National Institute for Health and Care Excellence

Draft for consultation

Addendum to Psychosis and schizophrenia in children and young people

Clinical Guideline Addendum 155.1

Methods, evidence and recommendations

January 2016

Draft for consultation

Developed by the National Institute for Health and Care Excellence

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Clinical guidelines update

The NICE Clinical Guidelines Update Team update discrete parts of published clinical guidelines as requested by NICE's Guidance Executive.

Suitable topics for update are identified through the new surveillance programme (see surveillance programme interim guide).

These guidelines are updated using a standing Committee of healthcare professionals, research methodologists and lay members from a range of disciplines and localities. For the duration of the update the core members of the Committee are joined by up to 5 additional members who are have specific expertise in the topic being updated, hereafter referred to as 'topic expert members'.

In this document where 'the Committee' is referred to, this means the entire Committee, both the core standing members and topic expert members.

Where 'standing Committee members' is referred to, this means the core standing members of the Committee only.

Where 'topic expert members' is referred to this means the recruited group of members with topic expertise.

All of the core members and the topic expert members are fully voting members of the Committee.

Details of the Committee membership and the NICE team can be found in appendix A. The Committee members' declarations of interest can be found in appendix B.

1 Summary section

1.1 Update information

The NICE guideline on psychosis and schizophrenia in children and young people (NICE clinical guideline CG155) was reviewed in April 2015 as part of NICE's routine surveillance programme to decide whether it required updating. The surveillance report identified new evidence relating to adverse effects associated with olanzapine, particularly weight gain and metabolic effects. NICE CG155 does not specifically state that olanzapine should not be used for first line treatment. The aim of this update was to review new evidence in this area.

The review question that the Committee considered was:

1) What is the adverse effects profile of olanzapine compared to other 'second generation' antipsychotics (SGAs) for treating children and young people with psychosis and schizophrenia?

The original guideline can be found here:
https://www.nice.org.uk/guidance/cg155/resources/guidance-psychosis-and-schizophrenia-in-children-and-young-people-pdf

The full surveillance report can be found here:

https://www.nice.org.uk/guidance/cg155/resources/cg155-psychosis-and-schizophrenia-in-children-and-young-people-surveillance-review-decision3

Some recommendations can be made with more certainty than others. The Committee makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Committee is confident that, given the information it has looked at, most people would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the person about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Recommendations that must (or must not) be followed

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Recommendations that should (or should not) be followed– a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of people, following a recommendation will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that actions will not be of benefit for most people.

Recommendations that could be followed

We use 'consider' when we are confident that following a recommendation will do more good than harm for most people, and be cost effective, but other options may be similarly cost

effective. The course of action is more likely to depend on the person's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the person.

Information for consultation

You are invited to comment on the new recommendations in this update. These are marked as **[new 2016] or [2016]** if the evidence has been reviewed but no change has been made to the recommended action.

1.2 Recommendations

1. **The choice of antipsychotic medication[a] should be made by the parents or carers of younger children, or jointly with the young person and their parents or carers, and healthcare professionals. Provide age-appropriate information and discuss the likely benefits and possible side effects of each drug including:**
    - metabolic (including weight gain and diabetes)
    - extrapyramidal (including akathisia, dyskinesia and dystonia)
    - cardiovascular (including prolonging the QT interval)
    - hormonal (including increasing plasma prolactin)
    - other (including unpleasant subjective experiences). **[2016]**

2. **When choosing between olanzapine and other 'second generation' antipsychotic medications[a], discuss with the young person and their parents or carers the possibility of greater weight gain with olanzapine.**

   Inform them that this effect is likely to happen soon after starting treatment [new 2016].

1.3 Patient-centred care

This guideline offers best practice advice on the care of children and young people with psychosis and schizophrenia.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the person is under 16, their family or carers should also be given information and support to help the child or young person make decisions about their treatment. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have the capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

[a] At the time of consultation (January 2016), most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

NICE has also produced guidance on the components of good service user experience. All healthcare professionals and social care practitioners working with people using adult NHS mental health services should follow the recommendations in Service user experience in adult mental health.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with psychosis and schizophrenia. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1.43 Methods

This update was developed based on the process and methods described in the guidelines manual 2014.

2 ,Evidence review and recommendations

2.1 Introduction

Medication has formed the mainstay of treatment for psychosis since the introduction of chlorpromazine in the 1950s. Today, antipsychotic medication is considered an important part of a comprehensive package, which should also include psychological treatments and psychoeducation for the service user and their family. There has been a substantial increase in the prescription of antipsychotic medications for children and young people with evidence also of a change of use from so-called 'first generation' antipsychotics (FGAs) such as haloperidol to 'second generation' antipsychotics (SGAs) such as olanzapine and risperidone. The latter drugs were introduced and marketed as being more effective and less likely to cause side effects, particularly extrapyramidal movement disorders and parkinsonism. However, weight gain, risk of diabetes, and metabolic problems associated with SGAs raise important public health concerns given the widespread use of these medications. The surveillance review identified new evidence relating to adverse effects associated with olanzapine, particularly weight gain and metabolic effects, suggesting that olanzapine may not be suitable for first-line treatment in children and young people with first episode psychosis. In light of the new evidence, this update aims to assess adverse effects of olanzapine compared to other 'second generation' antipsychotics.

2.2 Review question

What is the adverse effects profile of olanzapine compared to other 'second generation' antipsychotics (SGAs) for treating children and young people with psychosis and schizophrenia?

2.3 Clinical evidence review

An update search using the original search strategy was conducted (see Appendix D) which identified 5184 articles. The titles and abstracts were screened and 358 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol (Appendix C). Of these, 354 were excluded as they did not meet the criteria. Three direct studies (i.e. age ≤18 years) and one indirect study (i.e. mean age <25 years) met the criteria and were included with an additional 9 direct studies from the original NICE guideline on psychosis and schizophrenia in children and young people. Therefore, there were a total of 13 included studies for the update.

A review flowchart is provided in Appendix E and the excluded studies (with reasons for exclusion) are shown in Appendix F.

2.3.1 Methods

Summary of review protocols

For the above review question, the population included children and young people (aged 18 years and younger) with psychosis and schizophrenia. Studies with a mean age of greater than 18 years but less than 25 years were also included if they reported on additional comparisons or outcomes not covered by the direct data (i.e. studies with a mean age of 18 years or younger) – this included one study reporting on quality of life.

The following subgroups were also specified:

a) Those with first episode psychosis

b) Those who did not respond adequately to treatment (they had first episode but did not respond to treatment)
c) Those with acute exacerbation or recurrence of symptoms
d) Those with mild learning disability
e) Ethnicity (particularly those from black and minority ethnic groups)

The intervention of interest was oral olanzapine (any dosage) compared against the following oral 'second generation' antipsychotics licensed in the UK for the treatment of psychosis and schizophrenia:

1) Amisulpride
2) Aripiprazole
3) Clozapine
4) Lurasidone hydrochloride
5) Paliperidone
6) Quetiapine
7) Risperidone

The topic experts outlined the following adverse outcomes for consideration:

1) Metabolic side effects (weight/BMI change, fasting serum glucose level change, cholesterol/lipoprotein level changes/triglyceride level changes, HbA1c levels
2) Neurological side effects (EPS scales, tardive dyskinesia)
3) Hormonal side effects (prolactin levels, thyroid stimulating hormone levels)
4) Cardiac side effects (blood pressure, QTc interval)
5) Leaving the study early for any reason including mortality
6) Quality of life
7) Developmental progress eg; school performance

GRADE methodology was used to assess the quality of evidence as follows:

Risk of bias:

For RCTs included in this review, criteria suggested by the GRADE methodology (http://www.gradeworkinggroup.org/) were used as a guide for assessing risk of bias. Specifically, the following areas were assessed: randomisation/allocation method, blinding and method used to evaluate the adverse effect in question. Dropout was assessed as a separate outcome (outcome 5 above) specified by the topic experts. For observational studies, equivalent areas including allocation to treatment groups, blinding and evaluation of the adverse outcome in question were assessed.

Indirectness:

Details from the Population, Intervention, Comparator and Outcomes sections of the review protocol(s) (see appendix C) were used to assess the directness of the included studies.

Inconsistency:

Conventional meta-analyses were not conducted due to heterogeneity in population and outcome measures across studies including:

- Indirect population:
  a) heterogeneity of diagnoses including schizophrenia spectrum disorders, mood spectrum disorders and aggression spectrum disorders in 6 studies.
  b) Subjects with comorbidities were included in 3 studies
  c) Use of concomitant medications such as antidepressants, mood stabilisers and psychostimulants in 9 studies
  d) Substance use including tobacco and alcohol in 2 studies

- Dose of intervention and comparators varied across the studies and were often flexible at the discretion of the clinician.

Imprecision:

A routine search of the COMET (Core Outcome Measures in Effectiveness Trials) Initiative database was conducted to identify any relevant thresholds for defining the clinical minimal important difference (MIDs). No information was identified in the COMET database. Information about specific MIDs used to assess imprecision were also not available from the original guideline CG155. The topic experts were consulted on the MIDs but were not aware of any published thresholds.

The consensus was to use the following universal/default thresholds defined by the GRADE working group to assess the precision of effect estimates:

- For dichotomous outcomes: Relative risk reduction or relative risk increase of 25%: 0.75 or 1.25
- For continuous outcomes: +/-0.5 standard deviation change

Overall quality:

For randomised controlled trials (RCTs) included in this systematic review, the quality rating of outcomes began at 'high' and were then further downgraded for potential sources of bias (if any) accordingly. For observational studies, the quality rating began at low and was similarly downgraded for potential sources of bias if any.

Statistical analysis:

Where appropriate, effect estimates including relative risks (95%CIs) and mean differences (95%CIs) were calculated using Review Manager 5.3

Overall summary of evidence

Overall, the majority of the evidence was of low to very low quality. Reasons for this included the allocation to treatment groups not being described in detail, lack of blinding and imprecision in the effect estimates due to small sample sizes. The eleven included studies covered the following comparisons:

Olanzapine versus risperidone: 4 new studies, 6 studies from original guideline

Olanzapine versus quetiapine: 3 new studies, 3 studies from original guideline

Olanzapine versus aripiprazole: 1 new study, 1 study from original guideline

Olanzapine versus clozapine: 0 new studies, 2 studies from original guideline

Some studies covered more than one comparison and so appear more than once in the summary of included studies (table 1 below) - for the full evidence tables please see appendix G and for full GRADE profiles please see appendix H.

