NICE National Institute for
Health and Care Excellence

Psychosis and schizophrenia in children and young people

Evidence Update March 2015

A summary of selected new evidence relevant to NICE
clinical guideline 155 'Psychosis and schizophrenia in children
and young people: recognition and management' (2013)

Evidence Update 76

Contents

Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

[1] **Psychosis and schizophrenia in children and young people. NICE clinical guideline 155 (2013)**

A search was conducted for new evidence from 1 May 2012 to 25 September 2014. A total of 1448 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 27 references underwent a rapid critical appraisal process and then were reviewed by an Evidence Update Advisory Group, which advised on the final list of 12 items selected for the Evidence Update. See Appendix A for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 155 (NICE CG155). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guidelines methods guides for further information about updating clinical guidelines.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

[1] Psychosis and schizophrenia in adults. NICE clinical guideline 178 (2014)

[1] Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years. NICE technology appraisal 213 (2011)

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[1] NICE-accredited guidance

NICE Pathways

NICE Pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathway covers advice and recommendations related to this Evidence Update:

- [Psychosis and schizophrenia](#). NICE Pathway

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on NICE CG155. Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from NICE CG155.

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

Key point	Potential impact on guidance	
	Yes	**No**
General principles of care **Long-term outcomes of early-onset schizophrenia** • The early onset of schizophrenia in children and young people appears to be associated with poor long-term outcomes.		✓
Possible psychosis **Cognitive deficits in people at risk of psychosis** • Cognitive deficits appear to be evident in people at familial or clinical risk of psychosis, and the level of deficit appears to have some correlation with eventual transition to psychosis.		✓
Cognitive behavioural therapy (CBT) for people at risk of psychosis • In people at high risk of psychosis, a mean of 9 sessions of CBT plus monitoring of mental state does not appear to reduce transition to psychosis or distress from symptoms of psychosis, but does appear to reduce the severity of psychotic symptoms.		✓
CBT with or without an antipsychotic for people at risk of psychosis • Rates of transition to psychosis in people at high risk of psychosis appear to be similar following CBT (with or without risperidone[2]) and supportive therapy.		✓
First episode psychosis **Short-term efficacy and safety of quetiapine** • After 6 weeks, quetiapine[2] appears to improve schizophrenia symptoms in young people aged 13–17 years, with a safety profile similar to that in adult populations.		✓
Long-term safety and tolerability of quetiapine • In children and young people aged 10–17 years with schizophrenia or bipolar disorder, safety and tolerability of quetiapine[2] over 26 weeks can be limited by a number of adverse effects, including potentially clinically significant lipid disturbance, weight gain, and raised blood pressure.		✓

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[2] At the time of publication of this Evidence Update, risperidone and quetiapine did not have a UK marketing authorisation for this indication in children and young people.

Key point	Potential impact on guidance	
	Yes	**No**
Long-term safety and tolerability of olanzapine • Following long-term (>24 weeks) treatment with olanzapine[3], the types of metabolic changes seen in young people aged 12−18 years are similar to those seen in adults. However, the magnitude of changes in parameters such as body weight and some blood lipid levels appears to be greater in young people.	✓*	
Risk of diabetes with antipsychotics • Children and young people aged 6–17 years prescribed antipsychotics appear to have an increased risk of type 2 diabetes. This risk can remain for up to 1 year after stopping antipsychotics.		✓
Cardiometabolic risk in people with schizophrenia • People with first episode schizophrenia spectrum disorders (with a mean lifetime antipsychotic treatment duration of less than 7 weeks) appear to have higher rates of smoking, metabolic syndrome, dyslipidemia and prehypertension than the general population. Body composition issues (such as higher BMI) appear to correlate with duration of psychiatric illness, and metabolic issues (such as higher triglycerides) appear to correlate with antipsychotic treatment duration.		✓
Group psychoeducation for young people with psychosis and their families • A structured psychoeducational group intervention for young people with psychosis and their parents or carers, comprising problem solving activities and provision of written materials, appears to reduce visits to the emergency department.		✓
Promoting recovery and providing possible future care in secondary care ***Risk of neutropenia with clozapine*** • In children and young people aged 6–18 years with schizophrenia treated with clozapine[3], mild neutropenia appears to develop in about one-third of patients and moderate neutropenia in about one-fifth (higher rates than adult populations). There appears to be no evidence of serious adverse events (such as agranulocytosis or serious infection), although younger, male, and African American children appear to be at greater risk of neutropenia.		✓
Areas not currently covered by NICE CG155 ***Genetic basis of weight gain associated with antipsychotic drugs*** • A genetic locus near the melanocortin 4 receptor gene (mutations of which are linked to extreme obesity in children and young people) appears to be associated with weight gain and other adverse metabolic effects in response to antipsychotic drugs.		✓

[3] At the time of publication of this Evidence Update, olanzapine did not have a UK marketing authorisation for this indication in children and young people, and clozapine had a UK marketing authorisation for treatment-resistant schizophrenia only in young people aged 16 years and older.
* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.

1   Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from NICE CG155.

1.1   General principles of care

Long-term outcomes of early-onset schizophrenia

NICE CG155 recommends:

- 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; and are not passed from one team to another unnecessarily.
- Helping the child or young person to continue their education.
- Anticipating 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. Ensuring 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.
- 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.
- Children and young people with psychosis or schizophrenia who are being treated in an early intervention in psychosis service should have access to that service for up to 3 years (or until their 18th birthday, whichever is longer) whatever the age of onset of psychosis or schizophrenia.
- Providing supported employment programmes for those young people with psychosis or schizophrenia above compulsory school age who wish to return to work or find employment.

A systematic review and meta-analysis by **Clemmensen et al. (2012)** analysed the long-term outcome and prognosis of early-onset schizophrenia. Study inclusion criteria were: participants with a mean age of 18 years or under; retrospective or prospective studies; and reporting data on early-onset schizophrenia alone, or combined data on early-onset schizophrenia and other psychotic illnesses. Exclusion criteria were: single case studies; reporting only single or specific parameters (such as mortality) but no overall broad outcome measures allowing a classification of participants into 'good', 'moderate', or 'poor' outcome; reporting only mean outcome parameters; not using internationally accepted diagnostic criteria; follow-up less than 1 year; and poor description of outcome criteria. A total of 21 studies were identified (n=716) with a mean duration of follow-up ranging from 1.5 to 42.0 years (mean=14.4 years).

The 3 review authors scored the outcome in each study as either good, moderate, or poor based on scores in the various scales used across the studies: the General Functioning Scale (including Global Assessment of Functioning, Children's Global Assessment Scale, and Global Assessment Scale) or Study-Specific Functioning outcomes. Consensus on scoring was reached between authors for all studies. The frequencies of the 3 outcome categories (good, moderate, poor) were calculated as percentages and weighted by study size.

For studies looking only at early-onset schizophrenia (n=422), 15.4% of patients had a good outcome, 24.5% had a moderate outcome, and 60.1% had a poor outcome. Outcomes were significantly better (although still mainly poor) in studies reporting data on both early-onset schizophrenia and other psychotic illnesses (n=294; good=19.6%, moderate=33.6%, poor=46.8%; p<0.001 for each category versus the respective category in early-onset schizophrenia only studies). In sub-analyses examining factors affecting the outcomes of studies in early-onset schizophrenia only, worse outcomes were associated with: sample attrition (possibly explained by people with successful treatment dropping out); a follow-up period longer than 10 years; male gender; and diagnosis before 1970.

Limitations of the evidence included that:

- Studies included by the review were not quality assessed.
- The studies varied in their methodology (such as diagnosis criteria, outcomes, follow-up, and design).
- The review included studies from 1980 onwards, which allowed inclusion of long follow-up periods. However, this approach meant that the studies spanned a large period of time during which time diagnosis and management of psychosis has changed considerably.
- Given some heterogeneous definitions of the 3 outcome categories in a minority of the original studies, the authors performed some revised categorisations.

The evidence suggests that the early onset of schizophrenia in children and young people appears to be associated with poor long-term outcomes. This is consistent with NICE CG155 that long-term care strategies should be in place for children and young people with psychosis, including continuity of services, management of transition between services, long-term monitoring, and support for education and employment needs.

Key reference
Clemmensen L, Vernal DL, Steinhausen HC (2012) A systematic review of the long-term outcome of early onset schizophrenia. BMC Psychiatry 12: 150

1.2   Possible psychosis

Cognitive deficits in people at risk of psychosis
NICE CG155 recommends that a child or young person who experiences transient or attenuated psychotic symptoms or other experiences suggestive of possible psychosis, should be referred for assessment to a specialist mental health service such as CAMHS or an early intervention in psychosis service (14 years or over). Assessments in CAMHS should include a consultant psychiatrist, and assessments in early intervention in psychosis services should be multidisciplinary. If a clear diagnosis of psychosis cannot be made, regular monitoring for further changes in symptoms and functioning should be performed for up to 3 years. The frequency and duration of monitoring should be determined 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.

