.	No significant adaptation required

8.8 RECOMMENDATIONS

8.8.1 Assessment and care planning in secondary care

8.8.1.1 For children and young people with first episode psychosis who are unable to attend school or college, facilitate alternative educational input in line with their capacity to engage with educational activity. Where necessary, liaise with the school and education authority to provide education at home.

8.8.2 Education, employment and occupational activities

8.8.2.1 For children and young people of compulsory school age, liaise with the child or young person's school and educational authority to ensure that ongoing education is provided.

8.8.2.2 Liaise with the child or young person's school and with their parents or carers 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.

8.8.2.3 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.

8.8.2.4 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. [87]

8.8.2.5 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. [88]

8.8.2.6 Routinely record the daytime activities of children and young people with psychosis or schizophrenia in their care plans, including educational and occupational outcomes.[89]

[87] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[88] Adapted from 'Schizophrenia' (NICE clinical guideline 82).
[89] Adapted from 'Schizophrenia' (NICE clinical guideline 82).

1
2

9 SUMMARY OF RECOMMENDATIONS

All of the recommendations set out in the same order as the NICE guideline, will be inserted here prior to publication.

10 APPENDICES

APPENDIX 1: SCOPE FOR THE DEVELOPMENT OF THE CLINICAL GUIDELINE

Final version

Date

1 Guideline title

Psychosis and schizophrenia in children and young people: recognition and management

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

a. 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.
b. 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.
c. According to the Office for National Statistics (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 (10–18 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.

d. 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.
e. 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.
f. 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.
g. 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.
h. 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

a. 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). 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.

b. 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.
c. 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.
d. 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).
e. 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.
f. 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 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.
g. 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 1–4) 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 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. 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 '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 schizophrenia in people aged 15 to 17 years. NICE technology appraisal guidance 213 (2011). Available from www.nice.org.uk/guidance/TA213

5.1.2 Other related NICE guidance

- Schizophrenia (update). NICE clinical guideline 82 (2009). 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'

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).

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 families 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 families 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 families 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 member of your 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 you have made about individuals with psychosis and substance misuse problems, 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 - lectured on social impairments in ADHD at a meeting sponsored by Janssen-Cilag. This payment was non-specific i.e. it does not relate to a product or service under consideration by this guideline.
Personal family interest	None
Non-personal pecuniary interest	Nottingham University Psychiatry department receives grant income to undertake research in schizophrenia (MRC, Wellcome Trust, NIHR) and evaluation of treatments (Cochrane Collaboration Schizophrenia Centre). Collaboration with Tim Kendall on a National Institute for Health Research (NIHR) Health Technology Assessment Programme (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 advisor to the Prescribing Observatory for Mental Health (POMH) regarding antipsychotic prescribing in children and adolescents. Has given expert advice to the EMEA (EU) on use of aripiprazole for young people with schizophrenia. Has given expert advice to the EMEA (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 8th 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 Pharmaceutical company sponsored educational or

	promotional events during his tenure as GDG chair. Has been commissioned to revise a chapter on 'Schizophrenia and Allied Disorders' for the 6th edition of 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 and 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 (approx.) from NICE for guideline development work. Carried out funded work for NICE International. Undertook research into mental health and the mental health workforce for DH, Royal College of Psychiatrists and Academy of Medical Royal Colleges. Received funding of £80,000 (approx.) from the Academy of Medical Royal Colleges to carry out 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 (CAG) on Specialised Services. The CAG 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 a National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA) evidence synthesis systematic review on 'Treatment for tics in children with Tourette's syndrome'.
Personal non-pecuniary interest	Has published various selective publications by pharmaceutical companies and early intervention services for young people and young adults with schizophrenia. Has written an editorial entitled 'Treating negative symptoms of schizophrenia' for the British Medical Journal [volume 344, page 8, 10 March 2012]. A collaboration with David Shiers and others on a study of a Health Economic model on the key drivers for physical ill health for LSE 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 and 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, etc.
Personal non-pecuniary interest	Variety of publications related to treatment of young people with psychosis.
Action Taken	None
Ms Ejaeta 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 CNWL 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 and Involvement Worker and Young Person's Panel Advisor for ReThink
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 (SIRS)
Action Taken	None
Mr Tim McDougall	
Employment	Nurse Consultant / Clinical Director (Tier 4 CAMHS) / 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, Collingham Child and Family Centre, 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 advisor to the National Audit of Schizophrenia (The Royal College of Psychiatrists) and Rethink 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 ISBN978-1-4051-4894-8. Published 2010 (Royalties received for first time of £169.14 on March 23rd 2012)
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	Co-author of *Tobacco Use Before, At, and After First-Episode Psychosis: A Systematic Meta-Analysis* (Myles, N., Newall, H., Curtis, J., Olav Nielssen, O., PhD, David Shiers, D., Large, M. accepted for publication by The Journal of Clinical Psychiatry). Co-authoring an early intervention in psychosis guidelines produced by IRIS Imitative Ltd (a social enterprise). Co-author of *Efficacy of metformin for prevention of weight gain in psychiatric populations: a review* (Newall, H., Mylesa, H., Ward, P.B., Samaras, K., Shiers, D. and Curtis, J. International Journal of Clinical Psychopharmacology 27(2):69-75 DOI: 10.1097/YIC.0b013e32834d0a5b). 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 LSE and the Institute of Psychiatry.
Action Taken	None
Dr Kirsty Smedley	
Employment	Consultant Clinical Psychologist, Young People's Service, Affinity Healthcare (Priory Group), Cheadle Royal Hospital 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 Early Intervention in Psychosis and CAMHS Services
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
National Collaborating Centre for Mental Health 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
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Linnea Larsson	
Employment	Project Manager and Research Assistant, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Ms. Katherine Leggett	
Employment	Project Manager, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None
Dr Ifigeneia Mavranezouli	
Employment	Senior Health Economist, NCCMH
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
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
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
Dr Craig Whitttington	
Employment	Associate Director – Clinical Effectiveness, NCCMH
Personal pecuniary interest	None
Personal family interest	None
Non-personal pecuniary interest	None
Personal non-pecuniary interest	None

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APPENDIX 3: SPECIAL ADVISORS TO THE GUIDELINE DEVELOPMENT GROUP

Peter Pratt
Chief Pharmacist, Sheffield Care Trust

Mr Andrew Richards,
Educational Psychology, Exeter University

Janette Steel OBE
Principal, Chelsea Community Hospital School

APPENDIX 4: STAKEHOLDERS AND EXPERTS WHO SUBMITTED COMMENTS IN RESPONSE TO THE CONSULTATION DRAFT OF THE GUIDELINE

Stakeholders

Experts

[To be inserted after consultation]

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 Maranon, 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, Schlősslistrasse, 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 Tony 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 Alison Yung
Associate Professor, Department of Psychiatry, University of Melbourne and ORYGEN Research Centre, Australia.

Dr Sébastien Urben
Psychologue, Responsable de Recherche, Service Universitaire de Psychiatrie de l'Enfant et de l'Adolescent (SUPEA), Lausanne, Switzerland.

APPENDIX 6: CLINICAL 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): a) What is the course of these behaviours and symptoms? b) What are the specific behaviours and symptoms that prompt initial recognition of psychoses or prompt diagnosis of schizophrenia?	Chapter 5 At Risk section

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 and/or psychological or psychosocial interventions improve outcomes?	Chapter 5 At Risk section
B2	Does the efficacy profile of continuous antipsychotic drug treatment, compared to alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children and young people and adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 7 – Pharmacological Interventions
B3	Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared to adults with psychosis and schizophrenia (in particular, the metabolic, neurological and cognitive impairments)? The following subgroups should be considered: a) I Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 7 – Pharmacological Interventions

B4	Do clinicians manage and monitor side effects of antipsychotic treatment differently in children and young people with psychosis and schizophrenia compared to adults with psychosis and schizophrenia?[1] The following subgroups should be considered: a) I Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 7 – Pharmacological Interventions
B5	For initial treatment in children and young people with psychosis or schizophrenia: a) Should the dose/duration (and where relevant frequency) be different compared to adult patients? b) Are there any different factors (including patient populations, age etc.) which predict the nature and degree of response to medication, which should be considered in children and young people with psychosis and schizophrenia that are not considered necessary to consider in adults with psychosis and schizophrenia?[1]	Chapter 7 – Pharmacological Interventions
B6	Are the same baseline measurements/ monitoring procedures taken before initiating antipsychotic medication used in children and young people with psychosis and schizophrenia compared to adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 7 – Pharmacological Interventions
B7	For children and young people with psychosis and schizophrenia in whom antipsychotic medication is ineffective (treatment resistance), 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 – Pharmacological Interventions
B8	Does the most appropriate treatment strategy in cases where antipsychotic medication is effective but not tolerated, differ between children and young people with psychosis and schizophrenia compared to adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 7 – Pharmacological Interventions
B9	Does the length of antipsychotic medication that is continued for prevention of relapse (maintaining and promoting recovery) differ between children and young people and adults with psychosis and schizophrenia? Does the risk of adverse events associated with antipsychotic augmentation differ between children and young people and adults with psychosis and schizophrenia that is in remission?	Chapter 7 – Pharmacological Interventions
B10	Does the risk of adverse events associated with antipsychotic augmentation differ between children and young people and adults with psychosis and schizophrenia that is in remission?	Chapter 7 – Pharmacological Interventions

B11	Do the advantages and disadvantages of psychological or psychosocial interventions, compared to alternative management differ between children and young people and adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 6 – Psychological/ Psychosocial Interventions
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 to adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 6 – Psychological/ Psychosocial Interventions
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 to adults with psychosis and schizophrenia? Is the most effective format for particular psychological/ psychosocial interventions (e.g. group or individual) the same for children and young people with psychosis and schizophrenia compared to adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 6 – Psychological/ Psychosocial Interventions
B14	Is the most effective format for particular psychological/ psychosocial interventions (e.g. group or individual) the same for children and young people with psychosis and schizophrenia compared to adults with psychosis and schizophrenia? The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 6 – Psychological/ Psychosocial Interventions
B15	Do the competencies or training requirements for practitioners to be able to deliver such interventions differ for those working with children and young people with psychosis and schizophrenia compared to those working with adults with psychosis and schizophrenia?[1] The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 6 – Psychological/ Psychosocial Interventions

B16	Are there any different factors (including patient populations, age etc.) which 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 are not considered necessary to consider in adults with psychosis and schizophrenia?[1] The following subgroups should be considered: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery	Chapter 6 – Psychological/ Psychosocial Interventions

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2 *C. Service settings and educational needs*

3 *Scope Section 4.3.1 (i) & (j)*

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No.	Review questions	Guideline Chapter
C1	For children and young people with psychosis and schizophrenia: **a)** Are there any psychological or psychosocial interventions (cognitive remediation) 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?[1]	Chapter 8 – Cognitive, Employment and Education
C2	*Access to and delivery of services:* c) For children and young people with psychosis and schizophrenia, do specialised intensive services (early intervention in psychosis [EIP] services; specialised CAHMS) improve access and engagement with mental health services for children and young people with schizophrenia (particularly from black and minority ethnic groups)? *Experience of care:* d) For children and young people with psychosis and schizophrenia, what can be done to improve their experience of care?	Chapter 4 – Access to and Delivery of Services and Experience of Care
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?[1]	Chapter 8 – Cognitive, Employment and Education

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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 – Access to and Delivery of Services and Experience of Care

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1 APPENDIX 7: REVIEW PROTOCOLS

2 Access to and Delivery of Services for children and young people with psychosis
3 and schizophrenia

Topic	**Access to and Delivery of Services**
Scope	4.3.1 (i) & (j)
Review question(s) (RQs)	**RQC2** For children and young people with psychosis and schizophrenia: a) Do specialised intensive services improve access and engagement with mental health services for children and young people with schizophrenia (particularly in black and minority ethnic groups)?
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, regarding the organisation and integration of services; a care pathway outline including primary care, CAMHS, EIS and tertiary CAMHS (inpatient services); and way to improve access to and engagement with mental health services 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. Data from studies in which the study sample consists of children and young people meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when 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 schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of Bipolar Disorder.
Intervention	Specialised intensive services (CAMHS, EIS)
Comparison	Alternative management strategies
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 trial (unless adequate statistical methodology has been applied to account for missing data)
Study setting	Any
Databases searched	Mainstream databases: Embase, Medline, PreMedline, 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
Database search dates	SR: 1995 to May 2012; RCT: inception of databases to May 2012
General search strategy used	Mainstream/topic specific databases – generic search: [(population terms – version 1) AND (SR/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	
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 ≤13 years need to be made

* AEI (Australian Education Index), AMED (Allied and Complementary Medicine Database), ASSIA (Applied Social Services Index and Abstracts), BEI (British Education Index), CDSR (Cochrane Database of Systematic Reviews), CINAHL, (Cumulative Index to Nursing and Allied Health Literature), DARE (Database of Abstracts of Reviews and Effectiveness), ERIC (Education Resources in Curriculum), HMIC (Health Management Information Consortium), HTA (Health Technology Assessment database), IBSS (International Bibliography of Social Science), SSA (Social Services Abstracts), SSCI (Social Sciences Citation Index – Web of Science)

[1] Sub-questions were addressed via GDG consensus in accordance with the methods set out in Chapter 3 and are discussed within Chapter 4.