1

2 **Table 1: Summary of included studies**

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Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
Olanzapine versus amisulpride				
No studies identified				
Olanzapine versus aripiprazole				
Carbon 2015 Prospective cohort	• Children and adolescents initiating antipsychotic treatment based on clinician and family choice • Mean age: 14.2 vs 12.97 years	Olanzapine versus aripiprazole	• Neurological side effects • Leaving study early for any reason	• Heterogeneous sample of diagnoses, comorbidities, comedications, prior antipsychotic users and antipsychotic naïve subjects included.
Correll 2009 (CG155) Prospective cohort	• Psychiatric illness prompting antipsychotic medication initiation • Mean age 14.7 vs 13.4 years respectively	Olanzapine versus aripiprazole (dose depending on clinical necessity)	• Metabolic side effects	• 1 week or less of lifetime antipsychotic treatment for inclusion • Heterogeneous sample of diagnoses, comedications permitted but numbers not reported
Olanzapine versus Clozapine				
Shaw 2006 (CG155) RCT	• Children with schizophrenia resistant to treatment with ≥2 antipsychotics, onset before 13 years • Mean age 12.8 and	Olanzapine (5mg increased to 15mg) versus clozapine (12.5mg increased to 150mg) for 8	• Metabolic side effects • Hormonal side effects • Cardiac side effects	• All prior antipsychotic users as ‘resistant to treatment with ≥2 antipsychotics’ is one inclusion critetia • Comorbidities • Concomitant medications

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
	11.7 years for treatment and comparator arms respectively	weeks	• Leaving the study early	permitted
Kumra 2008 (CG155) RCT	• Schizophrenia or schizoaffective disorder • Mean age 15.5 and 15.8 years respectively	Olanzapine (5mg/day increased in 5mg increments every 3 days to a maximum of 30mg/day) versus clozapine (25mg/day increased in 25mg or 50mg increments every 3 days to a max dose of 900mg/day) over 12 weeks	• Metabolic side effects • Leaving the study early	• Concomitant medications permitted • All subjects were prior antipsychotic users
Olanzapine versus lurasidone hydrochloride				
No studies identified				
Olanzapine versus paliperidone				
No studies identified				
Olanzapine versus Quetiapine				
Arango 2009 (CG155) RCT	• First episode of psychosis before 18 years lasting less than 1 year after onset of first symptom for inclusion • Mean age 15.7 and	Olanzapine versus Quetiapine – flexible doses at discretion of clinician for 6 months: mean	• Metabolic side effects • Neurological side effects • Hormonal side effects	• Heterogeneous sample of diagnoses (schizophrenia, bipolar, psychosis NOS, schizoaffective disorder, schizophreniform disorder, major depressive disorder) • Prior antipsychotic users and

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
	16.3 years for treatment and comparator arms respectively	doses were 12.11mg/day and 438mg/day respectively for intervention and comparator arms.	• Cardiac side effects • Leaving the study early	drug naïve subjects included. • Concomitant medications • All subjects prescribed risperidone at discretion of clinician prior to randomisation
Arango 2014 Prospective cohort	• Psychiatric diagnosis other than a primary eating disorder • Mean age 15.36 versus 15.74 years respectively	Olanzapine versus quetiapine (mean dose 143.52mg/day vs 78mg/day)	• Metabolic side effects • Cardiac side effects • Leaving the study early	• Heterogeneous sample of diagnoses • Occasional substance use • Concomitant medications • Prior antipsychotic users and antipsychotic-naïve subjects
Carbon 2015 Prospective cohort	• Children and adolescents initiating antipsychotic treatment based on clinician and family choice • Mean age: 14.2 vs 13.3 years	Olanzapine versus quetiapine	• Neurological side effects • Leaving study early for any reason	• Heterogeneous sample of diagnoses, comorbidities, comedications, prior antipsychotic users and antipsychotic naïve subjects included.
Castroforniles 2008 (CG155) Prospective cohort	• Positive psychotic symptoms of less than 6 months duration for inclusion • Mean age 15.7 and 16.4 years respectively	Olanzapine (mean dose 11.6mg/day) vs Quetiapine (mean dose 405.1mg/day) over 6 months	• Metabolic side effects • Neurological side effects	• Heterogenous sample of diagnoses (schizophrenia type disorder, psychotic disorder NOS, depressive disorder, bipolar, manic episodes with psychotic symptoms) • Prior antipsychotics users and drug naïve subjects included • Concomitant medications permitted

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
Correll 2009 (CG155) Prospective cohort	• Psychiatric illness prompting antipsychotic medication initiation • Mean age 14.7 vs 14.0 years respectively	Olanzapine versus quetiapine (dose depending on clinical necessity)	• Metabolic side effects	• 1 week or less of lifetime antipsychotic treatment for inclusion • Heterogeneous sample of diagnoses, comedications permitted but numbers not reported
Noguera 2013 Prospective cohort	• Positive psychotic symptoms • Mean age 15.6 and 15.2 years respectively	Olanzapine (mean dose 11.7mg/d) versus Quetiapine (614.5mg/d)	• Metabolic effects • Neurological side effects • Leaving the study early	• Heterogeneous sample of diagnoses (schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder NOS, major depressive disorder, bipolar disorder • Occasional substance use • Concomitant medications • Subjects allowed to change treatment during course of study • Prior antipsychotic users and antipsychotic naïve subjects included.
Olanzapine versus Risperidone				
Arango 2014 Prospective cohort	• Psychiatric diagnosis other than a primary eating disorder • Mean age 15.36 versus 14.03 years respectively	Olanzapine versus risperidone (mean dose 143.52mg/day vs 91.5mg/day)	• Metabolic side effects • Cardiac side effects • Leaving the study early	• Heterogeneous sample of diagnoses • Occasional substance use • Concomitant medications Prior antipsychotic users and antipsychotic-naïve subjects
Carbon 2015 Prospective	• Children and adolescents initiating	Olanzapine versus	• Neurological side	• Heterogeneous sample of diagnoses, comorbidities,

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
cohort	antipsychotic treatment based on clinician and family choice • Mean age: 14.2 vs 13.7 years	risperidone	effects • Leaving study early for any reason	comedications, prior antipsychotic users and antipsychotic naïve subjects included.
Correll 2009 (CG155) Prospective cohort	• Psychiatric illness prompting antipsychotic medication initiation • Mean age 14.7 vs 13.6 years respectively	Olanzapine versus risperidone (dose depending on clinical necessity)	• Metabolic side effects	• 1 week or less of lifetime antipsychotic treatment for inclusion • Heterogeneous sample of diagnoses, comedications permitted but numbers not reported
Montes 2003 Prospective cohort	• Confirmed diagnosis of schizophrenia according to ICD-10 criteria – first episode • Mean age 24 and 22.6 years respectively	Olanzapine (mean dose 13.5mg/day versus risperidone (5.4mg.day)	• Quality of life	• Indirect age group; mean age <25 years • Concomitant medications permitted
Noguera 2013 Prospective cohort	• Positive psychotic symptoms • Mean age 15.6 and 15.2 years respectively	Olanzapine (mean dose 11.7mg/d) versus Risperidone (3.1mg/d)	• Metabolic effects • Neurological side effects • Leaving the study early	• Heterogeneous sample of diagnoses (schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder NOS, major depressive disorder, bipolar disorder • Occasional substance use • Concomitant medications • Subjects allowed to change treatment during course of study • Prior antipsychotic users and

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
				antipsychotic naïve subjects included.
Sikich 2004 (CG155) RCT	• ≥1 positive psychiatric symptom of moderate or greater severity on the Brief Psychiatric Rating Scale for Children • Mean age 14.6 years for both treatment arms	Olanzapine (2.5 to 12.5 mg in 2.5mg increments) versus risperidone (0.5 to 3mg in 0.5mg increments) for 8 weeks	• Metabolic side effects • Neurological side effects • Hormonal side effects • Cardiac side effects • Leaving the study early	• Heterogeneous sample of diagnoses (schizophrenia spectrum disorders and affective disorders) • Concomitant medications received • Prior antipsychotic users and drug naïve subjects included
Sikich 2008 (CG155) RCT	• Schizophrenia, schizophreniform and schizoaffective disorder • Mean age not reported, range 8 to 19 years	Olanzapine versus risperidone (doses variable, mean Olanzapine dose 11.4mg/day, mean risperidone dose 2.8mg/day) over 8 weeks	• Metabolic side effects • Neurological side effects • Hormonal side effects • Cardiac side effects • Leaving the study early	• Concomitant medications • Prior antipsychotic users and drug naïve subjects
Crocq 2007 (CG155) Prospective cohort	• Diagnosis of schizophreniform disorder • Mean age 16.5 and 15.2 years respectively	Olanzapine versus risperidone (mean dose 16.6mg/day vs 2.8 mg/day over 12 weeks).	• Metabolic side effects	• 75% antipsychotic naïve
Castroforniles 2008	• Positive psychotic	Olanzapine (mean dose	• Metabolic side	• Heterogenous sample of

Study reference (including study design)	Study population	Intervention & comparator	Outcomes reported	Comments
(CG155) Prospective cohort	symptoms of less than 6 months duration for inclusion • Mean age 15.7 and 15.1 years respectively	11.6mg/day) vs Risperidone (mean dose 3.3mg/day) over 6 months	effects • Neurological side effects • Leaving the study early	diagnoses (schizophrenia type disorder, psychotic disorder NOS, depressive disorder, bipolar, manic episodes with psychotic symptoms) • Prior antipsychotics users and drug naïve subjects included • Concomitant medications permitted
Mozes 2006 (CG155) RCT	• Criteria for inclusion not reported however subjects included those with schizophreniform disorder, disorganised schizophrenia, paranoid schizophrenia and unspecified schizophrenia • Mean age 11.5 and 10.71 years respectively	Olanzapine versus risperidone (dose depending on clinical response and side effects however mean dose was 8.18mg/day versus 1.62mg/day over 12 weeks	• Metabolic side effects • Neurological side effects • Leaving the study early	• Concomitant medications received • Comorbidities • Prior antipsychotic use permitted

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2.41 Health economic evidence review

2.4.12 Methods

3 Evidence of cost effectiveness

4 The Committee is required to make decisions based on the best available evidence of both
5 clinical and cost effectiveness. Guideline recommendations should be based on the expected
6 costs of the different options in relation to their expected health benefits rather than the total
7 implementation cost.

8 Evidence on cost effectiveness related to the key clinical issues being addressed in the
9 guideline update was sought. The health economist undertook a systematic review of the
10 published economic literature.