However, the guideline does not specifically refer to assessment or monitoring of cognitive deficits in children or young people at risk of psychosis. Though for children and young people with first episode psychosis, NICE CG155 recommends ensuring they receive a comprehensive multidisciplinary assessment, which should include assessment of the developmental domain (social, cognitive and motor development and skills, including coexisting neurodevelopmental conditions).

A systematic review and meta-analysis by **Bora et al. (2014)** examined the association between cognitive deficits and the risk of, and transition to, psychosis among people at risk of psychosis. Studies reporting performance on cognitive tasks were included that: compared

outcomes of people seeking help for symptoms suggestive of psychosis ('clinical risk'), or unaffected relatives of people with schizophrenia ('familial risk'), with healthy controls; compared at-risk people who had and had not transitioned to psychosis (each group had to include at least 5 participants); and had a mean age in the at-risk study population of between 15 and 29 years. Studies were excluded that: compared at-risk individuals with help-seeking controls; used screening to recruit people at clinical risk of psychosis who had not sought help; or defined risk on the basis of psychometric risk or schizotypal personality.

'Familial risk' meant having a parent or sibling with schizophrenia, or at least 2 relatives with schizophrenia. 'Clinical risk' meant a person seeking help associated with 1 or more of the following circumstances:

- recent onset or worsening of attenuated positive symptoms (such as hallucinations and delusions)
- recent onset of clear psychotic symptoms that were significant but not sufficiently sustained to meet the criteria for psychotic disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV; or
- familial risk of psychosis plus deterioration in functioning.

A total of 44 studies were identified (people at clinical or familial risk, n=2113; healthy controls, n=1748). Cognitive performance was measured by combining individual cognitive tasks into domains, because there were not enough studies to perform meta-analyses for all tasks. The domains were: premorbid and current intelligence quotient; processing speed; verbal and visual memory; executive functions; verbal and visuospatial working memory; attention; and fluency. The size of between-group differences was measured by Cohen's d.

Compared with controls, deficits were seen in every cognitive domain for people at clinical risk (Cohen's d values ranged from 0.34 to 0.71) and familial risk of psychosis (Cohen's d values ranged from 0.24 to 0.81). Where data were reported, deficits were also significantly worse for every individual cognitive task (except the Stroop test of processing speed) both in people at clinical and in those at familial risk (p≤0.04 for all). People at clinical risk who went on to transition to psychosis had more severe cognitive deficits than those who did not transition in all cognitive domains (Cohen's d values ranged from 0.31 to 0.49) except sustained attention. For people at familial risk, the only study examining transition to psychosis found that verbal memory was impaired in people who transitioned to psychosis versus those who did not.

Limitations of the evidence included that;

- Studies included by the review were not quality assessed, and many did not report variables such as antipsychotic use.
- The included studies varied in their methodology (such as follow up, risk criteria, and exclusion criteria), although heterogeneity of effect sizes across the studies was modest (I^2=0–0.18%).

The evidence suggests that cognitive deficits appear to be evident in people at familial or clinical risk of psychosis, and the level of deficit appears to have some correlation with eventual transition to psychosis. NICE CG155 does not currently recommend assessment or monitoring of cognitive deficits in children or young people at risk of psychosis, however cognitive assessment is recommended for children and young people with first episode psychosis, It may be that the same principles of assessing children and young people with first episode psychosis should potentially also be applied to those with possible psychosis. Further longer-term studies are needed to fully investigate the timing and development of cognitive deficits in psychosis. Further research is also needed to establish the utility of measuring cognitive deficits in the context of assessment, monitoring, prognosis and early intervention.

Key reference
Bora E, Lin A, Wood SJ et al. (2014) Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatrica Scandinavica 130: 1–15

Cognitive behavioural therapy (CBT) for people at risk of psychosis

NICE CG155 recommends that when transient or attenuated psychotic symptoms or other mental state changes associated with distress, impairment or help-seeking behaviour are not sufficient for a diagnosis of psychosis or schizophrenia, individual CBT should be considered. It is recommended that CBT should be delivered on a one-to-one basis over at least 16 planned sessions (although longer may be needed).

A multicentre randomised controlled trial (RCT; n=288) in the UK by **Morrison et al. (2012)** examined the effect of CBT on transition to psychosis and psychotic symptoms among people at high risk of psychosis. Participants aged 14–35 years (mean=20.74 years) at high risk of psychosis, and actively seeking help, were identified from primary and secondary care settings in 5 UK regions. Patients were assessed on the Comprehensive Assessment of the At-Risk Mental State (CAARMS), and eligible diagnoses for inclusion were: brief limited intermittent psychotic symptoms; attenuated psychotic symptoms; or state plus trait factors ('state'=characteristics during episodes of illness; 'trait'=enduring characteristics). Exclusion criteria were: current or previous receipt of antipsychotic drugs; moderate to severe learning disability; and organic (non-psychiatric) mental disorders.

Patients (as well as receiving treatment as usual) were randomised to either CBT (up to 26 sessions over 6 months) plus monitoring of mental state, or to monitoring of mental state only. The mean number of sessions received by the CBT group was 9.11 (range 0–26), with 6.3% (9/144) of patients attending 0 sessions and 75.0% (108/144) of patients having at least 4 sessions. Primary outcomes were CAARMS scores at 12 months for: transition to psychosis (using intention-to-treat analysis and discrete time survival models); and severity of psychotic symptoms and distress (using random effects regression adjusted for site and baseline symptoms).

No significant difference was seen in the number of patients transitioning to psychosis between the CBT group and the control group (proportional odds ratio=0.73, 95% confidence interval [CI] 0.32 to 1.68, p=0.45). Distress from psychotic symptoms did not differ significantly between groups (estimated difference=−3.03, 95% CI −6.95 to 0.94, p=0.14), but psychotic symptom severity was significantly lower in the CBT group (estimated difference=−3.67, −6.71 to −0.64, p=0.018). A regression model examining the effect of the number of CBT sessions on outcomes suggested that a higher number of sessions was associated with a greater reduction in psychosis severity (estimated effect=−0.78 per session, 95% CI −1.33 to –0.23, p=0.005).

Limitations of the evidence included that:

- The observed rates of transition to psychosis (10/144 [6.9%] in the CBT group and 13/144 [9.0%] in the control group) were lower than expected. This may have resulted from using an adjudication panel to establish cases of transition – a more rigorous process than might have been used by other studies. The unexpectedly low rates of psychosis transition meant that the trial was therefore significantly underpowered to detect a difference in this outcome.
- A high rate of withdrawal and loss to follow-up at 12 months (34.7%) was observed, although an attempt to account for the expected high number of dropouts was made during recruitment. However, the proportion of dropouts were similar in both groups, and attempts to identify transition to psychosis in patients lost to follow-up suggested a transition in only 1 participant.

- Treatment as usual was likely to have differed across the 5 sites, although randomisation was stratified by site to attempt to control for this.

The evidence suggests that in people at high risk of psychosis, a mean of 9 sessions of CBT plus monitoring of mental state does not appear to reduce transition to psychosis or distress from symptoms of psychosis, but does appear to reduce the severity of psychotic symptoms. This is broadly consistent with recommendations in NICE CG155 to consider CBT when symptoms are not sufficient for a diagnosis of psychosis or schizophrenia.

However, reduction in the severity of psychotic symptoms may be achievable in less than the 16 sessions of CBT currently recommended by the guideline. The recommended number of sessions was taken from the NICE clinical guideline 'Schizophrenia' (now replaced by 'Psychosis and schizophrenia in adults' [NICE CG178]), and is therefore drawn from an evidence base among adult populations. Current evidence suggests that children at risk of psychosis could benefit from fewer than 16 sessions of CBT, and further research is needed to examine the optimum number of sessions.

Key reference

Morrison AP, French P, Stewart SL et al. (2012) Early detection and intervention evaluation for people at risk of psychosis: multisite randomised controlled trial. BMJ 344: e2233

CBT with or without an antipsychotic for people at risk of psychosis

NICE CG155 recommends that when transient or attenuated psychotic symptoms or other mental state changes associated with distress, impairment or help-seeking behaviour are not sufficient for a diagnosis of psychosis or schizophrenia, individual CBT should be considered.

The guideline also states: '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.'