1 Experience of Care

Topic	**Experience of Care**
Scope	The GDG considered this an important topic to consider post scope finalization
Review question(s) (RQs)	**RQD1** 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	Recommendations will be developed by identifing key issues and areas of concern for children and young people in their experience of care using NHS mental health services; and by reviewing and assessing the recommendations from *Service User Experience in Adult Mental Health* (NICE, 2011; NCCMH, 2012) and *Schizophrenia* (NICE, 2009a) guidance for their relevancy to children and young people with psychosis and schizophrenia; specifically in relation to issues and concerns identified
Population	**Inclusion** Children and young people (aged 18 years and younger) with first episode psychosis will be the target group under consideration. Consideration should also be given to the specific needs of children and young people with schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusion:** Individuals with a formal diagnosis of Bipolar Disorder will not be considered.
Intervention	Specialised intensive services (CAMHS, EIS)
Comparison	Alternative management strategies
Primary outcomes	Experience of Care
Secondary outcomes	None
Other outcomes	None
Study design	N/A
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* (NICE, 2011; NCCMH, 2012) • *Schizophrenia* (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, 2011) and *Schizophrenia* (NCCMH, 2010; NICE, 2009a) for their relevancy to children and young people with psychosis and schizophrenia, bearing in mind the identified key issues and areas of concern. The topic group discussion wwill 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, 2011) and *Schizophrenia* (NICE, 2009a) identified by the topic group as being relevant to children and young people with psychosis and schizophrenia. Recoomedations from the guidance used, will be adapted using the method set out in Chapter 3.

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2 'At risk' mental states in 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) (RQs)	**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): 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?
Sub-question(s)	**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 and/or psychological or psychosocial interventions improve outcomes?[2]
Chapter	Chapter 5
Sub-section	None
Topic Group	None
Sub-section lead	n/a
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding early recognition and management of at risk mental states and early psychosis before a formal diagnosis of schizophrenia has been made.
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 meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when only limited evidence for children and young people aged 18 and younger is available. Consideration will be given to individuals with 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 or schizophrenia, including considerations related to the age of children and young people (e.g. dose modifications). Off label use may be considered if clearly supported by evidence (e.g. 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. Licensed antipsychotics include: • 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:* • Cognitive behavioural therapy • Cognitive remediation • Counselling and supportive psychotherapy • Family interventions (including family therapy) • Psychodynamic psychotherapy and psychoanalysis • Psychoeducation • Social skills training • Art therapies
Comparison	Alternative Management Strategies
• 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 events (including effects on metabolism; extrapyramidal side effects; hormonal changes; and , cardiotoxicity)
Other	None

outcomes	
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	Mainstream databases: Embase, Medline, PreMedline, PsycINFO Topic specific databases: CDSR*, CENTRAL, DARE*, HTA* *Note: any evidence resulting from generic guideline searches also mapped to RQ*
Database search dates	SR: 1995 to May 2012; RCT: inception of databases to May 2012
General search strategy used	[(population terms – version 2) AND (at risk terms) AND (SR/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	
• 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 <13 years need to be made.

* CDSR (Cochrane Database of Systematic Reviews), DARE (Database of Abstracts of Reviews and Effectiveness), HTA (Health Technology Assessments)

[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 Sub-questions were addressed via GDG consensus in accordance with the methods set out in Chapter 3 and are discussed within the chapter.

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3 Treatment (psychological therapy and psychosocial interventions)

Topic	Psychological therapy and psychosocial interventions in the treatment and management of schizophrenia
Scope	4.3.1 (b), (d) - (h) & (k)
Review question(s) (RQs)	**RQB11*** Do the advantages and disadvantages of psychological or psychosocial interventions, compared to alternative management differ between children and young people and adults with schizophrenia? **RQB12*** 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 schizophrenia compared to adults with schizophrenia? **RQB13** Should the duration (and where relevant frequency) of an initial psychological/ psychosocial intervention be different in children and young people with schizophrenia compared to adults with schizophrenia? **RQB14*** Is the most effective format for particular psychological/ psychosocial interventions (e.g. group or individual) the same for children and young people with schizophrenia compared to adults with schizophrenia? *The following subgroups will be considered for each RQ: a) Initial treatment (first episode psychosis) b) Acute treatment (not FEP) c) Treatment resistance d) Remission e) Maintaining and promoting recovery
Sub-question(s)	**RQB15** Do the competencies or training requirements for practitioners to be able to deliver such interventions differ for those working with children and young people with schizophrenia compared to those working with adults with schizophrenia?[1] **RQB16** Are there any different factors (including patient populations, age etc) which predict the nature and degree of response to psychological /psychosocial interventions, which should be considered in children and young people with schizophrenia that are not considered necessary to consider in adults with schizophrenia?[1]
Chapter	Chapter 6
Sub-section	None
Topic Group	None
Sub-section lead	n/a
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding the psychological and psychosocial treatment and management of children and young people with psychosis and schizophrenia, including a review of NICE Clinical Guidance 82 for its relevancy 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. Data from studies in which the study sample consists of children and young people meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when only limited evidence for children and young people aged 18 and younger is available. Consideration will also be given to the specific needs of children and young people with schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusions**: Study samples consisting only of individuals with a formal diagnosis of Bipolar Disorder.
Intervention	• Cognitive Behavioural Therapy • Counselling and Supportive Psychotherapy • Family Interventions (including family therapy) • Psychodynamic Psychotherapy and Psychoanalysis • Psychoeducation • Social Skills Training • Art Therapies
Comparison	Alternative Management Strategies
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	Mainstream databases: Embase, Medline, PreMedline, 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
Database search dates	SR: 1995 to May 2012; RCT: inception of databases to May 2012
General search strategy used	Mainstream/topic specific databases – generic search: [(population terms – version 1) AND (SR/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	
• Updated	Schizophrenia in Adults
• 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 ≤13 years need to be made.

* AEI (Australian Education Index), AMED (Allied and Complementary Medicine Database), ASSIA (Applied Social Services Index and Abstracts), BEI (British Education Index), CDSR (Cochrane Database of Systematic Reviews), CINAHL, (Cumulative Index to Nursing and Allied Health Literature), DARE (Database of Abstracts of Reviews and Effectiveness), ERIC (Education Resources in Curriculum), HMIC (Health Management Information Consortium), HTA (Health Technology Assessment database), IBSS (International Bibliography of Social Science), SSA (Social Services Abstracts), SSCI (Social Sciences Citation Index – Web of Science)

[1] Sub-questions were addressed via GDG consensus in accordance with the methods set out in Chapter 3 and are discussed within the chapter.

Treatment (pharmacological interventions) for schizophrenia in children or young people

Topic	Pharmacological interventions in the treatment and management of schizophrenia
Scope	4.3.1 (c) – (h) & (k)
Review question(s) (RQs)	RQB2* Does the efficacy profile of continuous antipsychotic drug treatment, compared to alternative management strategies (placebo, another drug treatment, psychological interventions, psychosocial interventions) differ between children and young people and adults with schizophrenia? RQB3* Are children and young people with psychosis[1] and schizophrenia more susceptible to side effects of antipsychotic medication, compared to adults with psychosis and schizophrenia[1] (in particular, the metabolic, neurological and cognitive impairments)? RQB5 For initial treatment in children and young people with schizophrenia: Should the dose/duration (and where relevant frequency) be different compared to adult patients? RQB7 For children and young people with schizophrenia in whom antipsychotic medication is ineffective (treatment resistance), what is the next most effective treatment strategy and when do you decide to change treatment? Does this differ from adults with schizophrenia? RQB8* Does the most appropriate treatment strategy in cases where antipsychotic medication is effective but not tolerated, differ between children and young people with schizophrenia compared to adults with schizophrenia? RQB9 Does the length of antipsychotic medication that is continued for prevention of relapse (maintaining and promoting recovery) differ between children and young people and adults with schizophrenia?[2] RQB6* Are the same baseline measurements/ monitoring procedures taken before initiating antipsychotic medication used in children and young people with schizophrenia compared to adults with schizophrenia? RQB10 Does the risk of adverse events associated with antipsychotic augmentation differ between children and young people and adults with psychosis[1] and schizophrenia that is in remission?[2] *The following subgroups will be considered: • Initial treatment (first episode psychosis) • Acute treatment (not FEP) • Treatment resistance • Remission[2] • Maintaining and promoting recovery[2]
Sub-question(s)	RQB4 Do clinicians manage and monitor side effects of antipsychotic treatment differently in children and young people with psychosis[1] and schizophrenia compared to adults with psychosis[1] and schizophrenia?[3] RQB5 For initial treatment in children and young people with schizophrenia: Are there any different factors (including patient populations, age etc) which predict the nature and degree of response to medication, which should be

	considered in children and young people with schizophrenia that are not considered necessary to consider in adults with schizophrenia?[3]
Chapter	Chapter 7
Sub-section	None
Topic Group	None
Sub-section lead	n/a
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding the pharmacological (antipsychotic) treatment and management of children and young people with psychosis and schizophrenia, including a review of NICE Clinical Guidance 82 for its relevancy 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. Data from studies in which the study sample consists of children and young people meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when only limited evidence for children and young people aged 18 and younger is available. Children and young people with psychosis will be included to address review questions pertaining to the possible side effects of antipsychotic medication. Consideration will also be given to the specific needs of children and young people with schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusion** 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 or schizophrenia, including considerations related to the age of children and young people (e.g. dose modifications). Off label use may be considered if clearly supported by evidence (e.g. 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. Licensed antipsychotics include: • 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
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 events (including effects on metabolism; extrapyramidal side effects; 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, B5, B6, B7, B8, B9** Mainstream databases: Embase, Medline, PreMedline, 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, B4, B10** Mainstream databases: Embase, Medline, PreMedline, PsycINFO Topic specific databases: CDSR*, CENTRAL, DARE*
Database search dates	SR: 1995 to May 2012; RCT/Observational studies: inception of databases to May 2012
General search strategy used	RQ B2, B5, B6, B7, B8, B9 Mainstream/topic specific databases – generic search: [(population terms – version 1) AND (SR/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	
• Updated	Schizophrenia in Adults
• 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[1] 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 ≤13 years need to be made.

* AEI (Australian Education Index), AMED (Allied and Complementary Medicine Database), ASSIA (Applied Social Services Index and Abstracts), BEI (British Education Index), CDSR (Cochrane Database of Systematic Reviews), CINAHL, (Cumulative Index to Nursing and Allied Health Literature), DARE (Database of Abstracts of Reviews and Effectiveness), ERIC (Education Resources in Curriculum), HMIC (Health Management Information Consortium), HTA (Health Technology Assessment database), IBSS (International Bibliography of Social Science), SSA (Social Services Abstracts), SSCI (Social Sciences Citation Index – Web of Science)

[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] Evidence not found

[3] Sub-questions were addressed via GDG consensus in accordance with the methods set out in Chapter 3 and are discussed in Chapter 4.