11 Economic literature search

12 A systematic literature search was undertaken to identify health economic evidence within
13 published literature relevant to the review questions. The evidence was identified by
14 conducting a broad search relating to psychosis and schizophrenia in children and young
15 people in the NHS Economic Evaluation Database (NHS EED) and the Health Technology
16 Assessment database (HTA). The search also included Medline and Embase databases
17 using an economic filter. Studies published in languages other than English were not
18 reviewed. The search was conducted on 13 October 2015. The health economic search
19 strategies are detailed in appendix I.

20 The health economist also sought out relevant studies identified by the surveillance review or
21 Committee members.

22 Economic literature review

23 The health economist:

24 • Identified potentially relevant studies for each review question from the economic search
25 results by reviewing titles and abstracts. Full papers were then obtained.
26 • Reviewed full papers against prespecified inclusion and exclusion criteria to identify
27 relevant studies.

28 Inclusion and Exclusion criteria

29 Full economic evaluations (studies comparing costs and health consequences of alternative
30 courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequence
31 analyses) and comparative costing studies that address the review question in the relevant
32 population were considered potentially includable as economic evidence.

33 Studies that only reported burden of disease or cost of illness were excluded. Literature
34 reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and
35 studies not in English were excluded.

36 Remaining studies were prioritised for inclusion based on their relative applicability to the
37 development of this guideline and the study limitations. For example, if a high quality, directly
38 applicable UK analysis was available, then other less relevant studies may not have been
39 included. Where selective exclusions occurred on this basis, this is noted in the excluded
40 economic studies table (appendix K).

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist contained in *Appendix H* of *Developing NICE Guidelines: the manual 2014*.

In the absence of economic evidence

When no relevant economic studies were found from the economic literature review, and de novo modelling was not feasible or prioritised, the Committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the Committee and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

2.4.2 Results of the economic literature review

688 articles were identified by the literature search. 671 of these were excluded based on title and abstract. 17 full papers were obtained. All of these articles were excluded so there are no included studies in the economic systematic review. The flowchart summarising the number of studies included and excluded at each stage of the review process can be found in appendix J. Appendix K contains a list of excluded studies and the reason for their exclusion.

2.4.3 Unit costs

The basic unit costs related to this review question are provided in Table 2. Prices are taken from the Drug Tariff unless they do not appear there in which case the BNF was used. Formulations of 25 mg or less are included - this is the maximum dose that would be used according to topic experts – except for quetiapine where all doses are provided. Only medicines that appeared in the studies included in the clinical evidence review have been provided. The cost of clozapine has not been provided because it would only be used as a third-line option.

Table 2: Unit costs of oral formulations of 'second generation' antipsychotics

Medicine	Quantity per pack	Cost per pack (£)	Cost per tablet	Source
Olanzapine 10mg oral lyophilisates sugar free	28	87.4	3.12	Drug Tariff December 2015
Olanzapine 10mg orodispersible tablets	28	2.81	0.10	Drug Tariff December 2015
Olanzapine 10mg orodispersible tablets sugar free	28	2.78	0.10	Drug Tariff December 2015
Olanzapine 10mg tablets	28	1.44	0.05	Drug Tariff December 2015

Medicine	Quantity per pack	Cost per pack (£)	Cost per tablet	Source
Olanzapine 15mg oral lyophilisates sugar free	28	131.1	4.68	Drug Tariff Decembe r 2015
Olanzapine 15mg orodispersible tablets	28	3.36	0.12	Drug Tariff Decembe r 2015
Olanzapine 15mg orodispersible tablets sugar free	28	3.48	0.12	Drug Tariff Decembe r 2015
Olanzapine 15mg tablets	28	1.77	0.06	Drug Tariff Decembe r 2015
Olanzapine 2.5mg tablets	28	0.99	0.04	Drug Tariff Decembe r 2015
Olanzapine 20mg oral lyophilisates sugar free	28	174.79	6.24	Drug Tariff Decembe r 2015
Olanzapine 20mg orodispersible tablets	28	4.32	0.15	Drug Tariff Decembe r 2015
Olanzapine 20mg orodispersible tablets sugar free	28	5.04	0.18	Drug Tariff Decembe r 2015
Olanzapine 20mg tablets	28	1.78	0.06	Drug Tariff Decembe r 2015
Olanzapine 5mg oral lyophilisates sugar free	28	48.07	1.72	Drug Tariff Decembe r 2015
Olanzapine 5mg orodispersible tablets	28	2.46	0.09	Drug Tariff Decembe r 2015
Olanzapine 5mg orodispersible tablets sugar free	28	2.05	0.07	Drug Tariff Decembe r 2015
Olanzapine 5mg tablets	28	1.22	0.04	Drug Tariff Decembe r 2015
Olanzapine 7.5mg tablets	28	1.05	0.04	Drug Tariff

Medicine	Quantity per pack	Cost per pack (£)	Cost per tablet	Source
				December 2015
Aripiprazole 10mg tablets	28	43.81	1.56	Drug Tariff December 2015
Aripiprazole 15mg tablets	28	43.37	1.55	Drug Tariff December 2015
Aripiprazole 30mg tablets	28	131.99	4.71	Drug Tariff December 2015
Aripiprazole 5mg tablets	28	43.99	1.57	Drug Tariff December 2015
Aripiprazole 10mg oridispersible tablets	28	96.04	3.43	BNF accessed 17.12.2015
Aripiprazole 1mg/ml oral solution	150mL	102.9	#VALUE!	BNF accessed 17.12.2015
Quetiapine 100mg immediate-release tablets	60	2.42	0.04	Drug Tariff December 2015
Quetiapine 150mg modified-release tablets	60	113.1	1.89	Drug Tariff December 2015
Quetiapine 150mg immediate-release tablets	60	3.05	0.05	Drug Tariff December 2015
Quetiapine 200mg modified-release tablets	60	113.1	1.89	Drug Tariff December 2015
Quetiapine 200mg immediate-release tablets	60	3.35	0.06	Drug Tariff December 2015
Quetiapine 25mg immediate-rlease tablets	60	1.44	0.02	Drug Tariff December 2015
Quetiapine 300mg modified-release tablets	60	170	2.83	Drug Tariff December 2015

Medicine	Quantity per pack	Cost per pack (£)	Cost per tablet	Source
Quetiapine 300mg immediate-release tablets	60	4.44	0.07	Drug Tariff Decembe r 2015
Quetiapine 400mg modified-release tablets	60	226.2	3.77	Drug Tariff Decembe r 2015
Quetiapine 50mg modified-release tablets	60	67.66	1.13	Drug Tariff Decembe r 2015
Risperidone 1mg orodispersible tablets sugar free	28	21.07	0.75	Drug Tariff Decembe r 2015
Risperidone 1mg tablets	20	1.01	0.05	Drug Tariff Decembe r 2015
Risperidone 1mg/ml oral solution sugar free	100 mL	6.27	#VALUE!	Drug Tariff Decembe r 2015
Risperidone 2mg orodispersible tablets sugar free	28	38.73	1.38	Drug Tariff Decembe r 2015
Risperidone 2mg tablets	60	1.8	0.03	Drug Tariff Decembe r 2015
Risperidone 3mg orodispersible tablets sugar free	28	33.5	1.20	Drug Tariff Decembe r 2015
Risperidone 3mg tablets	60	2.24	0.04	Drug Tariff Decembe r 2015
Risperidone 4mg orodispersible tablets sugar free	28	37.95	1.36	Drug Tariff Decembe r 2015
Risperidone 4mg tablets	60	2.61	0.04	Drug Tariff Decembe r 2015
Risperidone 500microgram orodispersible tablets sugar free	28	23.85	0.85	Drug Tariff Decembe r 2015
Risperidone 500microgram tablets	20	1.05	0.05	Drug Tariff

Medicine	Quantity per pack	Cost per pack (£)	Cost per tablet	Source
				December 2015
Risperidone 6mg tablets	28	3.95	0.14	Drug Tariff December 2015

2.5 Evidence statements

2.5.1 Clinical evidence statement

Olanzapine versus aripiprazole

Two studies (n=124 and 86 respectively) compared olanzapine with aripiprazole for neurological side effects in subjects with a mean age ≤18 years. Treatment duration was 12 weeks. Very low quality evidence indicated olanzapine with lower rates of drug induced parkinsonism at 12 weeks when compared to aripiprazole. However the treatment groups were imbalanced at baseline with 10% of subjects in the aripiprazole arm already experiencing parkinsonism at the start of treatment. The same study was inconclusive for dyskinesia and akathisia at 12 weeks and for discontinuation due to extrapyramidal side effects. Very low quality evidence from the other study indicated olanzapine was associated with a number of metabolic factors including weight gain and cholesterol change but with uncertain clinical significance.

Olanzapine versus quetiapine

Six studies (n= 29 to 124) compared olanzapine with quetiapine for metabolic side effects, neurological side effects, cardiac side effects, hormonal side effects and discontinuation in subjects with a mean age ≤18 years. Treatment duration ranged from 12 weeks to 6 months. Evidence from 2 studies was inconclusive for neurological side effects (including parkinsonism, dyskinesia, akathisia, concentration difficulties and tremor) and another 2 studies found no difference between groups. Two studies were inconclusive for cardiac side effects (including systolic and diastolic blood pressure, palpitations/tachycardia) and the only study reporting on hormonal side effects was also inconclusive. Three studies reporting on leaving the study early for any reason were inconclusive. For metabolic side effects, 5 studies indicated olanzapine was associated with more weight gain compared to quetiapine, but with uncertain clinical significance in some studies. Evidence for all outcomes was of very low quality.

Olanzapine versus risperidone

Eight studies (n= 25 to 195) compared olanzapine with risperidone for metabolic side effects, neurological side effects, cardiac side effects, hormonal side effects and leaving the study early for any reason in subjects with a mean age ≤18 years. Treatment duration was 8 weeks to 6 months. Low to very low quality evidence from seven studies indicated olanzapine was associated with more weight gain compared to risperidone, with uncertain clinical importance in 1 study. Very low quality evidence from a further study was inconclusive for weight gain and the evidence for other metabolic factors such as glucose and cholesterol change were inconsistent across the studies. Evidence was largely inconclusive for the 6 studies reporting

neurological side effects (including parkinsonism, dyskinesia, akathisia) and inconsistent for cardiac side effects (systolic and diastolic blood pressure change), prolactin levels and leaving the study early for any reason. Furthermore, very low quality evidence from the only study reporting on quality of life (n=145) in subjects with a mean age <25 years found no difference in subjects receiving olanzapine compared to risperidone.