An RCT (n=115) in Australia by **McGorry et al. (2013)** compared the effect of CBT plus risperidone[4], CBT plus placebo, and supportive therapy plus placebo on transition to psychosis among people at high risk of psychosis. Participants aged 14–30 years (mean=18 years) were identified from a specialised clinic for young people at high risk of developing psychosis. Inclusion criteria were (in the previous 12 months): attenuated (sub-threshold) psychotic symptoms; history of brief self-limited psychotic symptoms, which spontaneously resolve; and a presumed genetic vulnerability to psychotic disorder plus persistent low functioning for at least 1 month. Exclusion criteria were: history of a psychotic or manic episode; history of a medical condition that may account for initial referral (such as epilepsy); clinically relevant neurological, biochemical, or haematological abnormalities; serious comorbidities; a lifetime antipsychotic dose of 15 mg haloperidol (or equivalent) or greater; any history of mood-stabilising drugs; history of severe drug allergy; intellectual disability (intelligence quotient<70); and pregnancy or lactation.

Patients were then randomised to 1 of 3 groups: CBT plus risperidone (n=43), CBT plus placebo (n=44), or supportive therapy plus placebo (n=28). Risperidone was started at a dose of 0.5 mg/day and gradually increased over 4 weeks to up to 2 mg/day if tolerated. CBT was provided by clinical psychologists and comprised 4 modules: stress management; reducing depression and negative symptoms (such as emotional apathy and self-neglect); coping with positive symptoms (such as hallucinations and delusions); and managing other comorbidities. Supportive therapy was also provided by clinical psychologists with the aim of providing emotional and social support, alongside problem solving, stress management, and

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[4] At the time of publication of this Evidence Update, risperidone did not have a UK marketing authorisation for this indication in children and young people.

psychoeducation. All participants were seen weekly by a blinded psychiatrist for 4 weeks and then monthly for 11 months. The primary outcome was transition to psychosis at 12 months assessed using the CAARMS. Data analysis was intention to treat, using Kaplan–Meier survival analysis and log-rank tests.

Rates of transition to psychosis in the 3 groups were:

- CBT plus risperidone: 10.7% (standard deviation [SD] 5.0%).
- CBT plus placebo: 9.6% (SD 4.6%).
- Supportive therapy plus placebo: 21.8% (SD 8.8%).

Transition rates did not differ significantly between the treatment groups (log-rank test p=0.60)

Limitations of the evidence included that:

- The attrition rate was relatively high (37% by 12 months across all groups), although number of dropouts did not differ significantly between groups.
- The psychosis transition rates observed in the trial were lower than those used to calculate sample sizes for the study, therefore the trial was underpowered. Additionally, the high levels of antidepressant use (39–63% across the 3 groups) may have reduced the psychosis transition rate, further reducing the power of the study.
- Adherence to risperidone was poor in 63% of patients and no patients showed full adherence, which may have reduced the likelihood of observing an intervention effect.

Limited evidence suggests that rates of transition to psychosis in people at high risk of psychosis appear to be similar following CBT (with or without risperidone) and supportive therapy. This is consistent with NICE CG155 to consider CBT when symptoms are not sufficient for a diagnosis of psychosis or schizophrenia. The similar efficacy seen in the study of CBT with or without risperidone is consistent with the recommendation not to offer antipsychotic medication when symptoms are not sufficient for a diagnosis of psychosis or schizophrenia. Further research is needed to establish the efficacy of CBT for young people at high risk of psychosis in adequately powered trials with a clinically important primary outcome.

Key reference

McGorry PD, Nelson B, Phillips LJ et al. (2013) Randomized controlled trial of interventions for young people at ultra-high risk of psychosis: twelve-month outcome. Journal of Clinical Psychiatry 74: 349–56

1.3 First episode psychosis

Antipsychotic medication

NICE CG155 recommends offering oral antipsychotic medication[5] in conjunction with psychological interventions for children and young people with first episode psychosis.

It further recommends that 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. The likely benefits and possible side effects of each drug should be discussed including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences).

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[5] At the time of publication of this Evidence Update, most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people.

The following should be monitored and recorded regularly and systematically throughout treatment, but especially during titration[6]:

- efficacy, including changes in symptoms and behaviour
- side effects of treatment, taking into account overlap between certain side effects and clinical features of schizophrenia (for example, the overlap between akathisia and agitation or anxiety)
- the emergence of movement disorders
- weight, weekly for the first 6 weeks, then at 12 weeks and then every 6 months (plotted on a growth chart)
- height every 6 months (plotted on a growth chart)
- waist circumference every 6 months (plotted on a percentile chart)
- pulse and blood pressure (plotted on a percentile chart) at 12 weeks and then every 6 months
- fasting blood glucose, glycosylated haemoglobin (HbA_{1c}), blood lipid and prolactin levels at 12 weeks and then every 6 months
- adherence
- physical health.

Short-term efficacy and safety of quetiapine

A 6-week multicentre RCT (n=222) in Asia, Europe, South Africa and the USA by **Findling et al. (2012)** evaluated the efficacy and safety of quetiapine[7] monotherapy in young people with schizophrenia. Unpublished data from this trial were available when NICE CG155 was developed (referred to in the full version of NICE CG155 as 'AstraZenecaD1441C00112').

Inpatients and outpatients aged 13–17 years (mean=15.4 years) were recruited from 43 centres. Inclusion criteria were: schizophrenia according to DSM-IV; confirmation of diagnosis on the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL); a Positive and Negative Syndrome Scale (PANSS) total score of 60 or more; and a score of 4 or more on at least 1 of the PANSS items of delusions (P1), conceptual disorganisation (P2), or hallucinations (P3). Exclusion criteria were: DSM-IV diagnosis of bipolar disorder, schizophreniform disorder, schizoaffective disorder, non-specified psychotic disorder, or acute post-traumatic stress disorder; psychosis caused by a medical condition or its treatment; history of suicide attempts, or homicidal risk or behaviour, in the past 3 months; drug abuse or dependence; laboratory test results outside normal ranges; hospital admission for diabetes or related illnesses in the past 3 months; unstable medical conditions that may have affected or been affected by study medication; and pregnancy or lactation.

Patients were randomised to 6 weeks of oral quetiapine (400 or 800 mg/day) or placebo. Quetiapine was titrated from a starting dose of 50 mg on day 1 to the target dose of 400 mg (by day 5) or 800 mg (by day 9). Continuation of certain antidepressants (citalopram, escitalopram, sertraline, bupropion, or venlafaxine[8] – if the dose was stabilised before enrolment) was allowed, as was use of lorazepam[8] (or equivalent) at a maximum of 4 mg/day for up to 4 days. Drugs prohibited during the study period were: other antipsychotics; psychostimulants; CYP3A4 inhibitors or inducers; monoamine oxidase inhibitors;

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[6] See the supplementary information in NICE CG155 for a table of baseline investigations and monitoring for children and young people who are prescribed antipsychotic medication (to be read in conjunction with the British national formulary, the British national formulary for children and summary of product characteristics for the drug).
[7] At the time of publication of this Evidence Update, quetiapine did not have a UK marketing authorisation for this indication in children and young people.
[8] At the time of publication of this Evidence Update, citalopram, escitalopram, sertraline, bupropion, venlafaxine and lorazepam did not have a UK marketing authorisation for this indication in children and young people.

atomoxetine; and antidepressants other than those noted above. The primary outcome was change in PANSS total score from baseline to 6 weeks (using mixed-model, repeated-measures analysis). Secondary outcomes examining safety issues included adverse events, biochemical markers, suicidality, and extrapyramidal symptoms. Data analyses were intention to treat.

By 6 weeks, least-squares mean change in PANSS total scores in the 3 groups were:

- Placebo: −19.15 (95% CI −25.14 to −13.16).
- Quetiapine 400 mg/day: −27.31 (95% CI −32.52 to −22.10; p=0.043 vs placebo).
- Quetiapine 800 mg/day: −28.44 (95% CI −32.04 to −24.85; p=0.009 vs placebo).

Safety data were reported but no statistical analysis comparing the groups was performed. Rates of medication-related adverse events were numerically higher in the 400 and 800 mg/day quetiapine groups than in the placebo group (56.2%, 46.0% and 22.7% respectively). The rates of adverse events potentially associated with extrapyramidal symptoms were also higher with quetiapine 400 and 800 mg/day than placebo (12.3%, 13.5%, and 5.3% respectively), but serious adverse event rates were similar (5.5%, 6.8% and 5.3% respectively). Mean changes in body weight for quetiapine 400 and 800 mg/day were 2.2 kg and 1.8 kg respectively, and −0.4 kg for placebo. Mean changes in some biochemical markers, including total cholesterol and triglycerides, were numerically greater with quetiapine than placebo. However the authors stated that differences in biochemical markers between the groups were not clinically significant. Mean changes in blood pressure were similar across the groups, but mean changes in standing pulse rate were numerically higher with quetiapine 400 and 800 mg/day (6.3 and 2.2 beats per minute respectively) than placebo (−2.5 beats per minute). No suicides were observed (although in the quetiapine groups, self-injury was reported in 2 patients and suicidal ideation in 1 patient).