1
2

Cognition, employment and educational in children and young people with psychosis and schizophrenia

Topic	**Cognition, employment and educational in children and young people with psychosis and schizophrenia**
Scope	4.3.1 (i) & (j)
Review question(s) (RQs)	RQC1 For children and young people with psychosis and schizophrenia: a) Are there any psychological or psychosocial interventions (cognitive remediation) that enhance cognition and/or improve engagement with education/occupational activities? RQC3 b) 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?1
Sub-question(s)	RQC1 For children and young people with psychosis and schizophrenia: a) What are the competencies or training requirements for practitioners to be able to deliver such interventions?[1]
Chapter	Chapter 8
Sub-section	None
Topic Group	None
Sub-section lead	n/a
Objectives	To provide evidence based recommendations, via GDG-consensus, regarding interventions that may enhance cognition of 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. Data from studies in which the study sample consists of children and young people meeting the above criteria AND young people over 18 years, but with a sample mean age of 25 years and younger will be extrapolated when 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 schizophrenia and mild learning disability; and children and young people from black and minority ethnic groups. **Exclusion**: Individuals with a formal diagnosis of Bipolar Disorder.
Intervention	• Cognitive Remediation • Psychoeducation • Social Skills Training
Comparison	Alternative management strategies
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	Mainstream databases: Embase, Medline, PreMedline, 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
Database search dates	SR: 1995 to May 2012; RCT: inception of databases to May 2012
General search strategy used	Mainstream/topic specific databases – generic search: [(population terms – version 1) AND (SR/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	
• 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 ≤13 years need to be made

* AEI (Australian Education Index), AMED (Allied and Complementary Medicine Database), ASSIA (Applied Social Services Index and Abstracts), BEI (British Education Index), CDSR (Cochrane Database of Systematic Reviews), CINAHL, (Cumulative Index to Nursing and Allied Health Literature), DARE (Database of Abstracts of Reviews and Effectiveness), ERIC (Education Resources in Curriculum), HMIC (Health Management Information Consortium), HTA (Health Technology Assessment database), IBSS (International Bibliography of Social Science), SSA

(Social Services Abstracts), SSCI (Social Sciences Citation Index – Web of Science)

[1] Sub-questions were addressed via GDG consensus in accordance with the methods set out in Chapter 3 and are discussed within Chapter 8.

1

APPENDIX 8: SEARCH STRATEGIES FOR THE IDENTIFICATION OF CLINICAL STUDIES

Each search was constructed using the groups of terms set out in Text Box 1. The full set of search terms is documented in sections 1 to 3.31. The selection of search terms was kept broad to maximise retrieval of evidence in a wide range of areas of interest to the GDG.

Text Box 1: Summary of systematic search strategies: Search strategy construction

Summary of systematic search strategies for clinical evidence					
Section 1					
Review area/s	**Search type**	**Search construction**	**Study design searched**	**Databases searched**	**Date range searched**
All review areas/RQs	Generic, evidence mapped to all review areas	Mainstream/topic specific databases – generic search: [(population terms – version 1) AND (SR/RCT filter)] Grey literature databases – generic search: (Population search terms only – version 1)	SR, RCT	Mainstream databases: Embase, Medline, PreMedline, PsycINFO Topic specific databases: AEI*, AMED* ASSIA*, BEI*, CDSR*, CENTRAL*, CINAHL*, DARE*, ERIC*, HTA*, IBSS*, Sociological Abstracts, SSA*, SSCI* Grey literature databases: HMIC*, PsycBOOKS,	SR: 1995 to May 2012 RCT: inception to May 2012

				PsycEXTRA	
Notes: ***Evidence resulting from generic searches mapped to all review areas***					
Section 2					
Review area/s	**Search type**	**Search construction**	**Study design searched**	**Databases searched**	**Date range searched**
At risk / treatment: RQ A1,A2,B1	Focused, supplements evidence retrieved from generic searches (indicated in Section 1)	Mainstream – focused search: [(population terms – version 2) AND (at risk terms) AND (SR/RCT filter)] Topic specific databases – focused search: [(population terms – version 2) AND (at risk terms)]	SR/RCT	Mainstream databases: Embase, Medline, PreMedline, PsycINFO Topic specific databases: CENTRAL, CDSR*, DARE*, HTA*	SR: 1995 to May 2012 RCT: inception to May 2012
Notes: ***Supplements SR/RCT evidence captured by generic searches indicated in Section 1***					
Section 3					

Review area/s	Search type	Search construction	Study design searched	Databases searched	Date range searched
Recognition / treatment: antipsychotic side effects. RQ B3,B4,B10	Focused, supplements evidence retrieved from generic searches (indicated in Section 1)	Mainstream databases – focused search: [(population terms – version 1) AND (antipsychotic terms) AND (side effect terms) AND (OS filter)]	Observational studies	Mainstream databases: Embase, Medline, PreMedline, PsycINFO	Inception to May 2012
Notes: ***Supplements SR/RCT evidence captured by generic searches indicated in Section 1***					
* AEI (Australian Education Index), AMED (Allied and Complementary Medicine Database), ASSIA (Applied Social Services Index and Abstracts), BEI (British Education Index), CDSR (Cochrane Database of Systematic Reviews), CENTRAL [COCHRANE database of RCTs and other controlled trials), CINAHL, (Cumulative Index to Nursing and Allied Health Literature), DARE (Database of Abstracts of Reviews and Effectiveness), ERIC (Education Resources in Curriculum), HMIC (Health Management Information Consortium), HTA (Health Technology Assessment database), IBSS (International Bibliography of Social Science), SSA (Social Services Abstracts), SSCI (Social Sciences Citation Index – Web of Science)					

STRATEGIES FOR THE IDENTIFICATION OF CLINICAL EVIDENCE

1 Population search terms – all databases

1.1 Version 1

1.1.1 STEM – Mainstream Medical Databases
Version 1
Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1	exp psychosis/ or thought disorder/
2	1 use emez
3	delusions/ or hallucinations/ or exp "schizophrenia and disorders with psychotic features"/ or schizophrenia, childhood/
4	3 use mesz, prem
5	auditory hallucinations/ or delusions/ or hallucinations/ or hypnagogic hallucinations/ or paranoia/ or exp psychosis/ or schizoaffective disorder/ or thought disturbances/ or visual hallucinations/
6	5 use psyh
7	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).ti,ab.
8	or/2,4,6-7
9	exp adolescence/ or exp adolescent/ or adolescent development/ or exp child/ or child development/ or exp childhood/ or disabled student/ or elementary student/ or high school student/ or high school/ or kindergarten/ or middle school student/ or middle school/ or exp newborn/ or nursery school/ or primary school/ or exp puberty disorders/ or school/ or student/
10	9 use emez
11	exp adolescent/ or adolescent development/ or exp child/ or exp child development/ or exp infant/ or minors/ or puberty/ or puberty, delayed/ or puberty, precocious/ or students/ or exp schools/
12	11 use mesz, prem
13	limit 8 to ((childhood or adolescence <13 to 17 years>) and (100 childhood or 120 neonatal or 140 infancy or 160 preschool age or 180 school age or 200 adolescence))
14	adolescent development/ or boarding schools/ or charter schools/ or exp child development/ or classmates/ or elementary schools/ or exp elementary school students/ or graduate schools/ or high school students/ or high schools/ or institutional schools/ or junior high school students/ or junior high schools/ or kindergarten students/ or kindergartens/ or middle schools/ or nongraded schools/ or nursery schools/ or exp preschool students/ or puberty/ or schools/ or special education students/ or students/ or vocational school students/
15	13 use psyh
16	14 use psyh
17	or/15-16
18	(adolescen$ or child$ or infan$ or juvenile$ or teen$).hw.
19	(adolescen$ or baby or babies or boy$1 or child$ or delinquen$ or girl$1 or graders or infant$ or junior$1 or juvenile$ or kindergarten or minors or neonate$ or newborn$ or new born$ or p?ediatric$ or postpubert$ or postpubescen$ or prepubert$ or prepubescen$ or preschool$ or preteen$ or pubertal or puberty or puberties or pubescen$ or school$ or student$ or teen$ or toddler$ or (young$ adj2 (inpatient$ or patient$ or people$ or person$ or population$)) or youngster$ or youth$1).tw.
20	or/10,12,17-19
21	8 and 20

1.1.2 STEM - topic specific databases
Version 1
Allied and Complementary Medicine (AMED) – OVID SP

1	delusions/ or hallucinations/ or psychotic disorders/ or schizophrenia/
2	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).ti,ab.
3	1 or 2
4	adolescent/ or exp child/ or child development/ or education, special/ or exp infant/ or puberty/ or schools/ or students/
5	(adolescen$ or child$ or infan$ or juvenile$ or teen$).hw.
6	(adolescen$ or baby or babies or boy$1 or child$ or delinquen$ or girl$1 or graders or infant$ or junior$1 or juvenile$ or kindergarten or minors or neonate$ or newborn$ or new born$ or p?ediatric$ or postpubert$ or postpubescen$ or prepubert$ or prepubescen$ or preschool$ or preteen$ or pubertal or puberty or puberties or pubescen$ or school$ or student$ or teen$ or toddler$ or (young$ adj2 (inpatient$ or patient$ or people$ or person$ or population$)) or youngster$ or youth$1).tw.
7	or/4-6
8	3 and 7

1.1.3 STEM - topic specific databases
Version 1
Australian Education Index (AEI), British Education Index (BEI), Education Resources in Curriculum (ERIC), Social Services Abstracts (SSA), Sociological Abstracts, Applied Social Sciences Index and Abstracts (ASSIA), International Bibliography of Social Sciences (IBSS) - ProQUEST

s1	all (delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*)
s1	all (delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*)
s2	all (adolescen* or baby or babies or boy or boyhood or boys or child* or delinquen* or girl or girls or girlhood or graders or infant* or junior or juniors or juvenile* or kindergarten or minors* or neonate* or newborn* or "new born*" or paediatric* or pediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or teen or teens or teenage* or toddler* or (young* near/2 (inpatient* or patient* or people* or person* or population*)) or youngster* or youth*)
s3	s1 and s2

1.14 STEM - topic specific databases
Version 1
CINAHL – EBSCO HOST

s19	s7 and s18
s18	s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17
s17	ti ((adolescen* or baby or babies or boy* or child* or delinquen* or girl* or graders or infant* or junior* or juvenile* or kindergarten or minors or neonate* or newborn* or "new born*" or

	paediatric* or pediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or student* or teen* or toddler* or (young* n2 (inpatient* or patient* or people* or person* or population*)) or youngster* or youth*)) or ab ((adolescen* or baby or babies or boy* or child* or delinquen* or girl* or graders or infant* or junior* or juvenile* or kindergarten or minors or neonate* or newborn* or "new born*" or paediatric* or pediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or student* or teen* or toddler* or (young* n2 (inpatient* or patient* or people* or person* or population*)) or youngster* or youth*))
s16	mj (adolescen* or child* or infan* or juvenile* or teen*)
s15	(mh "schools") or (mh "schools, special") or (mh "schools, secondary") or (mh "schools, nursery") or (mh "schools, middle") or (mh "schools, elementary")
s14	(mh "students, disabled")
s13	(mh "child development: adolescence (12-17 years) (iowa noc)") or (mh "child development: middle childhood (6-11 years) (iowa noc)") or (mh "child development: 5 years (iowa noc)") or (mh "child development: 4 years (iowa noc)") or (mh "child development: 3 years (iowa noc)") or (mh "child development: 2 years (iowa noc)")
s12	(mh "students") or (mh "students, high school") or (mh "students, middle school")
s11	(mh "puberty, delayed") or (mh "puberty, precocious")
s10	(mh "puberty")
s9	(mh "adolescent development") or (mh "child development") or (mh "infant development")
s8	(mh "adolescence+") or (mh "child+") or (mh "minors (legal)")
s7	s1 or s2 or s3 or s4 or s5 or s6
s6	ti ((delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*)) or ab ((delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*))
s5	(mh "psychotic disorders")
s4	(mh "paranoid disorders")
s3	(mh "schizoaffective disorder") or (mh "schizophrenia+")
s2	(mh "hallucinations") or (mh "hallucination management (iowa nic)")
s1	(mh "delusions+")

1.1.5 STEM - topic specific databases

Version 1

HTA, CDSR, DARE, CENTRAL – Wiley

#1	mesh descriptor **delusions**, this term only
#2	mesh descriptor **hallucinations**, this term only
#3	mesh descriptor **schizophrenia and disorders with psychotic features** explode all trees
#4	mesh descriptor **schizophrenia, childhood**, this term only
#5	(delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*):ti or (delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*):ab
#6	(#1 or #2 or #3 or #4 or #5)
#7	mesh descriptor **adolescent**, this term only
#8	mesh descriptor **child** explode all trees
#9	mesh descriptor **infant** explode all trees
#10	mesh descriptor **adolescent development**, this term only
#11	mesh descriptor **child development** explode all trees
#12	mesh descriptor **minors**, this term only