Olanzapine versus clozapine

Two studies (n=25 and 39 respectively) compared olanzapine (high-dose olanzapine in one study) with clozapine for metabolic side effects, discontinuation and/or cardiac side effects in subjects with a mean age ≤18 years with treatment resistant schizophrenia. Treatment duration was 8 and 12 weeks respectively. Low to very low quality evidence indicated inconclusive findings for the majority of metabolic side effects except for fasting glucose where olanzapine was associated with a smaller change compared to clozapine. Moderate quality evidence from one study indicated olanzapine was associated with lower rates of hypertension and tachycardia >100bpm compared to clozapine but with uncertain clinical importance. Low quality evidence indicated olanzapine may not be favoured in terms of leaving the study early for any reason but evidence was very low quality and inconclusive in the other study.

2.5.2 Health economic evidence statements

No studies were included in the economic stystematic review. Economic modelling was not conducted. The costs of tablet formulations of 'second generation' antipsychotics are similar ranging from 5 pence to £1.57. Orodispersible and lyophilisate formulations are more expensive.

2.6 Evidence to recommendations

	Committee discussions
Relative value of different outcomes	The aim of this question was to review new evidence on adverse effects of olanzapine. The Committee therefore prioritised the following outcomes for comparing the side effect profile of olanzapine with other 'second generation' antipsychotics. 1) Metabolic side effects (weight/Body Mass Index change, fasting serum glucose level change, cholesterol/lipoprotein level changes/triglyceride level changes, HbA1c levels) 2) Neurological side effects (Extrapyramidal symptoms, tardive dyskinesia) 3) Hormonal side effects (prolactin levels, thyroid stimulating hormone levels) 4) Cardiac side effects (blood pressure, QTc interval) 5) Leaving the study early for any reason including mortality 6) Quality of life 7) Developmental progress eg; school performance The Committee valued weight gain as the most important outcome for decision making because young people are especially vulnerable to rapid and early weight gain. These changes can develop within weeks of the intiation of antipsychotic drugs and are more pronounced in children and adolescents that in adults. Lifestyle factors that compound these changes include tobacco smoking, substance use, a sedentary lifestyle and poor nutrition, which are highly prevalent in young people with first episode psychosis. The Committee highlighted that early weight gain, particularly in the first epsiodes of psychosis, not only has immediate effects such as decline in fitness but also increases the risk of diabetes and cardiovascular

	Committee discussions
	disease in the future. The Committee noted that weight gain additionally increases the stigma young people already have about themselves, further lowering their self esteem and restricting their participation in social and physical activities. The Committee concluded that such consequences would in turn affect a young person's future engagement with medical care and therefore prioritised this outcome for review. Furthermore, neurological side effects were also prioritised as important because some such as tardive dyskinesia can be very serious, irreversible and stigmatising.
Quality of evidence	The Committee noted the evidence was largely of very low quality for the following reasons: ➢ Lack of blinding/blinding not described in 8 studies ➢ Treatment allocation not described in detail in 8 studies ➢ Heterogeneity of diagnoses including schizophrenia spectrum disorders, mood spectrum disorders and aggression spectrum disorders in 6 studies. ➢ Subjects with comorbidities were included in 3 studies ➢ Use of concomitant medications such as antidepressants, mood stabilisers and psychostimulants in 9 studies ➢ Substance use including tobacco and alcohol in 2 studies ➢ Unbalanced groups at baseline in 1 study comparing olanzapine with aripiprazole, quetiapine and risperidone. The Committee noted that the above variations in populations meant that the data could not be pooled and so inconsistency could not be assessed. In addition, though the lack of blinding could have affected outcome ascertainment, the objective nature of some of the outcome measures (e.g. BMI change) was reassuring. Despite these limitations, the Committee overall concluded that this was the most relevant data available for an age group where pharmacological research is limited. The Committee further noted that no evidence was idenitifed for 3 comparisons (amisulpride, lurasidone hydrochloride and paliperidone) and one of the outcomes (developmental progress) specified in the review protocol. The Committee also felt cautious about drawing conclusions from the only study that reported on quality of life given that the mean age of the subjects was greater than 18 years (24 years for the intervention arm and 22.6 years for the comparator arm of the study). Finally, given the lack of evidence for 2 subgroups specified in the review protocol (those with mild learning disability and ethnicity), the Committee were unable to form specific recommendations for these particular groups of interest.
Trade-off between benefits and harms	The Committee considered the evidence for this review from the underlying finding of the original guideline that there were minimal differences in efficacy between second generation antipsychotic medications including olanzapine relative to other second-generation antipsychotics for the treatment of first episode psychosis except for clozapine which is generally only given to those who have not responded to at least 2 other antipyschotics. Efficacy was therefore not considered as part of this review. The Committee disregarded the evidence on clozapine, which is only usually prescribed after trying at least 2 other antipsychotics (treatment-resistant psychosis) as the focus of this review was on first episode psychosis not treatment-resistant psychosis. Based on both the evidence identified and consensus from clinical experience of the topic experts, the Committee overall agreed that all second generation antipsychotics are associated with some weight gain however olanzapine was associated with sudden and greater risk of weight

	Committee discussions
	gain and metabolic disturbances compared to other 'second generation' antipsychotics. Olanzapine was associated with an additional 1.33 to 5.70 kg of weight gain compared with other second generation antipsychotics within 3 to 6 months of treatment, indicating evidence of additional weight gain from early stages of treatment and emphasising the need for close monitoring and review from early on. The Committee did not consider efficacy data, and did not think the evidence regarding side effects was of high enough quality for olanzapine to not be offered in any circumstances. However they highlighted that there is clearly some evidence of greater weight gain in the studies which clinicians and patients need to be aware of when when considering which antipsychotic to use. The Committee further noted that there was no evidence to suggest that patients already on olanzapine needed to change treatment in light of this review given efficacy may outweigh concerns about weight gain for these particular individuals, and that changing established and effective antipsychotic medication was associated with substantial risk of relapse. The Committee also noted that evidence regarding other side effects including neurological, hormonal and cardiac were inconsistent across the studies with no obvious trend.
Trade-off between net health benefits and resource use	There were no studies included in the economic systematic review. Economic modelling was not undertaken for this update because the cost effectiveness of olanzapine could be assessed by means of a qualitative discussion alone and evidence on efficacy, that would be required to populate a model, was not included in the clinical review due to the narrow review question on the side-effects of olanzapine only. The Committee considered the cost of alternative second generation antipsychotics. Because these are generic medicines, the cost of tablets is low, ranging from 5p for 1mg risperidone to £1.57 for 5mg aripiprizole. However the branded versions of these drugs are also available in more expensive or orodispersible forms but these are rarely used and the topic experts advised there are usually directives in place in local trusts to use the cheaper formulations. The Committee concluded there would be no increase in the direct cost of medicines if an alternative second generation antipsychotic to olanzapine were to be prescribed generically. The Committee considered the cost of side effects, particularly metabolic syndrome including weight gain, increased BMI, high cholesterol and insulin resistance. Because metabolic syndrome is associated with a range of high cost diseases such as diabetes, cardiovascular disease and cancer, choosing a second generation antipsychotic other than olanzapine provides an opportunity to reduce resource use in these areas. The Committee considered the costs of switching drugs. Some people need to be admitted to hospital when they switch antipsychotics and additional counselling sessions are usually required, both for the child or young person and their families.This highlights the importance of using a first-line antipsychotic with fewer side-effects. Overall, the Committee concluded that choosing a 'second generation' antipsychotic other than olanzapine may be a cost-effective treatment alternative because it increases health and reduces costs.
Other considerations	**Equalities considerations:** 1) Those with mild learning disability: assessing the mental state of a child with learning difficulties can be a complex process due to the difficulties associated with determining medical history and

	Committee discussions
	symptoms. Understanding a child's development and learning disability will therefore affect the assessment and what conclusions can be drawn from it. In light of this, the Committee specified those with mild learning disability as a subgroup for review; however no evidence was identified for this group. 2) Ethnicity: the Committee specified ethnicity as a subgroup for review as different ethnic groups have different rates and experiences of mental health problems, reflecting their different cultural and socio-economic contexts and access to culturally appropriate treatments. The Committee therefore specified ethnicity as a further subgroup however no relevant evidence was identified. 3) Sex: although schizophrenia affects males and females with equal frequency, the consequences of weight gain as an adverse effect of treatment may be experienced differently between the sexes, with the Topic Exerts reporting their experience of girls being more sensitive to an increase in weight than boys and that this is an important consideration with an impact on adherence . 4) English not first language: children and young people who do not speak English as a first language may not be able to fully describe their medical history or symptoms. Consequently it may be difficult to accurately establish clinical characteristics and symptom history which could lead to misclassification. This also has implications for discussing and understanding the different treatment options and benefits and harm associated with them. 5) Pregnancy – the Committee questioned the safety of antipsychotic medications during pregnancy but did not specify pregnancy as a subgroup of interest given there are separate NICE guidelines covering this area ('Antenatal and postnatal mental health' and 'Pregnancy and complex social factors: a model for service provision for pregnant women with complex social factors') 6) Looked after children – the Committee discussed that looked after children may experience a delay in access to services because of the complexity of various services involved in providing care for such children – the Committee noted the same could be apply to migrant workers and homeless populations who may also experience difficulty accessing services.

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2.7 Recommendations

1. **The choice of antipsychotic medication[b] should be made by the parents or carers of younger children, or jointly with the young person and their parents or carers, and healthcare professionals. Provide age-appropriate information and discuss the likely benefits and possible side effects of each drug including:**
    - metabolic (including weight gain and diabetes)
    - extrapyramidal (including akathisia, dyskinesia and dystonia)
    - cardiovascular (including prolonging the QT interval)
    - hormonal (including increasing plasma prolactin)
    - other (including unpleasant subjective experiences). **[2016]**

2. **When choosing between olanzapine and other 'second generation' antipsychotic medications[b], discuss with the young person and their parents or carers the possibility of greater weight gain with olanzapine.**

   Inform them that this effect is likely to happen soon after starting treatment [new 2016].