Limitations of the evidence included that:

- The trial was powered to detect a 15-point difference in PANSS score at 6 weeks between quetiapine and placebo. Although statistically significant changes were seen, the mean differences from placebo were less than 10 points in both quetiapine groups.
- Quetiapine was compared only with placebo therefore performance versus other antipsychotics was not established.
- Once titration to the allocated quetiapine dose was achieved, the dose was then fixed throughout the trial. This approach does not reflect the more flexible dosing policy recommended by NICE CG155.
- Rates of study completion were higher with quetiapine 400 and 800 mg/day (76.7% and 82.4%) than with placebo (62.7%), which may have biased results.
- The improvement in PANSS score in the placebo group reduced the effect on PANSS that could be attributed to quetiapine.
- The study lasted 6 weeks, so did not examine long-term safety or efficacy of quetiapine.
- Maintaining quality control of the trial may have been challenging across 43 centres.

The evidence suggests that after 6 weeks, quetiapine appears to improve schizophrenia symptoms in young people aged 13–17 years, with a safety profile similar to that in adult populations. The full version of NICE CG155 noted the paucity and low quality of evidence for antipsychotic drug use in children and young people with first episode psychosis, and therefore also drew on evidence in adults from the NICE clinical guideline 'Schizophrenia' (now replaced by 'Psychosis and schizophrenia in adults' [NICE CG178]). The trial by Findling et al. (2012) is consistent with NICE CG155 to offer oral antipsychotic medication for children and young people with first episode psychosis, and also adds to the evidence base for antipsychotic drugs in young people to aid clinicians in deciding on the most appropriate drug.

Key reference
Findling RL, McKenna K, Earley WR et al. (2012) Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. Journal of Child and Adolescent Psychopharmacology 22: 327–42

Long-term safety and tolerability of quetiapine
A 26-week open-label continuation study (n=381) in Asia, Europe, South Africa and the USA by **Findling et al. (2013)** evaluated the safety and tolerability of quetiapine[9] monotherapy in young people with schizophrenia or bipolar disorder. Patients were eligible for the study if they had completed or discontinued 1 of 2 clinical trials of quetiapine monotherapy:

- Findling et al. (2012; see above for details): young people aged 13–17 (n=176) years with a DSM-IV diagnosis of schizophrenia.
- Pathak et al. (2013): children and young people aged 10–17 years (n=205) with a DSM-IV diagnosis of a manic episode associated with bipolar I disorder (Young Mania Rating Scale total score ≥20).

Patients were recruited from 59 centres and all received open-label quetiapine for 26 weeks (50 mg on day 1, rising to 400 mg by day 5). At the investigator's discretion, the 400 mg dose was then either maintained, increased (to a maximum 800 mg/day), or decreased (to 200 mg/day). The mean daily dose was 599 mg. Drugs deemed necessary to the patient could be started or continued, except for: other antipsychotics; CYP3A4 inhibitors or inducers; fluoxetine; monoamine oxidase inhibitors; or atomoxetine. The primary outcome was safety and tolerability of quetiapine, including: metabolic and biochemical measures; vital signs; adverse events; and suicidality.

After 26 weeks, 14.9% of patients experienced decreases in high-density lipoprotein cholesterol (HDL-C) to below the potentially clinically significant threshold of 40 mg/100ml, and 10.2% of patients experienced increases in triglyceride levels to above the potentially clinically significant threshold of 200 mg/100ml. Mean change in body weight was 3.7 kg, and weight gain of 7% or more was seen in 35.6% of patients. After adjustment for normal growth, clinically significant weight gain (namely, an increase in BMI ≥0.5 standard deviations from baseline) was seen in 18.3% of patients. An increase in standing systolic blood pressure of at least 20 mmHg was seen in 5.3% of patients, and 14.0% of patients experienced an increase in standing diastolic blood pressure of at least 30 mmHg.

Overall, 84.5% of participants (78.3% of those with schizophrenia) experienced adverse events over the 26-week study period. Commonly reported adverse events included somnolence (22.9%), headache (18.7%), sedation (14.2%), and vomiting (10.8%). Adverse events potentially associated with extrapyramidal symptoms were reported in 10.0% of patients. No suicides were observed (although 2 cases of suicidal ideation, and 1 case each of suicide attempt, self-mutilation and self-injury were reported).

Limitations of the evidence included that:

- Only 62.2% of patients completed the 26-week study period.
- Maintaining quality control of the study may have been challenging across 59 centres.
- The study was an open-label, non-comparative design.

The evidence suggests that in children and young people aged 10–17 years with schizophrenia or bipolar disorder, safety and tolerability of quetiapine over 26 weeks can be limited by a number of adverse effects, including potentially clinically significant lipid disturbance, weight gain, and raised blood pressure. The full version of NICE CG155 noted the paucity and low quality of evidence for antipsychotic drug use in children and young

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[9] At the time of publication of this Evidence Update, quetiapine did not have a UK marketing authorisation for this indication in children and young people.

people with first episode psychosis, and therefore also drew on evidence in adults from the NICE clinical guideline 'Schizophrenia' (now replaced by 'Psychosis and schizophrenia in adults' [NICE CG178]). The trial by Findling et al. (2013) is consistent with NICE CG155, particularly that weight, blood pressure and blood lipids should be monitored throughout treatment. It also adds to the evidence base for antipsychotic drugs in young people to aid clinicians in deciding on the most appropriate drug.

Key reference
Findling RL, Pathak S, Earley WR et al. (2013) Safety, tolerability, and efficacy of quetiapine in youth with schizophrenia or bipolar I disorder: a 26-week, open-label, continuation study. Journal of Child and Adolescent Psychopharmacology 23: 490–501 [NIH Public Access author manuscript – full text]

Supporting reference
Pathak S, Findling RL, Earley WR et al. (2013) Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. Journal of Clinical Psychiatry 74: e100–9

Long-term safety and tolerability of olanzapine

A cohort study (n=179 young people, n=4280 adults) by **Kryzhanovskaya et al. (2012)** compared weight and other metabolic changes between young people and adults who had received olanzapine[10] treatment for at least 24 weeks. Data on people treated with olanzapine for at least 24 weeks were extracted from several studies of patients with an array of mental health disorders including schizophrenia, schizoaffective disorder, borderline personality disorder, bipolar I disorder, prodromal psychosis, and depression. Data on young people (aged 12–18 years) came from 6 studies; patients had a mean age of 15.8 years, a dose range of 2.5−20.0 mg/day, a mean modal dose of 11.30 mg/day, and a median follow-up of 201 days. Data on adults came from 86 studies; patients had a mean age of 38.8 years, a dose range of 5.0–20.0 mg/day, a mean modal dose of 13.30 mg/day, and a median follow-up of 280 days. Weight gain data were collected for all patients, whereas fasting glucose and lipids data were only collected in 68.2% of young people and 24.3% of adults.

Mean weight gain in young people was 11.24 kg (95% CI 10.1 to 12.4 kg) compared with 4.81 kg (95% CI 4.57 to 5.04 kg) in adults – weight gain in young people remained significant even when normal childhood growth was factored in. The non-overlapping CIs indicated a significant difference between the 2 populations. The percentage of young people with at least a 7% mean gain in body weight was significantly higher than in adults (89.4% vs 55.4%). Significant differences were also seen for gains of at least 15% body weight (55.3% of young people vs 24.1% of adults) and 25% body weight (29.1% vs 8.0%).

For fasting lipids, both young people and adults experienced a significant drop in HDL-C, which was significantly more pronounced in young people (−4.52 mg/100ml, 95% CI –5.97 to –3.08 mg/100 ml) than in adults (−1.17 mg/100ml, 95% CI –1.79 to –0.55 mg/100 ml). Young people and adults also both experienced a significant increase in triglycerides (20.49 mg/100 ml vs 16.72 mg/100 ml) but the between-group difference was not significant. Changes in fasting glucose values were similar between young people and adults (3.13 mg/100 ml vs 3.95 mg/100 ml).

The main limitation of the evidence was that data were pooled from many different studies with heterogeneous methodologies including study design, drug doses, patient selection, patient care, and monitoring. Additionally, no quality assessment of the included studies was reported, and it was not clear whether all studies were published or if some data were obtained from a manufacturer database.

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[10] At the time of publication of this Evidence Update, olanzapine did not have a UK marketing authorisation for this indication in children and young people.

The evidence suggests that following long-term (>24 weeks) treatment with olanzapine, the types of metabolic changes seen in young people aged 12–18 years are similar to those seen in adults. However, the magnitude of changes in parameters such as body weight and some blood lipid levels appears to be greater in young people. This is consistent with some aspects of NICE CG155, particularly to discuss possible side effects when choosing an antipsychotic drug, including metabolic issues (such as weight gain and diabetes), and to monitor weight, blood pressure, fasting blood glucose, HbA_{1c} and blood lipids throughout treatment.