#13	mesh descriptor **puberty, delayed**, this term only
#14	mesh descriptor **puberty, precocious**, this term only
#15	mesh descriptor **students**, this term only
#16	mesh descriptor **schools**, this term only
#17	mesh descriptor **puberty**, this term only all trees
#18	(adolescen* or child* or infan* or juvenile* or teen*):kw or (adolescen* or baby or babies or boy* or child* or delinquen* or girl* or graders or infant* or junior* or juvenile* or kindergarten or minors or neonate* or newborn* or new born* or pediatric* or paediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or student* or teen* or toddler* or (young* near/2 (inpatient* or patient* or people or person* or population)) or youngster* or youth*):ti or (adolescen* or baby or babies or boy* or child* or delinquen* or girl* or graders or infant* or junior* or juvenile* or kindergarten or minors or neonate* or newborn* or new born* or pediatric* or paediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or student* or teen* or toddler* or (young* near/2 (inpatient* or patient* or people or person* or population)) or youngster* or youth*):ab
#19	(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20	(#6 and #19)

1.1.6 STEM - topic specific databases

Version 1

SSCI – Web of Knowledge

#1	(topic=(delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*)) or (title=(delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*))
#2	(topic=(adolescen* or baby or babies or boy or boyhood or boys or child* or delinquen* or girl or girls or girlhood or graders or infant* or junior or juniors or juvenile* or kindergarten or minors or neonate* or newborn* or "new born*" or paediatric* or pediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or teen or teens or teenage* or toddler* or (young* near (inpatient* or patient* or people or person* or population)) or youngster* or youth*)) or (title=(adolescen* or baby or babies or boy or boyhood or boys or child* or delinquen* or girl or girls or girlhood or graders or infant* or junior or juniors or juvenile* or kindergarten or minors or neonate* or newborn* or "new born*" or paediatric* or pediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or teen or teens or teenage* or toddler* or (young* near (inpatient* or patient* or people or person* or population)) or youngster* or youth*))
#3	(topic=("young* inpatient*" or "young* patient" or "young* people" or "young* population*")) or (title=("young* inpatient*" or "young* patient" or "young* people" or "young* population*"))
#4	#2 or #3
#5	#1 and #4

1.1.7 STEM - grey literature databases

Health Management Information Consortium (HMIC), PsycBOOKS, PsycEXTRA – OVID SP [high spec]

1	((delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$) and (adolescen$ or baby or babies or boy$1 or child$ or

	delinquen$ or girl$1 or graders or infant$ or junior$1 or juvenile$ or kindergarten or minors or neonate$ or newborn$ or new born$ or paediatric* or pediatric* or postpubert$ or postpubescen$ or prepubert$ or prepubescen$ or preschool$ or preteen$ or pubertal or puberty or puberties or pubescen$ or school$ or student$ or teen$ or toddler$ or (young$ adj2 (inpatient$ or patient$ or people$ or person$ or population$)) or youngster$ or youth$1)).ti,ab,hw.

1.2 Version 2

1.2.1 STEM – Mainstream Medical Databases
Version 2
Embase, Medline, PreMEDLINE, PsycINFO – OVID SP
Search request #8 from 1.11

1.2.2 STEM - topic specific databases
Version 2
Allied and Complementary Medicine (AMED) – OVID SP
Search request #3 from 1.12

1.2.3 STEM - topic specific databases
Version 2
Australian Education Index (AEI), British Education Index (BEI), Education Resources in Curriculum (ERIC), Social Services Abstracts (SSA), Sociological Abstracts, Applied Social Sciences Index and Abstracts (ASSIA), International Bibliography of Social Sciences (IBSS) - ProQUEST
Search request #1 from 1.13

1.2.4 STEM - topic specific databases
Version 2
CINAHL – EBSCO HOST
Search request #7 from 1.14

1.2.5 STEM - topic specific databases
Version 2
HTA, CDSR, DARE, CENTRAL – Wiley
Search request #6 from 1.15

1.2.6 STEM - topic specific databases
Version 2
SSCI – Web of Knowledge
Search request #1 from 1.16

2. Question specific search strategies - all databases

2.1 High risk groups

- 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):

a) What is the course of these behaviours and symptoms?

b) What are the specific behaviours and symptoms that prompt initial recognition of psychoses or prompt diagnosis of schizophrenia?

-
- A2) In children and young people, who are at risk of developing psychosis and schizophrenia (i.e. what are the factors [e.g. socioeconomic, gender] that are associated with the future development of psychosis and/or a diagnosis of schizophrenia)?
-

B1) For children and young people who are at risk of developing psychosis and schizophrenia (at risk mental state), does the provision of pharmacological and/or psychological or psychosocial interventions improve outcomes?

2.1.1 Embase, Medline, PreMedline, PsycINFO – OVID SP

1	high risk patient/ or high risk population/ or ultra high risk criterion/ or ultra high risk population/
2	1 use emez
3	*risk factors/
4	3 use mesz
5	at risk populations/
6	5 use psyh
7	or/2,4,6
8	(symptom$ or symptomology).sh. or (prodrom$ or risk$).hw.
9	(blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory or pre monitory) adj2 (sign$ or symptom$)) or predelusion$ or prehallucin$ or prepsychos$ or prepsychotic$ or preschizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold$ or sub$ threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab.
10	or/8-9
11	(conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab.
12	10 and 11
13	ultra high risk.ti,ab.
14	((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).ab.
15	or/7,12-14

2.1.2 CDSR, DARE, CENTRAL, HTA – Wiley

#1	high risk patient/ or high risk population/ or ultra high risk criterion/ or ultra high risk population/
#2	mesh descriptor paranoid disorders, this term only
#3	mesh descriptor psychotic disorders explode all trees
#4	mesh descriptor schizophrenia, childhood, this term only
#5	mesh descriptor schizophrenia explode all trees
#6	(“delusional disorder*” or hebephreni* or psychosis or psychoses or psychotic* or schizo*):ti or (“delusional disorder*” or hebephreni* or psychosis or psychoses or psychotic* or

	schizo*):ab
#7	(((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):ti or (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):ab or (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):kw
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	mesh descriptor risk factors, this term only
#10	(prodrom* or symptom* or risk*):kw
#11	(blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory or "pre monitory") near/2 (sign* or symptom*)) or predelusion* or prehallucin* or prepsychos* or prepsychotic* or preschizo* or (pre near/1 (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold* or "sub* threshold*" or "at risk*" or ((high* or incipient or increas*) near/3 risk*))
#12	#10 or #11
#13	(conversion* or ((develop* or progress*) near/2 (psychos* or psychotic* or schiz*)) or "first episode*" or fullthreshold* or "full threshold*" or onset* or progression or transition* or transitory)
#14	#12 and #13
#15	"ultra high risk"
#16	(("at risk" or ((high or increase*) near/2 risk) or blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory) near/2 (sign* or symptom*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold or "sub* threshold") and (psychos* or psychotic* or schiz*)):ti. or (("at risk" or ((high or increase*) near/2 risk) or blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory) near/2 (sign* or symptom*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold or "sub* threshold") near/3 (psychos* or psychotic* or schiz*)):ab.
#17	#8 and (#9 or #14 or #15 or #16)

2.2 Adverse effects

B3) Are children and young people with psychosis and schizophrenia more susceptible to side effects of antipsychotic medication, compared to adults with psychosis and schizophrenia (in particular, the metabolic, neurological and cognitive impairments)? The following subgroups should be considered:

- Initial treatment (first episode psychosis)
- Acute treatment (not FEP)
- Treatment resistance
- Remission
- Maintaining and promoting recovery

B4) Do clinicians manage and monitor side effects of antipsychotic treatment differently in children and young people with psychosis and schizophrenia compared to adults with psychosis and schizophrenia? The following subgroups should be considered:

- Initial treatment (first episode psychosis)
- Acute treatment (not FEP)
- Treatment resistance
- Remission
- Maintaining and promoting recovery

B10) Does the risk of adverse events associated with antipsychotic augmentation differ between children and young people and adults with psychosis and schizophrenia that is in remission?

2.2.1 Embase, Medline, PreMedline, PsycINFO – OVID SP

1	exp neuroleptic agent/ use emez
2	exp antipsychotic agents/ use mesz, prem
3	exp neuroleptic drugs/ use psyh
4	(antipsychotic$ or anti psychotic$ or (major adj2 (butyrophenon$ or phenothiazin$ or tranquil$)) or neuroleptic$).ti,ab.
5	amisulpride/ use emez
6	(amisulprid$1 or aminosultoprid$1 or amisulpirid$1 or sertol$1 or socian or solian).ti,ab.
7	aripiprazole/ use emez, psyh
8	(aripiprazol$1 or abilify or abilitat).ti,ab.
9	benperidol/ use emez, mesz, prem
10	(benperidol$1 or anquil or benperidon$1 or benzoperidol$1 or benzperidol$1 or frenactil$1 or frenactyl or glianimon$1 or phenactil$1).ti,ab.
11	chlorpromazine$.sh. use emez, mesz, prem, psyh
12	(chlorpromazin$1 or aminazin$1 or chlorazin$1 or chlordelazin$1 or contomin$1 or fenactil$1 or largactil$1 or propaphenin$1 or thorazin$1).ti,ab.
13	chlorprothixene/ use emez, mesz, prem, psyh
14	(chlorprothixen$1 or aminasin$1 or aminasin$1 or aminazin$1 or aminazin$1 or ampliactil$1 or amplictil$1 or ancholactil$1 or chlopromazin$1 or chlor pz or chlorbromasin$1 or chlordelazin$1 or chlorderazin$1 or chloropromazin$1 or chlorpromanyl or chlorpromazin$1 or chlorprotixen$1 or clordelazin$1 or clorpromazin$1 or cloxan or contomin$1 or elmarin$1 or fenactil$1 or hibanil$1 or hibernal$1 or hibernol$1 or klorpromex or largactil$1 or largactyl or megaphen$1 or neurazin$1 or novomazin$1 or phenathyl or plegomazin$1 or plegomazin$1 or proma or promacid$1 or promactil$1 or promapar or promazil$1 or propaphen$1 or propaphenin$1 or prozil or psychozin$1 or sanopron$1 or solidon$1 or sonazin$1 or taractan$1 or taroctil$1 or thor prom or thorazen$1 or thorazin$1 or torazin$1 or truxal or vegetamin a or vegetamin b or wintamin$1 or wintermin$1 or zuledin$1).ti,ab.
15	clozapine$.sh. use emez, mesz, prem, psyh
16	(clozapin$1 or alemoxan$1 or azaleptin$1 or clopine or clozaril$1 or denzapin$1 or dorval or dozapin$1 or fazaclo or froidir or klozapol or lapenax or leponex or wander compound or zaponex).ti,ab.
17	flupentixol$.sh. use emez or flupenthixol/ use mesz, prem
18	(flupentixol$1 or flupenthixol$1 or depixol$1 or emergil$1 or fluanxol$1 or flupentixol$1 or emergil$1 or fluanxol$1 or piperazineethanol$1 or viscoleo).ti,ab.
19	fluphenazine$.sh. use emez, mesz, prem, psyh
20	(fluphena?in$ or anatensil or anatensol or antasol or dapotum or elinol or flufenazin$ or flumezin or fluorfenazine or ftorphenazine or luogen depot or lyogen or lyorodin or moditen or moditin or omca or pacinol or permitil or phthorphenazine or prolixan 300 or prolixene or prolixin or prolixine or s 94 or sevin?l or siqualine or siqualon or siqualone or siquoline or tensofin or trancin or valamina or vespazin or vespazine).ti,ab.
21	fluspirilene/ use emez, mesz, prem
22	(fluspirilen$1 or fluspi or imap or kivat or redeptin$1 or spirodiflamin$1).ti,ab.
23	haloperidol$.sh. use emez, mesz, prem, psyh
24	(haloperidol$1 or aloperidin$1 or bioperidolo or brotopon or celenase or cerenace or dozic or duraperidol or einalon s or eukystol or fortunan$1 or haldol or halidol or haloneural$1 or haloperitol$1 or halosten or keselan or linton or peluces or serenace or serenase or siegoperidol$1 or sigaperidol$1).ti,ab.
25	levomepromazine/ use emez or methotrimeprazine/ use mesz, prem
26	(levomepromazin$1 or 2 methoxytrimeprazin$1 or hirnamin$1 or levo promazin$1 or levomeprazin$1 or levopromazin$1 or levoprom$1 or mepromazin$1 or methotrimeprazin$1 or methotrimperazin$1 or milezin$1 or minozinan$1 or neozin$1 or neuractil$1 or neurocil$1 or nirvan or nosinan$1 or nozinan$1 or sinogan or tisercin$1 or tizercin$1 or tizertsin$1 or veractil$1).ti,ab.