[b] At the time of consultation (January 2016), most antipsychotic medication did not have a UK marketing authorisation specifically for children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

31 References

Arango,C., Robles,O., Parellada,M., Fraguas,D., Ruiz-Sancho,A., Medina,O., Zabala,A., Bombín,I., Moreno,D., Olanzapine compared to quetiapine in adolescents with a first psychotic episode, European child & adolescent psychiatry, 18, 418-428, 2009 (included in CG155)

Arango,C., Giraldez,M., Merchan-Naranjo,J., Baeza,I., Castro-Fornieles,J., Alda,J.-A., Martinez-Cantarero,C., Moreno,C., De,Andres P., Cuerda,C., De La Serna,E., Correll,C.U., Fraguas,D., Parellada,M., Second-generation antipsychotic use in children and adolescents: A six-month prospective cohort study in drug-naive patients, Journal of the American Academy of Child and Adolescent Psychiatry.53 (11) (pp 1179-1190.e4), 2014.Date of Publication: 2014., 1179-1190, 2014

Carbon,M., Kapoor,S., Sheridan,E., Al-Jadiri,A., Azzo,S., Sarkaria,T., Kane,J.M., Saito,E., Correll,C.U., Neuromotor Adverse Effects in 342 Youth during 12 Weeks of Naturalistic Treatment with 5 Second-Generation Antipsychotics, Journal of the American Academy of Child and Adolescent Psychiatry.54 (9) (pp 718-727), 2015.Date of Publication: 01 Sep 2015., 718-727, 2015

Castro-Fornieles,J., Parellada,M., Soutullo,C.A., Baeza,I., Gonzalez-Pinto,A., Graell,M., Paya,B., Moreno,D., Serna,E., Arango,C., Antipsychotic treatment in child and adolescent first-episode psychosis: a longitudinal naturalistic approach, Journal of child and adolescent psychopharmacology, 18, 327-336, 2008 (included in CG155)

Correll, C. U., Manu, P., Olshanskiy, V., et al. (2009) Cardiometabolic risk of second-generation antipsychotic medications during fi rst-time use in children and adolescents. Journal of the American Medical Association, 302, 1765–1773 (included in CG155)

Crocq, MA., Guillon, MS., Bailey, PE., Provost, D., Orally disintegrating olanzapine induces less weight gain in adolescents than standard oral tablets . 22, 453-454, 2007 (included in CG155)

Kumra,S., Kranzler,H., Gerbino-Rosen,G., Kester,H.M., Thomas,C., Kafantaris,V., Correll,C.U., Kane,J.M., Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: a 12-week randomized and double-blind comparison, Biological psychiatry, 63, 524-529, 2008 (included in CG155)

Montes,J.M., Ciudad,A., Gascón,J., Gómez,J.C., Safety, effectiveness, and quality of life of olanzapine in first-episode schizophrenia: a naturalistic study, Progress in neuro-psychopharmacology & biological psychiatry, 27, 667-674, 2003

Mozes,T., Ebert,T., Michal,S.E., Spivak,B., Weizman,A., An open-label randomized comparison of olanzapine versus risperidone in the treatment of childhood-onset schizophrenia, Journal of child and adolescent psychopharmacology, 16, 393-403, 2006 (included in CG155)

Noguera,A., Ballesta,P., Baeza,I., Arango,C., De La Serna,E., Gonzalez-Pinto,A., Parellada,M., Graell,M., Moreno,C., Otero,S., Castro-Fornieles,J., Twenty-four months of antipsychotic treatment in children and adolescents with first psychotic episode: Discontinuation and tolerability, Journal of Clinical Psychopharmacology.33 (4) (pp 463-471), 2013.Date of Publication: August 2013., 463-471, 2013

Shaw,P., Sporn,A., Gogtay,N., Overman,G.P., Greenstein,D., Gochman,P., Tossell,J.W., Lenane,M., Rapoport,J.L., Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison, Archives of general psychiatry, 63, 721-730, 2006 (included in CG155)

Sikich,L., Hamer,R.M., Bashford,R.A., Sheitman,B.B., Lieberman,J.A., A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial, Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 29, 133-145, 2004 (included in CG155)

Sikich,L., Frazier,J.A., McClellan,J., Findling,R.L., Vitiello,B., Ritz,L., Ambler,D., Puglia,M., Maloney,A.E., Michael,E., Jong,S., Slifka,K., Noyes,N., Hlastala,S., Pierson,L., McNamara,N.K., Delporto-Bedoya,D., Anderson,R., Hamer,R.M., Lieberman,J.A., Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder: findings from the treatment of early-onset schizophrenia spectrum disorders (TEOSS) study, The American journal of psychiatry, 165, 1420-1431, 2008 (included in CG155)

4 Glossary and abbreviations

Please refer to the NICE glossary.

Akathisia: is a movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. Antipsychotics particularly the first generation antipsychotics are known to cause akathisia.

At risk mental states for developing psychosis: psychosis may be preceded by a 'prodromal period', in which the child or young person's behaviour and experiences are altered. Although not all young people with an 'at risk mental state' will go on to develop psychosis, it is important to identify these individuals because psychological approaches have proven efficacy in reducing the risk of transition to psychosis. However antipsychotic treatment does not prevent transition and should not be offered.

Dyskinesia: refers to a category of movement disorders that are characterized by involuntary muscle movements, including movements similar to tics or chorea and diminished voluntary movements. Dyskinesia can be anything from a slight tremor of the hands to an uncontrollable movement of the upper body or lower extremities.

Dystonia: is a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. The movements may resemble a tremor. Dystonia is often initiated or worsened by voluntary movements, and symptoms may "overflow" into adjacent muscles

Extrapyramidal symptoms (EPS): also known as extrapyramidal side effects (EPSE), are drug induced movement disorders that include acute and tardive symptoms. These symptoms include dystonia (continuous spasms and muscle contractions), akathisia (motor restlessness), parkinsonism (characteristic symptoms such as rigidity, bradykinesia, and tremor), and tardive dyskinesia (irregular, jerky movements). Antipsychotics are often discontinued due to inefficacy or intolerable side effects such as extrapyramidal symptoms.

First generation antipsychotics (FGAs): are also known as typical antipsychotics. FGAs are a class of antipsychotic drugs first developed in the 1950s and used to treat psychosis (in particular, schizophrenia).

Metabolic syndrome: a cluster of conditions — increased blood pressure, high blood sugar level, excess body fat around the waist and abnormal cholesterol levels — that occur together, increasing one's risk of heart disease, stroke and diabetes.

Negative symptoms: such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect.

Psychosis and schizophrenia: represent a major psychiatric disorder, or cluster of disorders including schizoaffective disorders (where schizophrenic and affective symptoms are simultaneously present and both are equally prominent) and delusional disorders (but excluding bipolar disorder) that alters a person's perception, thoughts, mood and behaviour.

Positive symptoms: hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs).

Second-generation antipsychotics (SGAs): are known as 'atypical' antipsychotics. Both generations of medication tend to block receptors in the brain's dopamine pathways, but atypicals at the time of marketing were claimed to differ from typical antipsychotics in that they are less likely to cause extrapyramidal motor control disabilities in patients, which include unsteady Parkinson's disease-type movements, body rigidity and involuntary tremors.

Tardive dyskinesia: often incurable form of dyskinesia, a disorder resulting in involuntary, repetitive body movements. In this form of dyskinesia, the involuntary movements are tardive, meaning they have a slow or belated onset. This neurological disorder most frequently occurs as the result of long-term or high-dose use of antipsychotic drugs.

Treatment resistant schizophrenia: Schizophrenia that persists despite trials of medication that have been adequate in terms of dose, duration and adherence.

Appendices

Appendix A: Standing Committee members and NICE teams

A.1 Core members

Name	Role
Susan Bewley (Chair)	Chair
Gita Bhutani	Associate Director for Psychological Professions
Simon Corbett	Cardiologist
Gail Fortes Mayer	Commissioner
John Graham	Vice Chair (Oncologist)
Peter Hoskin	Oncologist
Roberta James	SIGN Programme Lead - methodologist
Jo Josh	Lay member
Asma Khalil	Obstetrician
Manoj Mistry	Lay member
Amaka Offiah	Reader in Paediatric Musculoskeletal Imaging and Honorary Consultant Paediatric Radiologist
Mark Rodgers	Research Fellow - methodologist
Nicholas Steel	PH/Academic in primary care
Sietse Wieringa	GP

A.2 Topic expert Committee members

Name	Role
Anthony James	Consultant Child and Adolescent Psychiatrist
Joanne Marshall	CAMHS Nurse
Caroline Parker	Consultant Pharmacist Adult Mental Health
David Shiers	Lay member
Anne Taylor	Consultant Child and Adolescent Psychiatrist

A.3 NICE project team

Name	Role
Phil Alderson	Clinical Adviser
Jessica Fielding	Public Involvement Adviser
Lyn Knott	Senior Medical Editor
Bhash Naidoo	Technical Lead (Health Economics)
Louise Shires	Guideline Commissioning Manager
Sharon Summers-Ma	Guideline Lead
Judith Thornton	Technical Lead
Trudie Willingham	Guideline Co-ordinator

A.4 Clinical guidelines update team

Name	Role
Phil Alderson	Clinical Adviser
Emma Banks	Co-ordinator
Paul Crosland	Health Economist
Jemma Dean	Information Specialist
Kathryn Hopkins	Technical Analyst Quality Assurance
Nick Lowe	Administrator
Hugh McGuire	Technical Adviser
Susannah Moon	Programme Manager
Nitara Prasannan	Technical Analyst
Lorraine Taylor	Associate Director

1 Appendix B: Declarations of interest

B.12 Core members

Name	Interest declared	Type of interest	Action
Susan Bewley	Self-employed academic and obstetric expert.	Non-specific Personal Financial	Declare and participate
Susan Bewley	100 hour per annum teaching contract with Kings College London.	Non-specific Personal Financial	Declare and participate
Susan Bewley	Received income/fee for Teaching (BSc law and ethics tutor at KCL, occasional fees for lectures on obstetrics)	Non-specific Personal Financial	Declare and participate
Susan Bewley	Received income/fee for Medico-legal reports (approx. 2/year) and Medical Defence Union cases committee and council	Non-specific Personal Financial	Declare and participate
Susan Bewley	Received income/fee for external reviews for NHS organisations related to my obstetric expertise (serious incident and maternal mortality investigations, RCOG review)	Non-specific Personal Financial	Declare and participate
Susan Bewley	Received royalties from edited books	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expressed views in publications about obstetric matters, largely based on evidence.	Non-specific Personal Non-financial	Declare and participate
Susan Bewley	A trustee and committee member of Healthwatch (a charity devoted to evidence and “for treatments that work”) and a trustee of Sophia (a charity devoted to women with HIV and the UK arm of the Global Coalition for Women and AIDS).	Non-specific Personal Non-financial	Declare and participate
Susan Bewley	Member of the following editorial boards: Medical Law Review, International Journal of Childbirth, Journal Article Summary Service; Member All-Parliamentary Party Group on Maternity; Trustee of Maternity Action (a charity which aims to end inequality and improve the health and well-being of pregnant women, partners and young children), one of seven members of the Women’s Health and Equality Consortium which is a Strategic Partner of the Department of Health.	Non-specific Personal Non-financial	Declare and participate
Susan Bewley	Part-time on call sexual offences examiner (forensic medical examinations) working at the Haven Camberwell Sexual Assault Referral Centre (Kings College Hospital)	Non-specific Personal Financial	Declare and participate
Susan Bewley	Received income/fee as Consultant for the World Health Organization (five days approx), for their updated guideline on Reproductive and Sexual Health and Human Rights for Women living with HIV	Non-specific Personal Financial	Declare and participate
Susan Bewley	Received fee as Chair of NICE Fertility Evidence Update	Non-specific Personal	Declare and participate