However, the considerable difference in the magnitude of metabolic effects caused by olanzapine (particularly weight gain) in young people compared with adults means that this drug may not be suitable for first-line treatment in children and young people with first episode psychosis. NICE CG155 does not specifically state that olanzapine should not be used first line, therefore these data may have a potential impact on the guideline. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Concerns about the adverse effects of olanzapine on weight and metabolism have also been reflected in guidance from other organisations. Recommendations from both the US Schizophrenia Patient Outcomes Research Team (PORT), and The Australian National Centre of Excellence in Youth Mental Health, and Early Psychosis Prevention and Intervention Centre (EPPIC), state that olanzapine should not be used as first-line treatment for people with first episode psychosis.

Metabolic and weight issues with olanzapine have also been noted in other studies. For example, Correll et al. 2014 (see '*Cardiometabolic risk in people with schizophrenia*' on p.19 for details) observed that higher levels of triglycerides (p=0.007), insulin (p=0.02) and insulin resistance (p<0.001) were associated with olanzapine therapy. Additionally, Malhotra et al. 2012 (see '*Genetic basis of weight gain associated with antipsychotic drugs*' on p.23 for details) noted patients who had taken olanzapine gained substantially more weight after 12 weeks than people taking other antipsychotics (quetiapine, risperidone and aripiprazole; p<0.05 for weight gain with each of these 3 drugs versus olanzapine).

Key reference
Kryzhanovskaya LA, Xu W, Millen BA et al. (2012) Comparison of long-term (at least 24 weeks) weight gain and metabolic changes between adolescents and adults treated with olanzapine. Journal of Child and Adolescent Psychopharmacology 22: 157–65

Supporting references
Buchanan RW, Kreyenbuhl J, Kelly DL et al. (2010) The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophrenia Bulletin 36: 71–93

The National Centre of Excellence in Youth Mental Health, and Early Psychosis Prevention and Intervention Centre (EPPIC) Medical management in early psychosis: a guide for medical practitioners

Risk of diabetes with antipsychotics
A retrospective case-control study (n=43,287) in the USA by **Bobo et al. (2013)** compared the risk of type 2 diabetes in people aged 6–24 years of age (mean=14.5 years) taking antipsychotic drugs with matched controls taking another psychotropic drug. Data were obtained from the Tennessee Medicaid programme and a state-wide hospital discharge database. The study cohort (n=28,858) were patients recently started on antipsychotic therapy with no antipsychotic use in the previous year. Exclusion criteria were (during the past year): life-threatening illness or institutional residence; diabetes; and pregnancy or polycystic ovarian syndrome. Also excluded were: patients with conditions for which antipsychotics are the only recommended treatments (including schizophrenia or related psychoses, organic psychoses, autism, mental retardation, Tourette syndrome, or other tic disorders); patients

prescribed clozapine or long-acting injectable preparations; and those with parenterally administered drugs.

The control cohort (n=14,429) were patients who had recently started other psychotropic drugs (such as mood stabilisers or antidepressants) and had not used antipsychotics in the previous year. The control group was matched with the antipsychotic group (for covariates that might be related to antipsychotic use and the development of type 2 diabetes) to ensure baseline comparability. The primary outcome was newly diagnosed diabetes.

During 55,984 person-years of follow-up, 106 cases of type 2 diabetes were seen. Antipsychotic users were at significantly greater risk of type 2 diabetes than controls (hazard ratio [HR]=3.03, 95% CI 1.73 to 5.32). This risk was apparent within the first year of follow-up (HR=2.49, 95% CI 1.27 to 4.88) and remained for up to 1 year after stopping antipsychotics (HR = 2.57, 95% CI 1.34 to 4.91). The increased risk was also present when the analysis was restricted to children and young people aged 6 to 17 years (HR=3.14, 95% CI 1.50 to 6.56).

Limitations of the evidence included that:

- The study excluded people with schizophrenia and related psychoses (namely, the population covered by NICE CG155). However, people with psychosis and schizophrenia are also likely to be vulnerable to the metabolic effects of antipsychotics seen in the study population.
- The study cohort consisted of Tennessee Medicaid enrollees (approximately 40% of the state's children). Because Medicaid is a social health care programme for families and individuals with low income and limited resources, generalisability of results may be limited. For example, economic and social factors may raise the incidence of type 2 diabetes in children covered by Medicaid. Applicability to the UK may also be limited.
- The study may have underestimated diabetes risk with antipsychotics because: diagnosis of diabetes relied on evidence of treatment of diabetes rather than routine blood glucose monitoring (potentially missing asymptomatic cases); and the control group were given psychotropic (though not antipsychotic) drugs, some of which may increase diabetes risk.
- The observational nature of the evidence can only show association not causality.

The evidence suggests that children and young people aged 6–17 years prescribed antipsychotics appear to have an increased risk of type 2 diabetes. This risk can remain for up to 1 year after stopping antipsychotics. These data are consistent with NICE CG155 to discuss possible side effects when choosing an antipsychotic drug, including metabolic issues (such as diabetes), and to monitor and record fasting blood glucose and HbA$_{1c}$ throughout treatment.

An RCT (n=30) in the USA by Teff et al. (2013) further examined the metabolic effects of antipsychotics. Healthy volunteers were randomised to olanzapine[11], aripiprazole[12] or placebo for 9 days. Before and after the intervention, participants underwent a mixed-nutrient meal challenge (to replicate physiological stimuli of daily life) and a euglycaemic-hyperinsulinaemic clamp (to evaluate insulin sensitivity and glucose disposal).

Compared with placebo, olanzapine caused significant increases in postprandial insulin, glucagon-like peptide 1, and glucagon coincident with insulin resistance. Aripiprazole also induced insulin resistance, but had no effect on postprandial hormones. The metabolic changes occurred without weight gain, increases in food intake and hunger, or psychiatric

[11] At the time of publication of this Evidence Update, olanzapine did not have a UK marketing authorisation in children and young people.
[12] At the time of publication of this Evidence Update, aripiprazole had a UK marketing authorisation for schizophrenia only in young people aged 15 years and older. See also 'Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years' (NICE TA213).

disease. This may indicate that antipsychotics act directly on tissue function, and that these effects appear to develop after only a few days of exposure (although the study did not investigate how this may affect patient-orientated outcomes such as morbidity and mortality). It also suggests that certain antipsychotic medications may cause greater metabolic disturbance than others, which may be useful information when selecting antipsychotics.

Key reference
Bobo WV, Cooper WO, Stein CM et al. (2013) Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry 70: 1067–75

Supporting reference
Teff KL, Rickels MR, Grudziak J et al. (2013) Antipsychotic-induced insulin resistance and postprandial hormonal dysregulation independent of weight gain or psychiatric disease. Diabetes 62: 3232–40

Cardiometabolic risk in people with schizophrenia
In addition to regular monitoring for adverse effects (including metabolic and cardiovascular changes) throughout antipsychotic treatment, NICE CG155 also recommends ensuring that children and young people with first episode psychosis receive a comprehensive multidisciplinary assessment. This should include physical health and wellbeing (including weight and height, and information about smoking, diet and exercise). Additionally, the use of alcohol, tobacco, prescription and non-prescription medication and illicit drugs should be discussed. The discussion should cover their possible interference with the therapeutic effects of prescribed medication and psychological interventions and the potential of illicit drugs to exacerbate psychotic symptoms.

A cross-sectional study (n=404) in the USA by **Correll et al. (2014)** assessed cardiometabolic risk and its moderators and mediators in people aged 15 to 40 years (mean=23.6 years) with first-episode schizophrenia spectrum disorders. The study examined baseline results of the Recovery After an Initial Schizophrenia Episode–Early Treatment Program (RAISE-ETP) study. The RAISE-ETP study is a cluster-randomised assessment of an integrated programme of drug treatment, psychotherapy and supported employment across 34 community mental health centres.

Inclusion criteria were: schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder not otherwise specified, or brief psychotic disorder; and less than 6 months of cumulative antipsychotic use (mean lifetime antipsychotic treatment duration=47.3 days). Exclusion criteria were: bipolar disorder, major depressive disorder with psychosis, substance-induced psychotic disorder, or psychotic disorder due to a general medical condition; current neurological disorders affecting diagnosis or prognosis; and clinically significant head trauma or another serious medical condition. Primary outcomes were body composition and fasting lipid, glucose, and insulin parameters compared with population data from the National Health and Nutrition Examination Survey.

The prevalence of several patient characteristics was considerably higher in people with psychosis or schizophrenia than in the age-matched general population. Smoking in males (55.9% vs 36.7%) and in females (36.8% vs 24.9%), and metabolic syndrome (13.2% vs 6.7%), were more common in people with psychosis or schizophrenia. However, prevalence of obesity (22.1%) was similar to the age-matched population (25.0%).