27	olanzapine/ use emez, psyh
28	(olanzapin$1 or lanzac or midax or olansek or olzapin or rexapin or zalasta or zolafren or zydis or zypadhera or zyprex$1).ti,ab.
29	paliperidone/ use emez
30	(paliperidon$1 or 9 hydroxyrisperidon$1 or invega).ti,ab.
31	paroxetine/ use emez, mesz, prem, psyh
32	(paroxetin$1 or aropax or deroxat or motivan or paxil$1 or pexeva or seroxat or tagonis).ti,ab.
33	periciazine/ use emez
34	(pericyazin$1 or aolept or neulactil$1 or neuleptil$1 or periciazin$1 or properciazin$1 or propericiazin$1).ti,ab.
35	perphenazine$.sh. use emez, mesz, prem, psyh
36	(perphenazin$1 or chlorperphenazin$1 or chlorpiprazin$1 or chlorpiprozin$1 or decentan$1 or etaperazin$1 or ethaperazin$1 or etrafon or fentazin$1 or perfenazin$1 or perfenazin$1 or perferazin$1 or perphenan$1 or perphenezin$1 or thilatazin$1 or tranquisan$1 or triavail or trifalon$1 or trilafan$1 or trilafon$1 or trilifan$1 or triliphan$1).ti,ab.
37	pimozide/ use emez, mesz, prem, psyh
38	(pimozid$1 or antalon$1 or opiran$1 or orap or pimocid$1 or pimorid$1 or pinozid$1).ti,ab.
39	prochlorperazine$.sh. use emez, mesz, prem, psyh
40	(prochlorperazin$1 or buccastem or capazin$1 or chlormeprazin$1 or chlorpeazin$1 or chlorperazin$1 or compazin$1 or dicopal$1 or emelent or kronocin$1 or meterazin$1 or metherazin$1 or nipodal$1 or phenotil or prochlor perazin$1 or prochlorpemazin$1 or prochlorperacin$1 or prochlorperzin$1 or prochlorpromazin$1 or proclorperazin$1 or stemetil or stemzine or tementil$1 or temetil$1).ti,ab.
41	promazine/ use emez, mesz, prem, psyh
42	(promazin$1 or alofen$1 or alophen$1 or ampazin$1 or amprazim$1 or centractyl or delazin$1 or esparin$1 or lete or liranol$1 or neo hibernex or neuroplegil$1 or piarin$1 or prazin$1 or pro tan or promantin$1 or promanyl$1 or promilen$1 or promwill or protactil$1 or protactyl$1 or romthiazin$1 or romtiazin$1 or sediston$1 or sinophenin$1 or sparin$1 or tomil or varophen$1 or verophen$1).ti,ab.
43	quetiapine/ use emez, mesz, prem, psyh
44	(quetiapin$1 or ketipinor or quepin or seroquel or tienapin$1).ti,ab.
45	risperidone/ use emez, mesz, prem, psyh
46	(risperidon$1 or belivon$1 or ridal or riscalin or risolept or rispen or risperdal$1 or sizodon).ti,ab.
47	sertindole/ use emez
48	(sertindol$1 or indole or serdolect or serlect).ti,ab.
49	sulpiride/ use emez, mesz, prem, psyh
50	(sulpirid$1 or abilit or aiglonyl$1 or arminol$1 or bosnyl or deponerton$1 or desisulpid$1 or digton or dobren or dogmatil$1 or dogmatyl or dolmatil$1 or eglonyl or ekilid or equilid or guastil$1 or isnamid$1 or leboprid$1 or levopraid or levosulpirid$1 or meresa or miradol$1 or modal or neogama or pontirid$1 or psicocen$1 or sulfirid$1 or sulp$1 or sulperid$1 or sulpitil$1 or sulpivert or sulpor or sulpyride or synedil$1 or tepavil$1 or vertigo meresa or vertigo neogama or vipral).ti,ab.
51	trifluoperazine$.sh. use emez, mesz, prem, psyh
52	(trifluoperazin$1 or apotrifluoperazine$1 or calmazin$1 or dihydrochlorid$1 or eskazin$1 or eskazin$1 or eskazinyl or fluoperazin$1 or flupazin$1 or jatroneural$1 or modalina or stelazin$1 or terfluzin$1 or terfluzin$1 or trifluoperazid$1 or trifluoperazin$1 or trifluoperzin$1 or trifluoroperazin$1 or trifluorperacin$1 or trifluperazin$1 or triflurin$1 or triftazin$1 or triftazinum or triphtazin$1 or triphthasin$1 or triphthazin$1).ti,ab.
53	zotepine/ use emez
54	(zotepin$1 or lodopin$1 or losizopilon or nipolept or setous or zoleptil).ti,ab.
55	(clopenthixol$ or zuclopenthixol$).sh. use emez
56	clopenthixol/ use mesz, prem
57	(zuclopenthixol$1 or acuphase or acutard or clopenthixol$1 or clopixol or cisordinol$1 or

	sedanxol$1 or zuclopentixol$).ti,ab.
58	or/1-57
59	exp endocrine disease/ or exp endocrine function/ or exp endocrine system/
60	(prolactin$ or thyroxine$).sh. or thyroid hormone/
61	or/59-60 use emez
62	exp endocrine system diseases/ or exp endocrine system/
63	prolactin$.sh. or exp thyroid hormones/
64	or/62-63 use mesz
65	exp endocrine disorders/ or exp endocrine system/
66	prolactin/ or exp thyroid hormones/
67	or/65-66 use psyh
68	(((endocrin$ or thyroid$) adj3 (abnormalit$ or chang$ or disease$ or disorder$ or disturbanc$ or dysfunction$ or dysregulat$ or effect$ or problem$ or risk$)) or (prolactin$ or thyroxin$)).ti,ab.
69	or/61,64,67-68
70	exp metabolic disorder/
71	glucose/ or glucose blood level/ or exp glucose metabolism/
72	insulin$.sh.
73	exp lipid/ or exp lipid blood level/ or triacylglycerol/
74	serum/
75	or/70-74 use emez
76	exp metabolic diseases/ or hyperprolactinemia/
77	exp glucose/
78	insulin$.sh.
79	cholesterol/ or exp lipids/
80	exp serum/
81	or/76-80 use mesz
82	exp metabolism disorders/ or metabolic syndrome/
83	exp glucose/ or glucose metabolism/
84	insulin$.sh.
85	cholesterol/ or lipoproteins/ or exp lipids/
86	blood serum/
87	or/82-86 use psyh
88	(blood sugar or cardiometaboli$ or cholesterol$ or diabet$ or glyc?emi$ or glucose or hypergl?c?emi$ or hyper gl?c?emi$ or hypertriglyceridem$ or insulin or lipo$ or lipid$ or metaboli$ or prediabet$ or serum or triglyceride$).ti,ab.
89	or/75,81,87-88
90	(cholester?emi$ or cholesterin?emia$ or cholesterol?emia$ or hypercholester?emia$ or hypercholesterin?emia$ or hypercholesterol?emia$).ti,ab.
91	(dyslip?emia$ or dyslipid?emia$ or dyslipoprotein?emia$).ti,ab.
92	((dysmetabolic or metabolic or reaven) adj2 syndrom$).ti,ab.
93	hypergl?c?emi$.ti,ab.
94	(hyperlip?emi$ or hyperlipid?emi$ or lip?emia$ or lipid?emia$).ti,ab.
95	(hyperprolactin?emi$ or (hypersecretion adj2 syndrome adj2 prolactin) or (inappropriate adj2 prolactin adj2 secretion) or prolactin?emi$).ti,ab.
96	(hypertriglycerid?emia$ or mckusick 14575 or triglyceride storage disease or triglyceride?emia$).ti,ab.
97	or/90-96
98	or/69,89,97
99	exp obesity/ or overnutrition/ or weight gain/
100	99 use emez
101	exp overnutrition/ or exp overweight/ or weight gain/
102	101 use mesz

103	exp overweight/ or weight gain/
104	103 use psyh
105	(bmi or body composition or body mass or (central$ adj3 fat) or fat mass or obese or obesit$ or over nutrition or overweight or waist circumference or (weight adj2 (abnormal$ or chang$ or disorder$ or disturbanc$ or dysfunction$ or dysregulat$ or elevat$ or gain$ or high$ or increas$ or over or problem$ or risk$))).ti,ab.
106	or/100,102,104-105
107	exp blood pressure/ or exp cardiovascular disease/ or sudden death/
108	107 use emez
109	blood pressure/ or exp cerebrovascular disorders/ or exp heart diseases/ or exp hypertension/ or exp pheriperal vascular diseases/
110	109 use mesz
111	blood pressure/ or exp cardiovascular disorders/
112	111 use psyh
113	((atrial and fibrillat*) or (ventricular and fibrillat*) or angina or arrythmi* or cardia* or cardio* or cerebrovascul* or coronary* or endocardi* or heart* or ischaem* or ischem* or myocard* or pericard* or tachycardi* or thromboembolism* or thrombosis or vascul* or ((blood adj2 pressure) or hypertensi$)).ti,ab.
114	or/108,110,112-113
115	or/98,106,114
116	(ae or po or si or to).fs.
117	exp adverse drug reaction/ or death/ or drug interaction/ or exp drug hypersensitivity/ or drug intoxication/ or drug safety/ or drug tolerability/ or drug tolerance/ or exp drug toxicity/
118	drug monitoring/ or intoxication/ or phase 4 clinical trial/ or exp postmarketing surveillance/ or risk/ or risk assessment/ or risk factor/ or exp side effect/ or toxemia/
119	or/116-118 use emez
120	(ae or ct or po or to).fs.
121	exp abnormalities, drug induced/ or exp adverse drug reaction reporting systems/ or exp death/ or drug hypersensitivity/ or drug interactions/ or drug monitoring/ or drug tolerance/ or exp drug toxicity/ or overdose/ or exp product surveillance, postmarketing/ or risk assessment/ or risk factors/
122	or/120-121 use mesz
123	"death and dying"/ or drug interactions/ or drug overdoses/ or drug tolerance/ or risk assessment/ or risk factors/ or exp "side effects (drug)"/ or "side effects (treatment)"/ or exp toxic disorders/ or exp toxicity/
124	123 use psyh
125	(((adverse or negativ$ or side or undesir$ or unwanted) adj2 (effect$ or event$ or outcome$ or reaction$)) or (causa$ or caution$ or complication$ or contraindicat$ or contra indicat$ or death$ or discontinuation effect$ or harm$ or hazard$ or interaction$1 or intolerab$ or lethal$ or noxious or overdos$ or safety or safe or tolerab$ or toxic$ or warning$) or (treatment emergent or adrs) or (extrapyramidal adj2 (effect$ or symptom$))).ti,ab.
126	or/119,122,124-125
127	58 and or/115,126

3 Study design filters – all databases

3.1 Systematic review study design filters

3.1.1 Systematic review study design filter
Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1	meta analysis/ or systematic review/
2	1 use emez

3	meta analysis.sh,pt. or "meta-analysis as topic"/ or "review literature as topic"/
4	3 use mesz, prem
5	(literature review or meta analysis).sh,id,md. or systematic review.id,md.
6	5 use psyh
7	(exp bibliographic database/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.)
8	7 use emez
9	(exp databases, bibliographic/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.)
10	9 use mesz, prem
11	(computer searching.sh,id. or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,pt. or systematic$.ti,ab.)
12	11 use psyh
13	((analy$ or assessment$ or evidence$ or methodol$ or quantitativ$ or systematic$) adj2 (overview$ or review$)).tw. or ((analy$ or assessment$ or evidence$ or methodol$ or quantitativ$ or systematic$).ti. and review$.ti,pt.) or (systematic$ adj2 search$).ti,ab.
14	(metaanal$ or meta anal$).ti,ab.
15	(research adj (review$ or integration)).ti,ab.
16	reference list$.ab.
17	bibliograph$.ab.
18	published studies.ab.
19	relevant journals.ab.
20	selection criteria.ab.
21	(data adj (extraction or synthesis)).ab.
22	(handsearch$ or ((hand or manual) adj search$)).ti,ab.
23	(mantel haenszel or peto or dersimonian or der simonian).ti,ab.
24	(fixed effect$ or random effect$).ti,ab.
25	((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
26	or/2,4,6,8,10,12-25

3.1.2 Systematic review study design filter
AMED – OVID SP

1	meta analysis/
2	(databases bibliographic/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,pt. or systematic$.ti,ab.)
3	((analy$ or assessment$ or evidence$ or methodol$ or qualitativ$ or quantativ$ or systematic$) adj2 (overview$ or review$)).tw. or ((analy$ or assessment$ or evidence$ or methodol$ or quantativ$ or qualitativ$ or systematic$).ti. and review$.ti,pt.) or (systematic$ adj2 search$).ti,ab.
4	(metaanal$ or meta anal$).ti,ab.
5	(research adj (review$ or integration)).ti,ab.
6	reference list$.ab.
7	published studies.ab.
8	relevant journals.ab.