Name	Interest declared	Type of interest	Action
		Financial	
Susan Bewley	Expert fee (one off piece of work) for medicolegal criminal case	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expert fee (one off piece of work) for obstetric and managerial advice (overseas not- hospital) for-profit	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expenses paid to lecture at the National RCOG trainees annual conference	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expenses only lecture at the Royal Society of Medicine	Non-specific Personal Non-financial	Declare and participate
Susan Bewley	Expenses only lecture at the GLADD Annual conference	Non-specific Personal Non-financial	Declare and participate
Susan Bewley	Expenses only lecture at the FIL Annual conference	Non-specific Personal Non-financial	Declare and participate
Susan Bewley	Expenses only lecture at the RCOG Review training	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expenses only lecture at the BPAS Annual Meeting Clinical Forum	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expenses only lecture at the WOW Festival	Non-specific Personal Financial	Declare and participate
Susan Bewley	Expenses only lectures relating to publicising NICE intrapartum guidelines	Non-specific Personal Financial	Declare and participate
Susan Bewley	Lecture fee, at ‘safe hands conference’ Bolton	Non-specific Personal Financial	Declare and participate
Susan Bewley	Unpaid (but travel, hotel and subsistence) trip to two not-for-profit maternity hospitals in return for four days teaching/ expert advice, India	Non-specific Personal Financial	Declare and participate
Susan Bewley	Al Jazeera: studio fee for commenting as an obstetric expert about egg freezing	Non-specific Personal Financial	Declare and participate
Susan Bewley	PRP: fee for review of NIHR policy research programme domestic violence report	Non-specific Personal Financial	Declare and participate
Susan Bewley	Birmingham University: fee for assisting NICE training tool development	Non-specific Personal Financial	Declare and participate
Susan Bewley	Choitham Hospitals, India: fee for maternity services advice	Non-specific Personal	Declare and participate

Name	Interest declared	Type of interest	Action
		Financial	
Susan Bewley	Fee for lecture on egg freezing (debate at British Fertility Society, January 2016)	Non-specific Personal Financial	Declare and participate
Susan Bewley	Fee for lecture on domestic violence (Faculty of Sexual and Reproductive Healthcare, RCOG)	Non-specific Personal Financial	Declare and participate
Susan Bewley	Fee for lecture on reproductive health as public health issue (European society for human reproduction and embryology)	Non-specific Personal Financial	Declare and participate
Susan Bewley	Fee for lecture on female genital mutilation (Liverpool medical society)	Non-specific Personal Financial	Declare and participate
Gita Bhutani	Chair of Psychological Professions Network North West	Non-specific Personal Non-financial	Declare and participate
Gita Bhutani	Member of British Psychological Society; Division of Clinical Psychology; Faculty of Leadership and Management Committee Member	Non-specific Personal Non-financial	Declare and participate
Gita Bhutani	Project lead on BPS Division of Clinical Psychology project on 'Comprehensively representing the complexity of psychological services'	Non-specific Personal Non-financial	Declare and participate
Gita Bhutani	Analytical support in partnership with Liverpool University on Liverpool Health Partners project on Patient Quality and Safety	Non-specific Personal Non-financial	Declare and participate
Gita Bhutani	Joint project lead on Health Education North West funded project on Schwartz Rounds	Non-specific Personal Non-financial	Declare and participate
Simon Corbett	Network Service Adviser for the British Cardiovascular Society. This role incorporates the regional specialty adviser role for the Royal College of Physicians.	Non-specific Personal Non-financial	Declare and participate
Simon Corbett	Director for Clinical Effectiveness for employer (University Hospital Southampton NHS Foundation Trust). Part of this role involves the dissemination and implementation of NICE guidance in the Trust.	Non-specific Personal Non-financial	Declare and participate
Simon Corbett	Independent cardiologist on the Trial Steering Committee of the randomised controlled AVATAR trial, a randomised trial of medical therapy vs ablation in patients with atrial fibrillation. The study is sponsored by Imperial College London and is part funded by Medtronic. Travel expenses are paid by Imperial.	Non-specific Personal Non-financial	Declare and participate
Gail Fortes Mayer	None	Not applicable	Declare and participate
John Graham	Director of National Collaborating Centre for Cancer – this post is funded through a contract with NICE to produce NICE's clinical guidelines.	Non-specific Non-personal Financial	Declare and participate
John Graham	Principal investigator for Ongoing clinical trials in prostate cancer: 1) With Custirsen funded by OncoGenex Technologies	Non-specific Non-personal Financial	Declare and participate

Name	Interest declared	Type of interest	Action
	Inc and Teva Pharmaceutical Industries Ltd. 2) Orteronel Affinity Trial funded by Millenium Pharmaceuticals Inc 3) Principal investigator for a study of radium-223 in prostate cancer that is funded by Bayer Pharmaceuticals 4) Principal investigator in 2 trials of radium-223 in breast cancer funded by Bayer Pharmaceuticals.		
John Graham	Principal investigator for 8 Ongoing clinical trials in breast and prostate cancer run via the National Cancer Research Network (not pharmaceutical industry funded)	Non-specific Non-personal Financial	Declare and participate
John Graham	Member of the trial management groups for 2 prostate cancer trials: RT01 and CHHIP. Both are closed to recruitment but continuing to report trial results.	Non-specific Personal Non-financial	Declare and participate
John Graham	Council member of the South-West England Clinical Senate	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Investigator in research studies sponsored by various companies with payment for expenses to NHS Trust and department which fund research staff. Recent studies have been on behalf of Millenium, Astellas, Ipsen and Amgen.	Non-specific Non-personal Financial	Declare and participate
Peter Hoskin	Fellow of the Royal College of Radiologists and member of Faculty Board, Specialist Training Board and Chair of Exam Board.	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Consultant to the IAEA; Undertake by invitation lectures and working group meetings for which expenses may be paid.	Non-specific Personal Financial	Declare and participate
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas.	Non-specific Non-personal Financial	Declare and participate
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation. and Astellas	Non-specific Non-personal Financial	Declare and participate
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	Non-specific Non-personal Financial	Declare and participate
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	Non-specific Non-personal Financial	Declare and participate
Peter Hoskin	Department received grants from Millennium for trials in prostate cancer.	Non-specific Non-personal Financial	Declare and participate
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies.	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Member of the Steering Group for National Cancer Intelligence Network (NCIN)	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Member of the faculty board of the Royal College of	Non-specific	Declare and

Name	Interest declared	Type of interest	Action
	Radiologists.	Personal Non-financial	participate
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Member of the East of England senate.	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Member of the NICE standing committee for rapid updates / and non-Hodgkin's lymphoma GDG.	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Member European Society for Radiotherapy and Oncology (ESTRO) Board	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Member HTA Clinical Evaluation and Trials Board	Non-specific Personal Non-financial	Declare and participate
Peter Hoskin	Clinical Editor, radiotherapy and Oncology	Non-specific Personal Non-financial	Declare and participate
Roberta James	Programme Lead at Scottish Intercollegiate Guidelines Network	Non-specific Personal Financial	Declare and participate
Roberta James	Member of Guideline Implementability Research and Application Network	Non-specific Personal Non-financial	Declare and participate
Roberta James	Expert group member of Project on a Framework for Rating Evidence in Public Health	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Governor at SASH NHS Foundation Trust: governor representing the voluntary sector.	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Steering Group Member at UK Community Advisory Board (UK-CAB)	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Trustee at Surrey Community Action	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Member of HIV ad hoc communications support	Non-specific Personal Non-financial	Declare and participate
Jo Josh	Mental health ad hoc communications support: member of ENRICH panel,	Non-specific Personal Non-financial	Declare and participate
Jo Josh	NHS East Surrey Clinical Commissioning Group:	Non-specific	Declare and

Name	Interest declared	Type of interest	Action
	patient representative	Personal Non-financial	participate
Asma Khalil	Member of the National Clinical Reference Group for Fetal Medicine	Non-specific Personal Non-financial	Declare and participate
Asma Khalil	Co-chair of the “Improving Outcomes” working group, South West London Maternity Network	Non-specific Personal Non-financial	Declare and participate
Asma Khalil	Associate Editor for the journal Biomedical Central Pregnancy and Childbirth	Non-specific Personal Non-financial	Declare and participate
Asma Khalil	Member of the Maternal and Fetal Medicine National Clinical Study Group	Non-specific Personal Non-financial	Declare and participate
Asma Khalil	Assistant Convenor for the MRCOG Part1 course, RCOG	Non-specific Personal Non-financial	Declare and participate
Asma Khalil	Principal Investigator at St George’s Hospital for several NIHR funded studies, e.g. Non-invasive Prenatal Testing	Non-specific Non-personal Financial	Declare and participate
Asma Khalil	Chief Investigator for Cardiovascular changes in Pregnancy study and Quantitative fetal fibronectin, Cervical length and ActimPartus® for the prediction of Preterm birth in Symptomatic women (QFCAPS)	Non-specific Non-personal Financial	Declare and participate
Asma Khalil	Collaboration with commercial companies, such as USCOM®, Roche Diagnostics®, Alere Diagnostics® and proact medical Ltd® (research equipment and/or consumables)	Non-specific Non-personal Financial	Declare and participate
Manoj Mistry	Public member of Pennine Care NHS FT in the capacity as a carer	Non-specific Personal Non-financial	Declare and participate
Manoj Mistry	PPI representative for the Primary Care Research in Manchester Engagement Resource group at the University of Manchester.	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Carer representative on NICE Guideline Development Group: ‘Transition between inpatient hospital settings and community or care home settings for adults with social care needs.’	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay representative for the MSc Clinical Bioinformatics at the University of Manchester	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay Educational Visitor with the Health and Care Professions Council, London	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay representative at the Clinical Research Facility (collaboration between Central Manchester University Hospital NHS FT/University of Manchester)	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Public Representative Interviewer at the Medical	Non-specific	Declare and