Prevalence of dyslipidemia (56.5%) was higher than that reported in the general population among adults around 20 years older (53.0%), as was prevalence of prehypertension (39.9% vs 20.9%). Body composition outcomes (higher BMI, fat mass, fat percentage, and waist circumference) correlated significantly with psychiatric illness duration (all p<0.01). Metabolic issues (higher non–HDL-C, higher triglycerides, higher triglycerides to HDL-C ratio [a marker of insulin resistance], lower HDL-C, and lower systolic blood pressure) correlated significantly with antipsychotic treatment duration (all p≤0.02). Higher levels of triglycerides (p=0.007),

insulin (p=0.02) and insulin resistance (p<0.001) were associated with olanzapine therapy, while a higher triglycerides to HDL-C ratio was associated with quetiapine (p=0.02).

Limitations of the evidence included that:

- Only 50 patients had never taken antipsychotics. Antipsychotic exposure varied in those who had previously taken them before study entry, and prescribing was not controlled. For example, patients at higher risk from cardiometabolic complications (such as overweight people) may have selectively been given lower risk antipsychotics, which may have confounded results. Data on antipsychotic history before study entry were not complete enough for further analysis.
- Fat mass, fat percentage and insulin resistance were assessed by general clinical measures and not gold-standard methods.
- Exercise and diet were not assessed.

The evidence suggests that people with first episode schizophrenia spectrum disorders (with a mean lifetime antipsychotic treatment duration of less than 7 weeks) appear to have higher rates of smoking, metabolic syndrome, dyslipidemia and prehypertension than the general population. Body composition issues (such as higher BMI) appear to correlate with duration of psychiatric illness, and metabolic issues (such as higher triglycerides) appear to correlate with antipsychotic treatment duration. This is consistent with NICE CG155 to regularly monitor weight, blood pressure, fasting blood glucose, HbA1c and blood lipids throughout antipsychotic treatment, and to provide information about smoking, diet and exercise to children and young people with first episode psychosis in the early treatment phase.

Key reference
Correll CU, Robinson DG, Schooler NR et al. (2014) Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA Psychiatry 71: 1350–63

Group psychoeducation for young people with psychosis and their families
NICE CG155 recommends that, for psychological interventions, 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.

An RCT (n=55) in Spain by **Calvo et al. (2014)** assessed a structured psychoeducational group intervention for young people with early-onset psychosis and their families. Inclusion criteria were: outpatients aged 14–18 years living at home with parents or carers; at least 1 positive psychotic symptom (delusions or hallucinations) before age 18 years; and a DSM-IV diagnosis of: schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, major depressive disorder with psychotic features, brief psychotic disorder, or psychosis not otherwise specified. Exclusion criteria were drug misuse or dependence, and any neurological developmental disorder.

Patients (accompanied by 1 or both parents or carers) were randomised to either a psychoeducational group intervention or a non-structured group intervention. Interventions were provided alongside any other current psychiatric or drug treatment. The psychoeducational group intervention comprised problem solving activities to help manage

everyday difficulties of psychosis, to mitigate crises, and to prevent relapses. The intervention comprised 2 phases:

- Initiation phase: Three 50-minute sessions in which patients and parents were interviewed separately.
- Group phase: Participants joined 2 separate groups (one for patients, one for parents) for twelve 90-minute sessions once every 15 days. Sessions were structured and written material was provided – topics discussed included medication, side effects, and crisis management.

The non-structured group intervention was similar in that it comprised 3 individual sessions followed by 12 group sessions, but it did not use a predefined structure and no written material was provided. Instead, members shared experience and advice (for example, about medication and side effects). Primary outcomes (assessed within 1 month of completing the intervention) were number of patients hospitalised, days of hospitalisation, and visits to the emergency department. Analyses were intention to treat.

At the end of the intervention, significantly fewer patients had visited the emergency department in the psychoeducational group than in the non-structured group (4 patients [14.8%] vs 11 patients [39.3%], p=0.039). However, no significant differences were seen between the psychoeducational group and the non-structured group for number of patients hospitalised (3 patients [11.1%] vs 9 patients [32.1%], p=0.057) or days of hospitalisation (4.1 days vs 7.4 days, p=0.142).

Limitations of the evidence included that:

- Findings may have been biased by the high dropout rates, which differed considerably between groups (60% of the non-structured group and 37% of the psychoeducational group dropped out before finishing the intervention).
- The primary outcomes (hospital admissions and emergency department visits) may not have fully reflected the benefits of group therapy – assessment of coping skills or wellbeing may have provided more insight.
- Follow-up was short, therefore the long-term effects of the intervention are uncertain.
- The frequent contact provided as part of the non-structured intervention may have reduced the level of hospitalisation in this group, leading to a non-significant difference versus the psychoeducational group.
- The trial was a small pilot study, which may have limited its ability to detect significant differences between the groups.

The evidence suggests that a structured psychoeducational group intervention for young people with psychosis and their parents or carers, comprising problem solving activities and provision of written materials, appears to reduce visits to the emergency department. This is consistent with recommendations in NICE CG155 for family-based psychological interventions. However, these recommendations were extrapolated from the NICE clinical guideline 'Schizophrenia' (now replaced by 'Psychosis and schizophrenia in adults' [NICE CG178]), and were therefore drawn from an evidence base among adult populations. The current evidence provides some data to confirm the efficacy of family-based interventions among young-people with psychosis – but limitations of the evidence (particularly the small size of the trial) mean that further research is needed.

Key reference
Calvo A, Moreno M, Ruiz-Sancho A et al. (2014) Intervention for adolescents with early-onset psychosis and their families: a randomized controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry 53: 688–96

1.4 Subsequent acute episodes of psychosis or schizophrenia

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.5 Referral in crisis and challenging behaviour

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.6 Early post-acute period

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.7 Promoting recovery and providing possible future care in primary care

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.8 Promoting recovery and providing possible future care in secondary care

Risk of neutropenia with clozapine

NICE CG155 recommends offering clozapine[13] to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs each used for 6–8 weeks. Additionally, the BNFc entry for clozapine states that white blood cell and differential blood counts must be normal before starting clozapine. Counts should be monitored every week for 18 weeks then at least every 2 weeks, and if clozapine is continued and blood counts are stable after 1 year, at least every 4 weeks (and 4 weeks after discontinuation). If the white blood cell count (WBC) falls below 3000/mm^3 or the absolute neutrophil count (ANC) falls below 1500/mm^3, clozapine should be discontinued permanently and the patient referred to a haematologist.

A retrospective cohort study (n=87) in the USA by **Maher et al. (2013)** analysed rates of and risk factors for neutropenia in hospitalised children and young people with schizophrenia treated with clozapine. A chart review was performed for all patients aged 6−18 years (mean age at first admission=13.4 years) who received clozapine during hospitalisation (mean length of stay=117 days) at the National Institute of Mental Health (NIMH) between 1990 and 2011. Eligibility criteria included: psychosis onset before age 13 years; no serious medical conditions; and a pre-psychotic intelligence quotient of above 70. After 2003, clozapine was started only if patients had an ANC above 2000/mm^3. Before 2003, patients only needed to have a WBC above 3500/mm^3. After starting clozapine, patients were monitored for adverse effects, including complete blood counts, at least once a week. If blood counts dropped, patients were more closely monitored. Clozapine was stopped for a WBC of less than 2000/mm^3 (before 2003) or an ANC of less than 1500/mm^3 (after 2003). Once ANC had recovered to more than 2000/mm^3, clozapine was re-started, often with adjunctive lithium carbonate. The mean clozapine dose on discharge was 349 mg (range 75–825 mg).

Mild neutropenia (lowest ANC between 1500 and 2000/mm^3) was seen in 27 (31%) patients and moderate neutropenia (any ANC less than 1500/mm^3) was seen in 17 (20%) patients. No cases of agranulocytosis or severe infection were reported, but the rates of neutropenia were

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[13] At the time of publication of this Evidence Update, clozapine had a UK marketing authorisation for treatment-resistant schizophrenia only in young people aged 16 years and older.

considerably higher than the incidence of approximately 3% reported among adults (Atkin et al. 1996). Of the 17 patients who developed moderate neutropenia, 16 had successfully re-started clozapine by the time of discharge (8 of whom needed adjunctive lithium carbonate).

Younger age was a significant risk factor for mild neutropenia (p<0.001) compared with no hematologic adverse effects (HAEs). Male gender was also a significant risk factor for both mild neutropenia (p=0.012) and moderate neutropenia (p=0.003) compared with no HAEs. Additionally, African-American boys had the highest rate of moderate neutropenia (47%), and neutropenia in African-American children was significantly more likely to be moderate than mild (p=0.017).