9	selection criteria.ab.
10	(data adj (extraction or synthesis)).ab.
11	(handsearch$ or ((hand or manual) adj search$)).ti,ab.
12	(mantel haenszel or peto or dersimonian or der simonian).ti,ab.
13	(fixed effect$ or random effect$).ti,ab.
14	or/1-13

3.1.3 Systematic review study design filter
Australian Education Index (AEI), British Education Index (BEI), Education Resources in Curriculum (ERIC), Social Services Abstracts (SSA), Sociological Abstracts, Applied Social Sciences Index and Abstracts (ASSIA), International Bibliography of Social Sciences (IBSS) - ProQUEST

S1	all (("meta anal*" or "systematic overview" or "systematic review" or "systematic search"))

3.1.4 Systematic review study design filter
CINAHL – EBSCO HOST

#	query
s33	s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s22 or s23 or s26 or s27 or s28 or s29 or s30 or s31 or s32
s32	ti (analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or quantativ* n5 review* or systematic* n5 review*) or ab (analy* n5 review* or assessment* n5 review* or evidence* n5 review* or methodol* n5 review* or quantativ* n5 review* or systematic* n5 review*)
s31	ti (analy* n5 overview* or assessment* n5 overview* or evidence* n5 overview* or methodol* n5 overview* or quantativ* n5 overview* or systematic* n5 overview*) or ab (analy* n5 overview* or assessment* n5 overview* or evidence* n5 overview* or methodol* n5 overview* or quantativ* n5 overview* or systematic* n5 overview*)
s30	ti (pool* n2 results or combined n2 results or combining n2 results) or ab (pool* n2 results or combined n2 results or combining n2 results)
s29	ti (pool* n2 studies or combined n2 studies or combining n2 studies) or ab (pool* n2 studies or combined n2 studies or combining n2 studies)
s28	ti (pool* n2 trials or combined n2 trials or combining n2 trials) or ab (pool* n2 trials or combined n2 trials or combining n2 trials)
s27	ti (pool* n2 data or combined n2 data or combining n2 data) or ab (pool* n2 data or combined n2 data or combining n2 data)
s26	s24 and s25
s25	ti review* or pt review*
s24	ti analy* or assessment* or evidence* or methodol* or quantativ* or systematic*
s23	ti "systematic* n5 search*" or ab "systematic* n5 search*"
s22	(s17 or s18 or s19) and (s20 or s21)
s21	ti systematic* or ab systematic*
s20	tx review* or mw review* or pt review*
s19	(mh "cochrane library")
s18	ti (bids or cochrane or index medicus or "isi citation" or psyclit or psychlit or scisearch or "science citation" or web n2 science) or ab (bids or cochrane or index medicus or "isi citation" or psyclit or psychlit or scisearch or "science citation" or web n2 science)
s17	ti ("electronic database*" or "bibliographic database*" or "computeri?ed database*" or "online database*") or ab ("electronic database*" or "bibliographic database*" or "computeri?ed database*" or "online database*")
s16	(mh "literature review")

s15	pt systematic* or pt meta*
s14	ti (“fixed effect*” or “random effect*”) or ab (“fixed effect*” or “random effect*”)
s13	ti (“mantel haenszel” or peto or dersimonian or “der simonian”) or ab (“mantel haenszel” or peto or dersimonian or “der simonian”)
s12	ti (handsearch* or "hand search*" or "manual search*") or ab (handsearch* or "hand search*" or "manual search*")
s11	ab "data extraction" or "data synthesis"
s10	ab "selection criteria"
s9	ab "relevant journals"
s8	ab "published studies"
s7	ab bibliograph*
s6	ab "reference list*"
s5	ti (“research review*” or “research integration”) or ab (“research review*” or “research integration”)
s4	ti (metaanal* or “meta anal*”) or ab (metaanal* or “meta anal*”)
s3	(mh "meta analysis")
s2	(mh "systematic review")
s1	(mh "literature searching+")

3.1.5 S ystematic review study design filter
SSCI – Web of Knowledge

#1	title=(“electronic database*” or “computer* database*” or “online database*” or bids or cochrane or embase or “index medicus” or “isi citation” or medline or psyclit or psychlit or scisearch or “science citation” or “web of science”)
#2	title=(review* or systematic*) or topic=(review* or systematic*)
#3	#1 and #2
#4	topic=((systematic* near search* or metaanal* or “meta anal*” or “research review*” or “research integration” or “reference list*” or bibliograph* or “published studies” or “relevant journals” or “selection criteria” or “data extraction” or “data synthesis” or handsearch* or “hand search*” or “manual search*” or “mantel haenszel” or peto or dersimonian or “der simonian” or “fixed effect*” or “random effect*” or ((pool* or combined or combining) near (data or trials or studies or results)))) or title=((systematic* near search* or metaanal* or “meta anal*” or “research review*” or “research integration” or “reference list*” or bibliograph* or “published studies” or “relevant journals” or “selection criteria” or “data extraction” or “data synthesis” or handsearch* or “hand search*” or “manual search*” or “mantel haenszel” or peto or dersimonian or “der simonian” or “fixed effect*” or “random effect*”) or ((pool* or combined or combining) near (data or trials or studies or results))))
#5	topic=(((analy* or assessment* or evidence* or methodol* or quantitativ* or systematic*) near (overview* or review*))) or title=(((analy* or assessment* or evidence* or methodol* or qualitativ* or quantitativ* or systematic*) near (overview* or review*)))
#6	#3 or #4 or #5

3.2 Randomised controlled trial filters

3.2.1 Randomized controlled trial study design filter
Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1	exp "clinical trial (topic)"/ or exp clinical trial/ or crossover procedure/ or double blind procedure/ or placebo/ or randomization/ or random sample/ or single blind procedure/
2	1 use emez
3	exp clinical trial/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or "randomized controlled trials as topic"/ or single-blind method/

4	3 use mesz, prem
5	(clinical trials or placebo or random sampling).sh,id.
6	5 use psyh
7	(clinical adj2 trial$).ti,ab.
8	(crossover or cross over).ti,ab.
9	(((single$ or doubl$ or trebl$ or tripl$) adj2 blind$) or mask$ or dummy or doubleblind$ or singleblind$ or trebleblind$ or tripleblind$).ti,ab.
10	(placebo$ or random$).ti,ab.
11	treatment outcome$.md. use psyh
12	animals/ not human$.mp. use emez
13	animal$/ not human$/ use mesz, prem
14	(animal not human).po. use psyh
15	(or/2,4,6-11) not (or/12-14)

3.2.2 Randomized controlled trial study design filter
AMED – OVID SP

1	(clinical trials or double blind method or placebos or random allocation).sh.
2	trial$.ti,ab.
3	(crossover or cross over).ti,ab.
4	(((single$ or doubl$ or trebl$ or tripl$) adj5 blind$) or mask$ or dummy or singleblind$ or doubleblind$ or trebleblind$ or tripleblind$).ti,ab.
5	(placebo$ or random$).ti,ab.
6	or/1-6

3.2.3 Randomized controlled trial study design filter
Australian Education Index (AEI), British Education Index (BEI), Education Resources in Curriculum (ERIC), Social Services Abstracts (SSA), Sociological Abstracts, Applied Social Sciences Index and Abstracts (ASSIA), International Bibliography of Social Sciences (IBSS) – PRO QUEST

S1	all ((clinical near/1 trial* or crossover or "cross over") or ((single* or doubl* or trebl* or tripl*) near/1 (blind* or mask* or dummy)) or (singleblind* or doubleblind* or trebleblind* or tripleblind* or placebo* or random*))

3.2.4 Randomized controlled trial study design filter
SSCI – Web of Knowledge

#1	topic=(((clinical near trial* or crossover or "cross over") or ((single* or doubl* or trebl* or tripl*) near (blind* or mask* or dummy)) or (singleblind* or doubleblind* or trebleblind* or tripleblind* or placebo* or random*))) or title=(((clinical near trial* or crossover or "cross over") or ((single* or doubl* or trebl* or tripl*) near (blind* or mask* or dummy)) or (singleblind* or doubleblind* or trebleblind* or tripleblind* or placebo* or random*)))

3.3 Observational study design filter

3.3.1 Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1	exp case control study/ or cohort analysis/ or cross-sectional study/ or follow up/ or longitudinal study/ or observational study/ or prospective

	study/ or retrospective study/
2	1 use emez
3	exp case control studies/ or exp cohort studies/ or cross-sectional studies/ or epidemiologic studies/
4	3 use mesz, prem
5	(cohort analysis or followup studies or longitudinal studies or prospective studies or retrospective studies).sh,id. or (followup study or longitudinal study or prospective study or retrospective study).md.
6	5 use psyh
7	((epidemiologic$ or observational) adj (study or studies)).ti,ab.
8	(cohort$1 or cross section$ or crosssection$ or followup$ or follow up$ or followed or longitudinal$ or prospective$ or retrospective$).ti,ab.
9	(case adj2 (control$ or series)).ti,ab.
10	or/2,4,6-9

APPENDIX 9: TEMPLATE DATA EXTRACTION FORM FOR CLINICAL STUDIES AND REVIEWS

The following tables set out the fields that were collected within the NCCMH data extraction database.

STUDY CHARACTERISTICS			
		Data to be extracted	**Instructions for Data Extraction**
Study Info		Trial ID	Enter an ID for the TRIAL (use the study ID for the first trial report, i.e. 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, etc. Enter N/A if not applicable.
Inclusion Criteria		Recruitment Location.	From what 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 (e.g. 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, etc. Enter 'Not reported' if information cannot 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 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 cannot be obtained.
		Run In 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 which 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?
		Inclusion Cut off Questionnaire1	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 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 1 diagnosis select either 'Psychosis - mixed, including bipolar'; or 'Psychosis - mixed, not including bipolar'.
		Diagnosis Format	Select the method by which participants were assessed. For studies with several screening steps (e.g. questionnaire then diagnostic interview), select the first method on the list.
		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 sub group category used to include participants (may not be reported).
		Diagnosis Sub-group category Q	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 (e.g. duration requirement, required comorbidities, etc.). DO NOT DUPLICATE information captured in other fields related to the inclusion and exclusion criteria.
Exclusion Criteria		Bipolar excluded?	Were individuals excluded from the study if they had a diagnosis of Bipolar?
		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?
		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

			(Columns AA-AC).
		Other psychiatric exclusions Quote	Enter a quote describing any other exclusions relating to 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 (e.g. heart disease, diabetes)? This does not include pregnancy.
		Physical health Quote.	Were individuals with any physical health conditions excluded from the study (e.g. heart disease, diabetes)? This does not include pregnancy.
		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 meds?
		Current 'Other Psychiatric'Meds	How did the study handle applicants who were currently using other psychiatric medication (other=not antipsychotic)?
		Current Physical or Neuro. Health Medications	How did the study handle applicants who were currently using medication for other health conditions (e.g. heart disease) or neurological conditions (e.g. 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 (e.g. 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.
		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.

		% 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.
		Race	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.
		Current 'Other Psychiatric' medication %	Other psychiatric=not antipsychotic. 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.
		Current Physical or Neuro medication %	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.
		Comorbidities Quote	If categorical data were converted to continuous data, give the number in each category.
		% Bipolar	If individuals with bipolar were included, enter % with bipolar as a decimal between 0 and 1. Do not round. Enter 'Not reported' if information cannot be obtained.
		% Substance induced	If individuals with substance induced psychosis were included, enter % as a decimal between

		psychotic disorder	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.
		% Physical health condition	If individuals with a physical health condition (e.g. 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 (e.g. 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 was 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 you judgement about risk of bias.
		Risk of bias	Sequence truly random = Low risk. Method not specified = Unclear. Not a 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?
		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	**Participants**	Participant blind	Were participants blind (unaware) of which treatment they were receiving?