Name	Interest declared	Type of interest	Action
	School, Lancaster University	Personal Financial	participate
Manoj Mistry	Public Member of NIHRs 'Research for Patient Benefit Programme Committee' (North West region)	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Member of the Patient Panel at NIHRs 'The Collaboration for Leadership in Applied Health Research and Care' Greater Manchester	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Member of the Patient and Public Involvement Group, Liverpool Clinical Trials Unit, University of Liverpool	Non-specific Personal Financial	Declare and participate
Manoj Mistry	PPI panel assisting research into Information Systems: Dashboard: Monitoring and Managing from Ward to Board at the University of Leeds	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Member of the Study Steering Committee for the research project: ''Comprehensive Longitudinal Assessment of Salford Integrated Care (CLASSIC): a study of the implementation and effectiveness of a new model of care for long term conditions ''(University of Manchester/ Salford Royal).	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Patient-Public Representative for the new postgraduate 'Advanced Clinical Skills' course at Manchester Pharmacy School, The University of Manchester, England, UK	Non-specific Personal Financial	Declare and participate
Manoj Mistry	PPI representative at the Centre for Engagement and Involvement, Faculty of Medicine and Human Sciences, University of Manchester	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay Member of the Prescribed Specialised Services Advisory Group, Department of Health	Non-specific Personal Financial	Declare and participate
Manoj Mistry	Lay Representative for the research project: "Understanding how frontline staff use patient experience data for service improvement- an exploratory case study evaluation and national survey " at the Department of Primary Care Health Sciences, University of Oxford, England.	Non-specific Personal Financial	Declare and participate
Amaka Offiah	Provision of expert advice to Her Majesty's Courts in cases of suspected child abuse.	Non-specific Personal Financial	Declare and participate
Amaka Offiah	Recipient of honoraria and/or expenses for lectures and/or guidelines development from BioMarin, InfoMed and Alexion.	Non-specific Personal Financial	Declare and participate
Amaka Offiah	Chairperson Skeletal Dysplasia Group for Teaching and Research	Non-specific Personal Non-financial	Declare and participate

Name	Interest declared	Type of interest	Action
Amaka Offiah	Chairperson Child Abuse Taskforce of the European Society of Paediatric Radiology.	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Member Joint RCR/RCPCH NAI Working Party for Guideline Update - Imaging in Suspected Non-Accidental Injury.	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Member of the Royal College of Radiology Academic Committee.	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Committee member of the International Consortium for Vertebral Anomalies and Scoliosis.	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Vice Chair of South Yorkshire (Sheffield) Research Ethics Committee.	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Medical Academic Staff Committee Representative of the Yorkshire Regional Council of the BMA	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Partner Governor of the Sheffield Children's NHS Foundation Trust (representing the University of Sheffield)	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Editorial Committee Member of the journal Paediatric Radiology	Non-specific Personal Non-financial	Declare and participate
Amaka Offiah	Recipient of research funding from NIHR, ARUK, The Sheffield Children's Charity, Skeletal Dysplasia Group for Teaching and Research	Non-specific Non-personal Financial	Declare and participate
Amaka Offiah	Member of the Sheffield Children's Hospital Research and Innovations Committee	Non-specific Personal Non-financial	Declare and participate
Mark Rodgers	Associate editor of the journal Systematic Reviews that publishes research on health and social care.	Non-specific Personal Non-financial	Declare and participate
Mark Rodgers	Research fellow in health services research; has provided independent academic reviews of clinical effectiveness and diagnostic accuracy evidence for funders including NIHR and NICE.	Non-specific Non-personal Financial	Declare and participate
Mark Rodgers	Employee of the Centre for Reviews and Dissemination (University of York) which provides Evidence Review Group reports and Technology Assessment Reports as part of the NICE technology appraisals process.	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Work as the principal investigator on a National Institute of Health Research funded project on: 'Are NICE clinical guidelines for primary care based on evidence from primary care?'	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	National Institute for Health Research Health Services & Delivery Research Programme Healthcare Delivery Research Panel member	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	NIHR Regional Advisory Committee for the Research for Patient Benefit Programme East of England region	Non-specific Personal	Declare and participate

Name	Interest declared	Type of interest	Action
		Non-financial	
Nicholas Steel	Norfolk & Suffolk Primary & Community Care Research Steering Group	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	Advisory Committee on Clinical Excellence Awards East of England	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	'Implementation Science' Editorial Board member	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	'Quality in Primary Care' Editorial Board member	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Examiner	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	Faculty of Public Health Part A MFPH Development Committee	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	Honorary Public Health Academic Consultant, Public Health England	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	Various publications on clinical practice guidelines and primary care	Non-specific Personal Non-financial	Declare and participate
Nicholas Steel	Research grant: 'Primary Care capacity building for GPs' (Principal investigator 5%); CLAHRC East of England Research Capability Funding	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Research grant: 'Anticholinergics, Benzodiazepines, Cognition and Dementia' (co-applicant 1%); Alzheimer's Disease Society	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Research grant: 'English Longitudinal Study of Ageing UK Funders application' (co-applicant 10%); Consortium of UK Government departments	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	Research grant: 'Can a practice based approach using Significant Event Audit identify key factors that might reduce avoidable non-elective hospital admissions? A feasibility study' (co-applicant 5%); National Institute for Health Research – Research for Patient Benefit	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	PhD supervision: 'Improving access to high quality primary care for socio-economically disadvantaged older people in rural areas'; National Institute for Health Research Doctoral Research Fellowship	Non-specific Non-personal Financial	Declare and participate
Nicholas Steel	PhD supervision: 'Life expectancy with chronic conditions'	Non-specific Non-personal Financial	Declare and participate
Sietse Wieringa	At the Centre for Primary care & Public Health at Barts & The London School of Medicine & Dentistry/Queen	Non-specific	Declare and participate

Name	Interest declared	Type of interest	Action
	Mary University I am working on a literature review of 'mindlines' (related to communities of practice) and a qualitative study of a large group of GPs on a virtual social network sharing medical knowledge. I was funded for this via an NIHR In practice fellowship.	Personal Financial	
Sietse Wieringa	Board member of the Platform of Medical Leadership in the Netherlands, via which I am involved in a mixed methods study for the development of a medical leadership competency framework. The study group receives funds from KNMG (Royal Dutch College of Medicine) and SBOH which receives its funds from the Dutch Ministry of Health.	Non-specific Non-personal Financial	Declare and participate
Sietse Wieringa	Member of Generation Next, a think tank and network of young GPs. It's indirectly funded by the Ministry of Health.	Non-specific Personal Non-financial	Declare and participate
Sietse Wieringa	Member of NHG (Dutch GP Society), which produces guidelines and I worked for this organisation in the past.	Non-specific Personal Non-financial	Declare and participate

B.2[1] Topic expert Committee members

[2]

Name	Interest declared	Type of interest	Action
Anthony James	None	Not applicable	Declare and participate
Caroline Parker	Director of Operations for NAPICU (National Association of Psychiatric Intensive Care Units)	Non-specific Personal Non-financial	Declare and participate
Caroline Parker	Number of publications relating to antipsychotics	Non-specific Personal Non-financial	Declare and participate
David Shiers	GP advisor to the National Audit of Schizophrenia (RCPsych CCQI) paid consultancy basis.	Non-specific Personal Financial	Declare and participate
David Shiers	North West AqUA NHS programme: paid consultancy for project 'Don't Screen, Intervene' project on early intervention in physical health of people with psychosis.	Non-specific Personal Financial	Declare and participate
David Shiers	Board member of National Collaborating Centre for Mental Health	Non-specific Personal Non-financial	Declare and participate
David Shiers	Member of IRIS, a social enterprise which supports a network of regional leads who collaborate to promote early intervention in psychosis. No financial trading.	Non-specific Personal Non-financial	Declare and participate
David Shiers	Current approved research grants for which I am a co-applicant: STEPWISE programme examining non-pharmacological ways to prevent weight gain for people with Schizophrenia	Non-specific Non-personal Financial	Declare and participate
David Shiers	Current approved research grants for which I am a co-applicant:	Non-specific Non-personal	Declare and participate

Name	Interest declared	Type of interest	Action
	A pilot study of a randomised controlled trial of antipsychotic medication in comparison to cognitive behaviour therapy and a combined treatment in adults with early psychosis.	Financial	
David Shiers	Research Grants in submission in which I am a co-applicant: "Cognitive behavioural therapy in comparison to treatment as usual in adults at high risk of developing bipolar disorder (Bipolar At Risk): A feasibility study"	Non-specific Non-personal Financial	Declare and participate
David Shiers	Research Grants in submission in which I am a co-applicant: “Keeping the body in mind: The Prevention and Treatment of Physical Ill-health in Young People with Psychotic Illness”	Non-specific Non-personal Financial	Declare and participate
David Shiers	Presentation on “Protecting the cardiometabolic health of people with psychosis; it’s about time” for NHS Scotland - Improving Physical Health Outcomes of those with Severe and Enduring Mental Health Problems.	Non-specific Personal Financial	Declare and participate
David Shiers	Annual royalty payment for French P, Smith J, Shiers D, Reed M, Rayne M (2010) Promoting Recovery in Early psychosis	Non-specific Personal Financial	Declare and participate
David Shiers	Presentation to the Early Intervention Teams of Tees, Esk and Wear Valleys (TEUV) Mental Health Trust – on development of EIP in UK.	Non-specific Personal Financial	Declare and participate
David Shiers	Member of National Expert Reference Group for Early Intervention in Psychosis Services development for the Improving Access and Waiting times initiative	Non-specific Personal Non-financial	Declare and participate
David Shiers	Provided keynote presentation entitled ‘It’s about time: positive cardiometabolic health for people experiencing a first episode of psychosis’ at Treating Schizophrenia 2015 Conference	Non-specific Personal Financial	Declare and participate
David Shiers	American Psychiatric Association; chaired symposium on ‘It's about time! - improving physical health outcomes in young people prescribed antipsychotic medications.’	Non-specific Personal Financial	Declare and participate
David Shiers	Review of book proposal for Routledge Mental Health on Helping people adapt to the onset of Psychosis.	Non-specific Personal Financial	Declare and participate
David Shiers	Speaker at Don’t just Screen, Intervene educational meeting of Cheshire and Wirral Partnership Foundation Mental Health Trust.	Non-specific Personal Financial	Declare and participate
David Shiers	Co-author for BMJ Learning a module on NICE guideline CG178	Non-specific Personal Financial	Declare and participate
David Shiers	Speaker on Carers perspective at Early Psychosis – The Way Forward. Organised by Centre for Mental Health Service Development Wales.	Non-specific Personal Financial	Declare and participate
David Shiers	Presenter at Ontario Early Psychosis Network (EPION) on physical health aspects of severe mental illness.	Non-specific Personal Financial	Declare and participate
David Shiers	Honorary Reader in Clinical Health within the School of Psychological Sciences, University	Non-specific Personal	Declare and participate