Limitations of the evidence included that:

- Clozapine was not compared with placebo or other antipsychotics.
- Clozapine dose changes or concomitant medications (neither of which were analysed), and the wide range of doses prescribed, may have affected ANC values.
- The study was a retrospective chart review and therefore did not involve randomisation or a standardised titration schedule, and may be subject to bias and confounding.
- The study took place over a period of 20 years, during which time clinical practices have changed (such as blood monitoring, and managing neutropenia).
- The UK has a mandatory clozapine monitoring service therefore generalisability of the study protocol to the UK may be limited.

The evidence suggests that in children and young people aged 6–18 years with schizophrenia treated with clozapine, mild neutropenia appears to develop in about one-third of patients and moderate neutropenia in about one-fifth (higher rates than adult populations). There appears to be no evidence of serious adverse events (such as agranulocytosis or serious infection), although younger, male, and African-American children appear to be at greater risk of neutropenia. This evidence is consistent with NICE CG155 to offer clozapine to children and young people with schizophrenia whose illness has not responded adequately to pharmacological treatment, and reinforces the need for long-term monitoring of blood counts.

Additionally, the full version of NICE CG155 noted the paucity and very low quality of evidence regarding relative efficacy and safety of antipsychotics in the treatment of children and young people whose illness has not adequately responded to treatment. The guideline therefore also drew on evidence in adults from the NICE clinical guideline 'Schizophrenia' (now replaced by 'Psychosis and schizophrenia in adults' [NICE CG178]). The trial by Maher et al. (2013) adds to the evidence base for clozapine in children and young people whose illness has not adequately responded to treatment.

Key reference
Maher KN, Tan M, Tossell JW et al. (2013) Risk factors for neutropenia in clozapine-treated children and adolescents with childhood-onset schizophrenia. Journal of Child and Adolescent Psychopharmacology 23: 110–6 [NIH Public Access author manuscript – full text]

Supporting reference
Atkin K, Kendall F, Gould D et al. (1996) Neutropenia and agranulocytosis in patients receiving clozapine in the UK and Ireland. British Journal of Psychiatry 169: 483–8

Areas not currently covered by NICE CG155

Genetic basis of weight gain associated with antipsychotic drugs
NICE CG155 recommends that side effects of antipsychotic drugs (including metabolic issues such as weight gain) should be discussed, and that weight should be monitored throughout treatment. However, it does not discuss genetic predisposition to weight gain and whether genetic testing can be used to predict which patients may be at greatest risk.

A cohort study (discovery cohort n=139; validation cohorts n=205) in the USA by **Malhotra et al. (2012)** aimed to identify single-nucleotide polymorphisms associated with antipsychotic-induced weight gain. A discovery cohort was first recruited from a general psychiatric hospital and comprised patients aged 19 years or under with a previous lifetime exposure to antipsychotics of 1 week or less. Exclusion criteria included: a current or prior eating disorder; thyroid dysfunction; any acute non-psychiatric medical disorder; and pregnancy or breastfeeding. Patients were treated with antipsychotics for 12 weeks. Choice of antipsychotic drug, dosage, and titration schedule were based on clinical indications. DNA was extracted from blood samples and a genome-wide association study was performed to identify any genetic markers associated with weight gain. Patients who had taken olanzapine[14] gained substantially more weight after 12 weeks than people taking other antipsychotics (quetiapine[14], risperidone[14] and aripiprazole[15]), and were therefore excluded from the study.

The genome-wide association study in the discovery cohort yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of $p<10^{-5}$. The locus was near the melanocortin 4 receptor gene, overlapping a region previously identified by large-scale genome-wide association studies of obesity in the general population. The effects of the polymorphisms were recessive – namely patients who were minor allele homozygotes gained considerable weight during the trial.

To validate these results, 3 additional cohorts were recruited from psychiatric hospitals in the USA and Germany and from a European antipsychotic drug trial. Patients aged 18–62 years with schizophrenia or schizoaffective disorder were treated with antipsychotics for 6 or 12 weeks. Five of the 20 single nucleotide polymorphisms found in the discovery cohort were tested against weight gain in 2 of the 3 validation cohorts, and the most promising of these (rs489693) was tested in the third validation cohort. It was found that rs489693 demonstrated consistent recessive effects, and meta-analysis of the discovery and validation cohorts together revealed a genome-wide significant effect ($p=5.59\times10^{-12}$). Additionally, rs489693 was also significantly related to increases in several metabolic indices, including triglycerides (p=0.011), leptin (p=0.028), and insulin levels (p=0.043).

Limitations of the evidence included that:
- The sample size in the discovery cohort was small compared with genome-wide association studies in the general population, and the authors noted that their initial result did not meet conventional thresholds for genome-wide significance.
- The strength of association between the rs489693 single nucleotide polymorphism and weight gain has not been widely replicated in other general population studies of obesity.

The evidence suggests that a genetic locus near the melanocortin 4 receptor gene (mutations of which are linked to extreme obesity in children and young people) appears to be associated with weight gain and other adverse metabolic effects in response to antipsychotic drugs. Although NICE CG155 does not discuss genetic predisposition to weight gain associated with antipsychotics, the preliminary nature of the evidence and its limitations mean that these data are currently unlikely to affect the guideline. Further research is needed to more firmly establish genetic markers that may be an indicator of greater risk of metabolic adverse effects following antipsychotic use.

Key reference
Malhotra AK, Correll CU, Chowdhury NI et al. (2012) Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. Archives of General Psychiatry 69: 904–12

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[14] At the time of publication of this Evidence Update, olanzapine, quetiapine and risperidone did not have a UK marketing authorisation for this indication in children and young people.
[15] At the time of publication of this Evidence Update, aripiprazole had a UK marketing authorisation for schizophrenia only in young people aged 15 years and older. See also 'Aripiprazole for the treatment of schizophrenia in people aged 15 to 17 years' (NICE TA213).

2   New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Possible psychosis

- Cognitive deficits in adolescents and young people with familial high risk or ultra high risk, and risk of transition to psychosis

Further evidence uncertainties for psychosis and schizophrenia in children and young people can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Psychosis and schizophrenia in children and young people. NICE clinical guideline 155 (2013)

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 May 2012 (the end of the search period of NICE clinical guideline 155) to 25 September 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO

Three separate searches were conducted for the Evidence Update to replicate the search process used for NICE CG155:

Search 1: A generic population search that included terms for the condition and age group. The search was run in conjunction with validated Scottish Intercollegiate Guidelines Network (SIGN) search filters for systematic reviews and RCTs.

Search 2: A search that included the condition search terms combined with search terms for the population at risk of psychosis. The search was also combined with SIGN search filters for systematic reviews and RCTs.

Search 3: A search focused on adverse effects of antipsychotic treatments. The search was run in conjunction with the SIGN search filter for observational studies.

Tables 1, 2 and 3 provide details of the three MEDLINE search strategies used, which were adapted to search the other databases listed above. Additionally, 1 study (Correll et al. 2014) was identified outside of the literature search.

Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the NICE newsletters and alerts page for a list of all published Evidence Updates.

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Table 1: Search 1 – MEDLINE population search strategy (adapted for individual databases)

1	delusions/ or hallucinations/ or exp "schizophrenia and disorders with psychotic features"/ or schizophrenia, childhood/
2	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).ti,ab.
3	1 or 2
4	exp adolescent/ or adolescent development/ or exp child/ or exp child development/ or exp infant/ or minors/ or puberty/ or puberty, delayed/ or puberty, precocious/ or students/ or exp schools/
5	(adolescen$ 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).ti,ab.
7	4 or 5 or 6
8	3 and 7

Table 2: Search 2 – MEDLINE search strategy for population at risk of psychosis (adapted for individual databases)

1	delusions/ or hallucinations/ or exp "schizophrenia and disorders with psychotic features"/ or schizophrenia, childhood/
2	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).ti,ab.
3	1 or 2
4	*risk factors/
5	(symptom$ or symptomology).sh. or (prodrom$ or risk$).hw.
6	(blips or brief limited intermittent psychotic symptom$ 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.
7	5 or 6
8	(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.
9	7 and 8
10	ultra high risk.ti,ab.
11	((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.
12	4 or 9 or 10 or 11
13	3 and 12