(performance and detection bias)		Quote	Where possible, enter a QUOTATION to support you judgement about risk of bias.
		Risk of bias	Participants aware of assignment = High risk Participants unaware = Low risk Most psychological 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'.
	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 you 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 (i.e. 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 you 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
		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)		Drop out 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 you 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'.
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.
		All_Out	Were all measured outcomes reported in sufficient detail to include in a meta-analysis?
		Quote - if unclear	Where possible, enter a QUOTATION to support you 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 (e.g. because the intervention was thought to be beneficial or harmful)?
		Risk of bias	Use this section sparingly.
		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 Info		Trial ID	Enter an ID for the TRIAL (use the study ID for the first trial report, i.e. 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.
		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 and do not round. (Exclude assessments before and after treatment for research purposes only) or 'Not reported' if relevant.
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 (e.g. psychotherapy) enter 'N/A'.
		Dose type	Was the dose stable throughout the study (fixed) or could participants/clinicians change the dose? For psychological interventions (e.g. psychotherapy) enter 'N/A'.
		Dose Quote	If the dose was NOT fixed, enter a quotation describing way in which it was adjusted during the trial. For psychological interventions (e.g. psychotherapy) enter 'N/A'.
		Hours	Enter psychological interventions (e.g. psychotherapy) as total hours of contact excluding assessment for research purposes. For pharmacological interventions enter 'N/A'.
		Frequency	Enter psychological interventions (e.g. psychotherapy) as total hours of contact excluding assessment for research purposes. For pharmacological interventions enter 'N/A'.
		Duration	Enter psychological interventions (e.g. psychotherapy) 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.
	Time point	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 SD		Intervention Mean	Enter the group mean. Do NOT enter change scores here.
		Intervention SD	Enter the Standard deviation 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 (e.g. by last observation carried forward)
		Control mean	Enter the group mean. Do NOT enter change scores here.
		Control SD	Enter the Standard deviation 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 (e.g. by last observation carried forward).
		Direction	Does this outcome favour the intervention group or control group? Hint: If lower scores represent a better outcome (e.g. reduced symptoms) and the intervention mean is lower than the control mean, select 'Favours intervention'.
Mean and SE		Intervention Mean	Enter the group mean. Do NOT enter change scores here.
		Intervention SE	Enter the Standard error 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 (e.g. by last observation carried forward).
		Control mean	Enter the group mean. Do NOT enter change scores here.
		Control SE	Enter the Standard error 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 (e.g. by last observation carried forward).
		Direction	Does this outcome favour the intervention group or control group? Hint: If lower scores represent a better outcome (e.g. 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 (e.g. by last observation carried forward)
		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 (e.g. by last observation carried forward)
Mean difference, SD		Intervention Difference	Enter the within group mean difference (e.g. change from baseline).
		Intervention SD	Enter the standard deviation 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 (e.g. by last observation carried forward)
		Control Difference	Enter the within group mean difference (e.g. change from baseline).
		Control SD	Enter the standard deviation 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 (e.g. by last observation carried forward)
		Direction	Does this outcome favour the intervention group or control group? Hint: If lower scores represent a better outcome (e.g. 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 (e.g. change from baseline).
		Intervention SE	Enter the standard error of the within group change.
		Intervention sample size	
		Control Difference	Enter the within group mean difference (e.g. change from baseline).
		Control SE	Enter the standard error 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 (e.g. by last observation carried forward)
		Direction	Does this outcome favour the intervention group or control group? Hint: If lower scores represent a better outcome (e.g. 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

Each search was constructed using the groups of terms set out in Text Box 1. The full set of search terms is documented in sections 1 to 3.11. The selection of search terms was kept broad to maximise retrieval of evidence in a wide range of areas of interest to the GDG.

Text Box 1: Summary of systematic search strategies: Search strategy construction

Summary of systematic search strategies for health economic evidence					
Section 1					
Review area/s	**Search type**	**Search construction**	**Study design searched**	**Databases searched**	**Date range searched**
All review areas/RQs	Generic, evidence mapped to all review areas	Mainstream databases – generic search: [(population terms – version 1) AND (HE/QoL filter)] Topic specific databases – generic search: (Population search terms only – version 1)	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	Mainstream databases: Embase, Medline, PreMedline, PsycINFO Topic specific databases: ECONLIT, HTA*, NHS EED*	1995 to May 2012
Notes: *Evidence resulting from generic searches mapped to all review areas*					
Section 2					
Review area/s	**Search type**	**Search construction**	**Study design searched**	**Databases searched**	**Date range searched**
At risk / treatment: RQ A1,A2,B1	Focused, supplements evidence retrieved from generic searches (indicated in Section 1)	Mainstream – focused search: [(population terms – version 2) AND (at risk terms) AND (HE/QoL filter)] Topic specific databases – focused search: [(population terms – version 2) AND (at risk terms)]	Economic evidence (including full and partial economic evaluations) and health technology assessment reports	Mainstream databases: Embase, Medline, PreMedline, PsycINFO Topic specific databases: ECONLIT, HTA*, NHS EED*	1995 to May 2012
Notes: *Supplements HE evidence captured by generic searches indicated in Section 1*					
HTA (Health Technology Assessment database), NHS EED (NHS Economic Evaluation Database)					

1 Population search terms – all databases

1.1 Version 1

1.1.1 STEM – Mainstream Medical Databases

Version 1
Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1	exp psychosis/ or thought disorder/
2	1 use emez
3	delusions/ or hallucinations/ or exp "schizophrenia and disorders with psychotic features"/ or schizophrenia, childhood/
4	3 use mesz, prem
5	auditory hallucinations/ or delusions/ or hallucinations/ or hypnagogic hallucinations/ or paranoia/ or exp psychosis/ or schizoaffective disorder/ or thought disturbances/ or visual hallucinations/
6	5 use psyh
7	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).ti,ab.
8	or/2,4,6-7
9	exp adolescence/ or exp adolescent/ or adolescent development/ or exp child/ or child development/ or exp childhood/ or disabled student/ or elementary student/ or high school student/ or high school/ or kindergarten/ or middle school student/ or middle school/ or exp newborn/ or nursery school/ or primary school/ or exp puberty disorders/ or school/ or student/
10	9 use emez
11	exp adolescent/ or adolescent development/ or exp child/ or exp child development/ or exp infant/ or minors/ or puberty/ or puberty, delayed/ or puberty, precocious/ or students/ or exp schools/
12	11 use mesz, prem
13	limit 8 to ((childhood or adolescence <13 to 17 years>) and (100 childhood or 120 neonatal or 140 infancy or 160 preschool age or 180 school age or 200 adolescence))
14	adolescent development/ or boarding schools/ or charter schools/ or exp child development/ or classmates/ or elementary schools/ or exp elementary school students/ or graduate schools/ or high school students/ or high schools/ or institutional schools/ or junior high school students/ or junior high schools/ or kindergarten students/ or kindergartens/ or middle schools/ or nongraded schools/ or nursery schools/ or exp preschool students/ or puberty/ or schools/ or special education students/ or students/ or vocational school students/
15	13 use psyh
16	14 use psyh
17	or/15-16
18	(adolescen$ or child$ or infan$ or juvenile$ or teen$).hw,id.
19	(adolescen$ or baby or babies or boy$1 or child$ or delinquen$ or girl$1 or graders or infant$ or junior$1 or juvenile$ or kindergarten or minors or neonate$ or newborn$ or new born$ or p?ediatric$ or postpubert$ or postpubescen$ or prepubert$ or prepubescen$ or preschool$ or preteen$ or pubertal or puberty or puberties or pubescen$ or school$ or student$ or teen$ or toddler$ or (young$ adj2 (inpatient$ or patient$ or people$ or person$ or population$)) or youngster$ or youth$1).tw.
20	or/10,12,17-19
21	8 and 20

1.1.2 STEM - topic specific databases
Version 1
HTA, NHS EED – Wiley

#1	mesh descriptor **delusions**, this term only
#2	mesh descriptor **hallucinations**, this term only

#3	mesh descriptor **schizophrenia and disorders with psychotic features** explode all trees
#4	mesh descriptor **schizophrenia, childhood**, this term only
#5	(delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*):ti or (delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or psychotic* or psychosis or psychoses or schizo*):ab
#6	(#1 or #2 or #3 or #4 or #5)
#7	mesh descriptor **adolescent**, this term only
#8	mesh descriptor **child** explode all trees
#9	mesh descriptor **infant** explode all trees
#10	mesh descriptor **adolescent development**, this term only
#11	mesh descriptor **child development** explode all trees
#12	mesh descriptor **minors**, this term only
#13	mesh descriptor **puberty, delayed**, this term only
#14	mesh descriptor **puberty, precocious**, this term only
#15	mesh descriptor **students**, this term only
#16	mesh descriptor **schools**, this term only
#17	mesh descriptor **puberty**, this term only all trees
#18	(adolescen* or child* or infan* or juvenile* or teen*):kw or (adolescen* or baby or babies or boy* or child* or delinquen* or girl* or graders or infant* or junior* or juvenile* or kindergarten or minors or neonate* or newborn* or new born* or pediatric* or paediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or student* or teen* or toddler* or (young* near/2 (inpatient* or patient* or people or person* or population)) or youngster* or youth*):ti or (adolescen* or baby or babies or boy* or child* or delinquen* or girl* or graders or infant* or junior* or juvenile* or kindergarten or minors or neonate* or newborn* or new born* or pediatric* or paediatric* or postpubert* or postpubescen* or prepubert* or prepubescen* or preschool* or preteen* or pubertal or puberty or puberties or pubescen* or school* or student* or teen* or toddler* or (young* near/2 (inpatient* or patient* or people or person* or population)) or youngster* or youth*):ab
#19	(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18)
#20	(#6 and #19)

1.1.3 STEM - topic specific databases

Version 1

EconLIT – OVID SP

1	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).tw,hw,kw.
2	(adolescen$ or child$ or infan$ or juvenile$ or teen$).hw,kw.
3	(adolescen$ or baby or babies or boy$1 or child$ or delinquen$ or girl$1 or graders or infant$ or junior$1 or juvenile$ or kindergarten or minors or neonate$ or newborn$ or new born$ or p?ediatric$ or postpubert$ or postpubescen$ or prepubert$ or prepubescen$ or preschool$ or preteen$ or pubertal or puberty or puberties or pubescen$ or school$ or student$ or teen$ or toddler$ or (young$ adj2 (inpatient$ or patient$ or people$ or person$ or population$)) or youngster$ or youth$1).tw.
4	1 and or/2-3

1.2 Version 2

1.2.1 STEM – Mainstream Medical Databases

Version 2

Embase, Medline, PreMEDLINE, PsycINFO – OVID SP
Search request #8 from 1.11

1.2.2 STEM - topic specific databases
Version 2
HTA, NHS EED – Wiley
Search request #6 from 1.12

1.2.3 STEM - topic specific databases
Version 2
EconLIT – OVID SP
Search request #1 from 1.13

2. Question specific search strategies - all databases

2.1 High risk groups

- 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):

c) What is the course of these behaviours and symptoms?
d) What are the specific behaviours and symptoms that prompt initial recognition of psychoses or prompt diagnosis of schizophrenia?

- A2) In children and young people, who are at risk of developing psychosis and schizophrenia (i.e. what are the factors [e.g. socioeconomic, gender] that are associated with the future development of psychosis and/or a diagnosis of schizophrenia)?

B1) For children and young people who are at risk of developing psychosis and schizophrenia (at risk mental state), does the provision of pharmacological and/or psychological or psychosocial interventions improve outcomes?

2.1.1 Embase, Medline, PreMedline, PsycINFO – OVID SP

1	high risk patient/ or high risk population/ or ultra high risk criterion/ or ultra high risk population/
2	1 use emez
3	*risk factors/
4	3 use mesz
5	at risk populations/
6	5 use psyh
7	or/2,4,6
8	(symptom$ or symptomology).sh. or (prodrom$ or risk$).hw.
9	(blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory or pre monitory) adj2 (sign$ or symptom$)) or predelusion$ or prehallucin$ or prepsychos$ or prepsychotic$ or preschizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold$ or sub$ threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab.
10	or/8-9
11	(conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab.