Table 3: Search 3 – MEDLINE search strategy for adverse effects of antipsychotic drugs (adapted for individual databases)

|			
1	delusions/ or hallucinations/ or exp "schizophrenia and disorders with psychotic features"/ or schizophrenia, childhood/		chlorazin$1 or chlordelazin$1 or contomin$1 or fenactil$1 or largactil$1 or propaphenin$1 or thorazin$1).ti,ab.
2	(delusion$ or hallucinat$ or hebephreni$ or oligophreni$ or paranoi$ or psychotic$ or psychosis or psychoses or schizo$).ti,ab.	17	chlorprothixene/
3	1 or 2	18	(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$1).ti,ab.
4	exp adolescent/ or adolescent development/ or exp child/ or exp child development/ or exp infant/ or minors/ or puberty/ or puberty, delayed/ or puberty, precocious/ or students/ or exp schools/		
5	(adolescen$ 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$1).ti,ab.		
7	4 or 5 or 6	19	clozapine$.sh.
8	3 and 7	20	(clozapin$1 or alemoxan$1 or azaleptin$1 or clopine or clozaril$1 or denzapin$1 or dorval or dozapin$1 or fazaclo or froidir or klozapol or lapenax or leponex or wander compound or zaponex).ti,ab.
9	exp antipsychotic agents/	21	flupenthixol/
10	(antipsychotic$ or anti psychotic$ or (major adj2 (butyrophenon$ or phenothiazin$ or tranquil$)) or neuroleptic$).ti,ab.	22	(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.
11	(amisulprid$1 or aminosultoprid$1 or amisulpirid$1 or sertol$1 or socian or solian).ti,ab.		
12	(aripiprazol$1 or abilify or abilitat).ti,ab.	23	fluphenazine$.sh.
13	benperidol/	24	(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
14	(benperidol$1 or anquil or benperidon$1 or benzoperidol$1 or benzperidol$1 or frenactil$1 or frenactyl or glianimon$1 or phenactil$1).ti,ab.		
15	chlorpromazine$.sh.		
16	(chlorpromazin$1 or aminazin$1 or		

	siqualone or siquoline or tensofin or trancin or valamina or vespazin or vespazine).ti,ab.	38	pimozide/
25	fluspirilene/	39	(pimozid$1 or antalon$1 or opiran$1 or orap or pimocid$1 or pimorid$1 or pinozid$1).ti,ab.
26	(fluspirilen$1 or fluspi or imap or kivat or redeptin$1 or spirodiflamin$1).ti,ab.	40	prochlorperazine$.sh.
27	haloperidol$.sh.	41	(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.
28	(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.		
29	methotrimeprazine/	42	promazine/
30	(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. (648)	43	(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.
31	(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.		
32	(paliperidon$1 or 9 hydroxyrisperidon$1 or invega).ti,ab.	44	quetiapine/
33	paroxetine/	45	(quetiapin$1 or ketipinor or quepin or seroquel or tienapin$1).ti,ab.
34	(paroxetin$1 or aropax or deroxat or motivan or paxil$1 or pexeva or seroxat or tagonis).ti,ab.	46	risperidone/
35	(pericyazin$1 or aolept or neulactil$1 or neuleptil$1 or periciazin$1 or properciazin$1 or propericiazin$1).ti,ab.	47	(risperidon$1 or belivon$1 or ridal or riscalin or risolept or rispen or risperdal$1 or sizodon).ti,ab.
36	perphenazine$.sh.	48	(sertindol$1 or indole or serdolect or serlect).ti,ab.
37	(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.	49	sulpiride/
		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.	69	(dyslip?emia$ or dyslipid?emia$ or dyslipoprotein?emia$).ti,ab.
51	trifluoperazine$.sh.		hypercholesterol?emia$).ti,ab.
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$1).ti,ab.	70	((dysmetabolic or metabolic or reaven) adj2 syndrom$).ti,ab.
		71	hypergl?c?emi$.ti,ab.
		72	(hyperlip?emi$ or hyperlipid?emi$ or lip?emia$ or lipid?emia$).ti,ab.
		73	(hyperprolactin?emi$ or (hypersecretion adj2 syndrome adj2 prolactin) or (inappropriate adj2 prolactin adj2 secretion) or prolactin?emi$).ti,ab.
		74	(hypertriglycerid?emia$ or mckusick 14575 or triglyceride storage disease or triglyceride?emia$).ti,ab.
		75	68 or 69 or 70 or 71 or 72 or 73 or 74
53	(zotepin$1 or lodopin$1 or losizopilon or nipolept or setous or zoleptil).ti,ab.	76	exp overnutrition/ or exp overweight/ or weight gain/
54	clopenthixol/	77	(bmi or body composition or body mass or (central$ 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.
55	(zuclopenthixol$1 or acuphase or acutard or clopenthixol$1 or clopixol or cisordinol$1 or sedanxol$1 or zuclopentixol$).ti,ab.		
56	or/9-55		
57	exp endocrine system diseases/ or exp endocrine system/		
58	prolactin$.sh. or exp thyroid hormones/	78	blood pressure/ or exp cerebrovascular disorders/ or exp heart diseases/ or exp hypertension/ or exp pheriperal vascular diseases/
59	(((endocrin$ 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$)).ti,ab.	79	((atrial and fibrillat*) or (ventricular and fibrillat*) or angina or arrythmi* or cardia* or cardio* or cerebrovascul* or coronary* or endocardi* or heart* or ischaem* or ischem* or myocard* or pericard* or tachycardi* or thromboembolism* or thrombosis or vascul* or ((blood adj2 pressure) or hypertensi$)).ti,ab.
60	57 or 58 or 59		
61	exp metabolic diseases/ or hyperprolactinemia/		
62	exp glucose/	80	76 or 77
63	insulin$.sh.	81	78 or 79
64	cholesterol/ or exp lipids/	82	(ae or ct or po or to).fs.
65	exp serum/	83	exp abnormalities, drug induced/ or exp adverse drug reaction reporting systems/ or exp death/ or drug hypersensitivity/ or drug interactions/ or drug monitoring/ or drug tolerance/ or exp drug toxicity/ or overdose/ or exp product surveillance, postmarketing/ or risk assessment/ or risk factors/
66	(blood sugar or cardiometaboli$ 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$).ti,ab.		
67	61 or 62 or 63 or 64 or 65 or 66		
68	(cholester?emi$ or cholesterin?emia$ or cholesterol?emia$ or hypercholester?emia$ or hypercholesterin?emia$ or		

84	(((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.

85	82 or 83 or 84
86	60 or 67 or 75 or 80 or 81 or 85
87	56 and 86
88	8 and 87

Figure 1 Flow chart of the evidence selection process
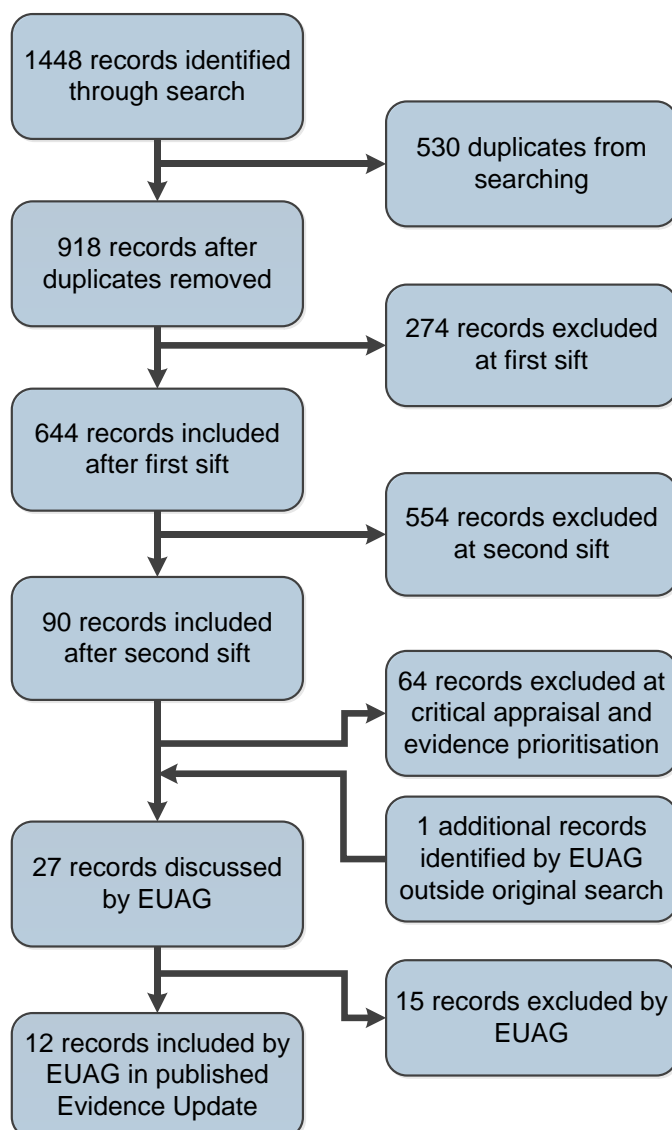
EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

Professor Chris Hollis – Chair

Professor of Child and Adolescent Psychiatry, University of Nottingham

Professor Max Birchwood

Professor of Youth Mental Health, University of Warwick

Professor Elena Garralda

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