12	10 and 11
13	ultra high risk.ti,ab.
14	((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).ab.
15	or/7,12-14

2.1.2 HTA, NHS EED – Wiley

#1	high risk patient/ or high risk population/ or ultra high risk criterion/ or ultra high risk population/
#2	mesh descriptor paranoid disorders, this term only
#3	mesh descriptor psychotic disorders explode all trees
#4	mesh descriptor schizophrenia, childhood, this term only
#5	mesh descriptor schizophrenia explode all trees
#6	("delusional disorder*" or hebephreni* or psychosis or psychoses or psychotic* or schizo*):ti or ("delusional disorder*" or hebephreni* or psychosis or psychoses or psychotic* or schizo*):ab
#7	(((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):ti or (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):ab or (((chronic* or serious or persistent or severe*) near/1 (mental* or psychological*) near/1 (disorder* or ill*))):kw
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	mesh descriptor risk factors, this term only
#10	(prodrom* or symptom* or risk*):kw
#11	(blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory or "pre monitory") near/2 (sign* or symptom*)) or predelusion* or prehallucin* or prepsychos* or prepsychotic* or preschizo* or (pre near/1 (delusion* or hallucin* or psychos* or psychotic* or schizo*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold* or "sub* threshold*" or "at risk*" or ((high* or incipient or increas*) near/3 risk*))
#12	#10 or #11
#13	(conversion* or ((develop* or progress*) near/2 (psychos* or psychotic* or schiz*)) or "first episode*" or fullthreshold* or "full threshold*" or onset* or progression or transition* or transitory)
#14	#12 and #13
#15	"ultra high risk"
#16	(("at risk" or ((high or increase*) near/2 risk) or blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory) near/2 (sign* or symptom*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold or "sub* threshold") and (psychos* or psychotic* or schiz*)):ti. or (("at risk" or ((high or increase*) near/2 risk) or blips or "brief limited intermittent psychotic symptom*" or ((attenuat* or early or premonitory) near/2 (sign* or symptom*)) or prodrom* or subclinical* or "sub clinical*" or subthreshold or "sub* threshold") near/3 (psychos* or psychotic* or schiz*)):ab.
#17	#8 and (#9 or #14 or #15 or #16)

2.1.3 EconLIT – OVID SP

1	(prodrom$ or risk$ or symptom$).kw,hw.
2	(blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory or pre monitory) adj2 (sign$ or symptom$)) or predelusion$ or prehallucin$ or prepsychos$ or prepsychotic$ or preschizo$ or (pre adj (delusion$ or hallucin$ or psychos$ or psychotic$ or schizo$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold$ or sub$ threshold$ or at risk$ or ((high$ or incipient or increas$) adj3 risk$)).ti,ab.
3	or/1-2
4	(conversion$ or ((develop$ or progress$) adj2 (psychos$ or psychotic$ or schiz$)) or first episode$ or fullthreshold$ or full threshold$ or onset$ or progression or transition$ or transitory).ti,ab.
5	3 and 4
6	ultra high risk.ti,ab.
7	((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) and (psychos$ or psychotic$ or schiz$)).ti. or ((at risk or ((high or increase$) adj2 risk) or blips or brief limited intermittent psychotic symptom$ or ((attenuat$ or early or premonitory) adj2 (sign$ or symptom$)) or prodrom$ or subclinical$ or sub$ clinical$ or subthreshold or sub$ threshold) adj3 (psychos$ or psychotic$ or schiz$)).ab.
8	or/5-7

3 Study design filters – all databases

3.1 Health economic study design filter

3.1.1 Health economic and quality of life study design filter
Embase, Medline, PreMEDLINE, PsycINFO – OVID SP

1	budget/ or exp economic evaluation/ or exp fee/ or funding/ or exp health care cost/ or health economics/ or exp pharmacoeconomics/ or resource allocation/
2	1 use emez
3	exp budgets/ or exp "costs and cost analysis"/ or economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or exp "fees and charges"/ or exp resource allocation/ or value of life/
4	3 use mesz
5	exp "costs and cost analysis"/ or "cost containment"/ or economics/ or finance/ or funding/ or health care economics/ or pharmacoeconomics/ or exp professional fees/ or resource allocation/
6	5 use psyh
7	(budget$ or cost$ or econom$ or expenditure$ or fee or fees or financ$ or fund or funds or funding$ or funded or (expenditure$ not energy) or pharmacoeconomic$ or price or prices or pricing or ration or rations or rationing$ or rationed or resource$ allocat$ or saving or (value adj2 (monetary or money))).ti,ab.
8	decision theory/ or decision tree/ or monte carlo method/ or *nonbiological model/ or (statistical model/ and exp economic aspect/) or stochastic model/ or *theoretical model/
9	8 use emez
10	exp decision theory/ or markov chains/ or exp models, economic/ or *models, organizational/ or *models, theoretical/ or monte carlo method/
11	10 use mesz
12	exp decision theory/ or exp stochastic modeling/
13	12 use psyh
14	((decision adj (analy$ or model$ or tree$)) or economic model$ or markov or monte carlo).ti,ab.
15	quality adjusted life year/ or "quality of life index"/ or short form 12/ or short form 20/ or

	short form 36/ or short form 8/ or sickness impact profile/
16	15 use emez
17	quality-adjusted life years/ or sickness impact profile/
18	17 use mesz
19	"quality of life"/
20	19 use psyh
21	(((disability or quality) adj adjusted) or (adjusted adj2 life)).ti,ab.
22	(disutili$ or (utilit$ adj1 (health or score$ or value$ or weigh$))).ti,ab.
23	(health year equivalent or hye or hyes).ti,ab.
24	(daly or qal or qald or qale or qaly or qtime$ or qwb$).ti,ab.
25	discrete choice.ti,ab.
26	(euroqol$ or euro qol$ or eq5d$ or eq 5d$).ti,ab.
27	(hui or hui1 or hui2 or hui3).ti,ab.
28	((quality or value$) adj3 (life or survival or well$)).ti,ab.
29	(qol or hql$ or hqol$or h qol$ or hrqol or hr qol or hr ql or hrql).ti,ab.
30	rosser.ti,ab.
31	sickness impact profile.ti,ab.
32	(standard gamble or time trade$ or tto or willingness to pay).ti,ab.
33	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
34	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
35	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab.
36	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab
37	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab.
38	or/ 2,4,6-7,9,11,13-14,16,18,20-37

APPENDIX 11: METHODOLOGY CHECKLIST FOR ECONOMIC STUDIES

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 Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

10.1.11. Long-term outcomes for children and young people with prodomal symptoms suggestive of psychosis

What are the long-term outcomes, both psychotic and non-psychotic, for children and young people with prodromal 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 10-20% of children and young people who have been identified as at high risk 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.

10.1.22. Omega-3 fatty acids for treatment of high-risk children and young people

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 RCT 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.

10.1.33. Family intervention with individual cbt for treament of high-risk children and young people

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 for 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 schizophrenia, 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.

10.1.44. Psychological treatment and/or antipsychotics for first-episode psychosis in children and young people

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 treatment,and antipsychotic medication combined, for young people with in the early stages of schizophrenia using an randomised controlled design and adequately powered. The combination of psychological treatments 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 established schizophrenia to the individual, to 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 side effects are so severe that there is considerable impetus to develop alternative treatment strategies. It has been recognised that psychological treatments as an adjunct to antipsychotic medication have an important part to play in the treatment of schizophrenia. The first NICE guideline identified family intervention and CBT as adjunctive treatments and current evidence suggests that these interventions are cost saving. There has been one recent positive trial of CBT as a first-line treatment, without antipsychotics, for young people with in the early stages of schizophrenia.

10.1.55. Clozapine for children and young people who are unresponsive to antipsychotics and psychological treatment combined

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, RCT-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.

REMAINING APPENDICES ON CD

Appendix 13: Clinical evidence – study characteristics tables

Appendix 14: Clinical evidence – forest plots

Appendix 15: Economic evidence – completed methodology checklists

Appendix 16: Economic evidence – evidence tables of published studies

Appendix 17: Clinical and economic evidence profiles.

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12 ABBREVIATIONS

AEI	Australian Education Index
AGREE	Appraisal of Guidelines for Research and Evaluation Instrument
AHRQ	United States Agency for Healthcare Research and Quality
AIMS	Abnormal Involuntary Movement Scale
AMED	Allied and Complementary Medicine
AMHS	adult mental health services
ARMS	at risk mental states
AS	attenuated subclinical
ASSIA	Applied Social Services Index and Abstracts
BARS	Barnes Akathesia Rating Scale
BDI	Beck depression inventory
BEI	British Education Index
BLIPS	brief limited intermittent psychotic symptoms
BMI	Body Mass Index
BMJ	*British Medical Journal*
BMT	body movement therapy
BNF	British National Formulary
BP	blood pressure
BPRS	Brief Psychiatric Rating Scale
BPRS-C	Brief Psychiatric Rating Scale for Children
BPRS-P	Brief Psychiatric Rating Scale for Psychosis
CAARMS	Comprehensive Assessment of At Risk Mental States
CAFAS	Child and Adolescent Functional Assessment Scale
CAMHS	Child and Adolescent Mental Health Services
CAU	care as usual
CBT	cognitive behavioural therapy
CCMD-II-R	Chinese Classification of Mental Disorders (2nd edition)
CDSR	Cochrane Database of Systematic Reviews
CDSS	Calgary Depression Scale for Schizophrenia
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Centre for epidemiologic studies depression scale
CGAS	Children's Global Assessment Scale
CGI	Clinical Global Impression scale
CHRTT	crisis resolution and home treatment team
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMA	Canadian Medical Association
CMHT	community mental health team
CPA	Care Programme Approach
CPRS	Children's Psychiatric Rating Scale
CRD	Centre for Reviews and Dissemination
CRT	cognitive remediation therapy

CT	computed tomography
DALY	Disability Adjusted Life Year
DARE	Database of Abstracts and Reviews of Effectiveness
DSM (-III, -IIIR, -IV, -V)	*Diagnostic and Statistical Manual of Mental Disorders* (3rd edition, revised, 4th edition, 5th edition)
DUP	duration of untreated psychosis
ECG	electrocardiogram
EconLit	American Economic Association's electronic bibliography
EED	Economic Evaluation Database
EEG	electroencephalogram
EIP	early intervention in psychosis
Embase	Excerpta Medica database
EPPIC	Early Psychosis Prevention and Intervention Centre, Australia
EPS	extra-pyramidal side effect
ERIC	Education Resources in Curriculum
ERI	Early Recognition Inventory
ES	effect size
FE	fixed effect
FEP	first episode psychosis
FGA	first generation antipsychotic
FIS	Family Interview Schedule
GAF	Global Assessment of Functioning
GAS	Global Assessment Scale
GDG	Guideline Development Group
G-I-N	Guidelines International Network
GP	general practitioner
GRADE	Grading of Recommendations: Assessment, Development and Evaluation
HAM-D	Hamilton Depression Rating Scale
Hb1Ac	glycosylated haemoglobin
HES	hospital episode statistics
HMIC	Health Management Information Consortium
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	integrated psychological therapy

IQ	intelligence quotient
ITT	intention-to-treat
K	number of studies
K-SADS-PL	Kiddie-SADS-Present and Lifetime Version
LEO	Lambeth Early Onset
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MD	mean difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
MRI	magnetic resonance imaging
n/N	number of participants
NBI	needs-based intervention
NCCMH	National Collaborating Centre for Mental Health
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NR	not reported
NTT	number needed to treat
OASIS	Outreach and Support in South London
OMNI	Organizing Medical Networked Information
ONS	Office for National Statistics
PACE	Personal Assessment and Crisis Evaluaton Clinic, Australia
PANSS	Positive and Negative Syndrome Scale
PICO	population, intervention, comparison and outcome
POMH-UK	Prescribing Observatory for Mental Health, United Kingdom
PSE-9	Present state examination (9th edition)
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
QLS	Quality of Life Scale
QNIC	Quality Network for Inpatient CAMHS
QOF	Quality and Outcomes Framework
RCT	randomised control trial

RE	random effect
RQ	review question
RR	relative risk / risk ratio
SADS-C	Schedule for Affective Disorders and Schizophrenia - Change Version
SANS	Scale for Assessment of Negative Symptoms
SAS	Simpson-Angus Extrapyramidal Side Effects Scale
SC	supportive counselling
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SCQ	Social Communication Questionnaire
SD/sd	standard deviation
SGA	second generation antipsychotic
SIGN	Scottish Intercollegiate Guidelines Network
SIPS	Structured Interview for Prodromal Symptoms
SMD	standardised mean difference
SOFAS	Social and Occupational Functioning Assessment Scale
SPI	specific preventive intervention
SR	systematic review
SSA	Social Services Abstracts
SSCI	Social Sciences Citation Index
TESS	Treatment Emergent Symptoms Scale
TG	Topic Group
TRIP	Turning Research Into Practice
TSH	Thyroid stimulating hormone
UHR	ultra high risk
UKU	Udvalg for Kliniske Undersogelser Neurologic Subscale
WHO	World Health Organisation
WTE	whole time equivalent
YMRS	Young Mania Rating Scale