Name	Interest declared	Type of interest	Action
	of Manchester	Financial	
David Shiers	NIHR grant application, "Developing and evaluating a diabetes self--- management education intervention for people with severe mental illness: The DIAMONDS programme.	Non-specific Non-personal Financial	Declare and participate
David Shiers	Contributed to 'Protecting cardiometabolic health, right from the start': promoting physical health in young people.	Non-specific Personal Financial	Declare and participate
David Shiers	Shortlisted by NIHR Health Technologies Assessment Clinical Evaluation and Trials Board for A randomised controlled trial of antipsychotic medication in comparison to psychological intervention and a combined treatment in children and young people with first episode psychosis: a feasibility study.	Non-specific Non-personal Financial	Declare and participate
David Shiers	NIHR grant application: 'Improving diabetes outcomes for people with severe mental illness'	Non-specific Non-personal Financial	Declare and participate
David Shiers	Australian-based Proposal - Centre of Research Excellence in Physical Health of Young People with First Episode Psychosis - I will act as an International link in the capacity of an associate applicant and act in an honorary capacity.	Non-specific Non-personal Financial	Declare and participate
David Shiers	NIHR grant application: 'Developing good practice guidelines to promote engagement with early intervention services for people with first episode psychosis'	Non-specific Non-personal Financial	Declare and participate
Anne Taylor	None	Not applicable	Declare and participate

Appendix C: Review protocol

	Details
Review question	What is the adverse effects profile of olanzapine compared to other second-generation antipsychotics (SGAs) for treating children and young people with psychosis and schizophrenia?
Background/ objectives	The NICE guideline on psychosis and schizophrenia in children and young people was reviewed in 2015 by the surveillance team and new evidence on adverse effects of olanzapine was identified. NICE CG155 does not specifically state that olanzapine should not be used first line; the guideline should therefore be updated to reflect evidence of its adverse effects. Efficacy will not be covered as the efficacy data is not believed to have changed for the past 15-20 years - they're all about the same for SGAs but have slightly different side effects profiles and tolerability, with the exception of clozapine (which needs regular blood monitoring).
Types of study to be included	RCTs; systematic reviews; comparative observational studies
Language	English language only
Status	Published papers (full text only) – searches to be run from the May 2012 to present
Population	Children and young people (aged 18 years and younger) with psychosis and schizophrenia. Subgroups: - Those with first episode psychosis - Those who have not responded adequately to treatment (they had first episode but did not respond to treatment) - Those with acute exacerbation or recurrence of symptoms - Those with mild learning disability - Ethnicity (particularly those from black and minority ethnic groups)
Intervention	Oral olanzapine (any dosage)
Comparator	Other 'second generation' antipsychotics (oral only) licensed in the UK for the treatment of psychosis and schizophrenia, including considerations related to the age of participants (for example, dose modifications). 1) Amisulpride 2) Aripiprazole 3) Clozapine 4) Lurasidone hydrochloride 5) Paliperidone 6) Quetiapine 7) Risperidone
Outcomes	Adverse effects: 8) Metabolic side effects (weight/BMI change, fasting serum glucose level change, cholesterol/lipoprotein level changes/triglyceride level changes, HbA1c levels 9) Neurological side effects (EPS scales, tardive dyskinesia) 10) Hormonal side effects (prolactin levels, thyroid stimulating hormone levels) 11) Cardiac side effects (blood pressure, QTc interval) 12) Leaving the study early for any reason including mortality 13) Quality of life 14) Developmental progress eg; school performance

	Details
	*Note treatment duration/duration of the adverse effects
Any other information or criteria for inclusion/exclusion	Inclusion 1) Main focus on those aged 14 to18 years (as prevalence increases rapidly from age 14 onwards). The review will seek to identify whether modifications in treatment and management of children at or under 13 years need to be made. Data from studies in which the study sample consists of children and young people under and over 18 years, but with a sample mean age of under 25, will be extrapolated if only limited evidence for children and young people aged 18 and younger is available and; 2) Studies with treatment duration of 4 weeks or more Exclusion: 1) Studies that only looked at adults 2) Study samples consisting only of individuals with a formal diagnosis of bipolar disorder. 3) Studies in subjects with comorbidities or substance misuse 4) Studies with ≤ 10 subjects per arm. 5) Studies with > 50% attrition from either arm of trial (unless adequate statistical methodology has been applied to account for missing data). Selection of papers: i) Selection based on titles and abstracts A full double-sifting of titles and abstracts will not be conducted due to the nature of the review question (very narrow question with clearly defined straightforward inclusion and exclusion criteria). ii) Selection based on full papers A full double-selecting of full papers for inclusion/exclusion will not be conducted due to the nature of the review question (as mentioned above). Other mechanisms will be in place for QA: The Committee will be sent the list of included and excluded studies prior to the Committee meeting, and the Committee will be requested to cross check whether any studies have been excluded inappropriately, and whether there are any relevant studies they have known of which haven't been picked up by the searches.
Analysis of subgroups or subsets	Children versus young people if data allows for this – arbitrary age groups include 3 to 11 year olds vs 12 to 18 year olds
Data extraction and quality assessment	- Key features of included studies and reported outcomes will be extracted into evidence tables. - The quality of evidence for each outcome will be assessed using the approach for intervention questions outlined by the GRADE working group. Reliability of quality assessment: A full double-scoring quality assessment will not be conducted due to the nature of the review question (as mentioned above) and the studies that are likely to be included. Other quality assurance mechanisms will be in place as the following: - Internal QA by CGUT technical adviser on the quality assessment that is being conducted.

	Details
	- The Committee will be sent the evidence synthesis prior to the Committee meeting and the Committee will be requested to comment on the quality assessment, which will serve as another QA function.
Strategy for data synthesis	- Data for each outcome from different studies will be synthesised using pairwise meta-analysis where possible. - Data will be pooled by duration of treatment where possible - Where synthesis by meta-analysis is not possible, data will be presented for individual studies.
Searches	Sources to be searched - Clinical searches - Medline, Medline in Process, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA, PsycInfo and PubMed. - Economic searches – Medline, Medline in Process, Embase, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques None identified Limits - Studies reported in English - Animal studies will be excluded from the search results - Conference abstracts will be excluded from the search results - A date limit of May 2012 to present will be applied

Appendix D: Search strategy

Databases that were searched, together with the number of articles retrieved from each database are shown in Table 6. The Medline and Medline in process search strategy is shown. The same strategy was translated for the other databases listed.

Table 3: Clinical search summary

Databases	Date searched	Version/files	No. retrieved	RefMan data
MEDLINE (Ovid)	5/10/2015	Ovid MEDLINE(R) 1946 to September Week 4 2015	607	129
MEDLINE In-Process (Ovid)	5/10/2015	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 02, 2015	372	200
EMBASE (Ovid)	5/10/2015	Embase 1974 to 2015 Week 40	3517	3195
Cochrane Central Register of Controlled Trials (CENTRAL)	5/10/2015	Issue 9 of 12, September 2015	1458	1334
Cochrane Database of Systematic Reviews (CDSR)	5/10/2015	Issue 10 of 12, October 2015	40	35
Database of Abstracts of Reviews of Effectiveness (DARE)	5/10/2015	Issue 2 of 4, April 2015	17	12
Health Technology Assessment (HTA)	5/10/2015	Issue 3 of 4, July 2015	5	2
PsycINFO (Ovid)	5/10/2015	PsycINFO 1967 to September Week 5 2015	630	232
PubMed	6/10/2015	-	59	48

Database: Medline and Medline in Process
Search Strategy: --- 1 exp "schizophrenia and disorders with psychotic features"/ 2 schizophrenia, childhood/ 3 delusions/ 4 hallucinations/ 5 (delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or paraphreni* or psychotic* or psychosis or psychoses or schizo*).tw. 6 or/1-5 7 olanzapine*.tw. 8 (aedon or amulsin or anzatric or anzorin or apsico or apzet or arenbil or arkolamyl or asterilon or atyzyo or axonium or bloonis or caprilon or cinol or clingozan or dopin or elynza or enolex or epilanz or expolid or exzapine or fordep or fredilan or jolyon or joyzol or kynapine or lano or lanopin or lansyn or lanza* or lanzek or lapenza or lapozan or lazap* or lupilan or ly170053 or manza or meltolan or midax or m-olan or neupine or newzypra or niolib or nolian or normiton or nykob or nylsanuc or nyzol or ofans or oferta or olace or oladay or olafer or olafid or olan* or olapax or olapin* or olastazen or olasyn or olaxinn or olazofren or olazax or oleanz or olenxa or oles or olexar or olfrex or olima or olivin or oliza or ollafax or olmyzem or olnegis or olpin* or oltal or olzadin or

Database: Medline and Medline in Process

olzanid or olzap* or olzin or onezyp or onza* or opin or opinox or opirap or oxatech or ozace or ozap* or ozilormar or ozin or parnassan or parnasan or pinolza or psycholanz or psychozap or ranofren or redilanz or relprevv or remittal or revertrix or rexapin or rolanzax or rolyprexa or sanza or sartina or simina or sincris or stygapon or synza or tanssel or tolanz or villamos or xoltiva or zalasta or zalepin or zamil or zanprex or zap or zapilux or zapinex or zappa or zapris or zelta or zeprex or zerpi or zolafren or zolapine or zolaxa or zonapi* or zophix or zopina or zopix or zopridoxin or zoxil or zydis or zylanza or zylap or zypadhera or zypefar or zypine or zyprex* or zyzapin).tw.

9 (ly adj4 "170053").tw.

10 or/7-9

11 6 and 10

12 Animals/ not Humans/

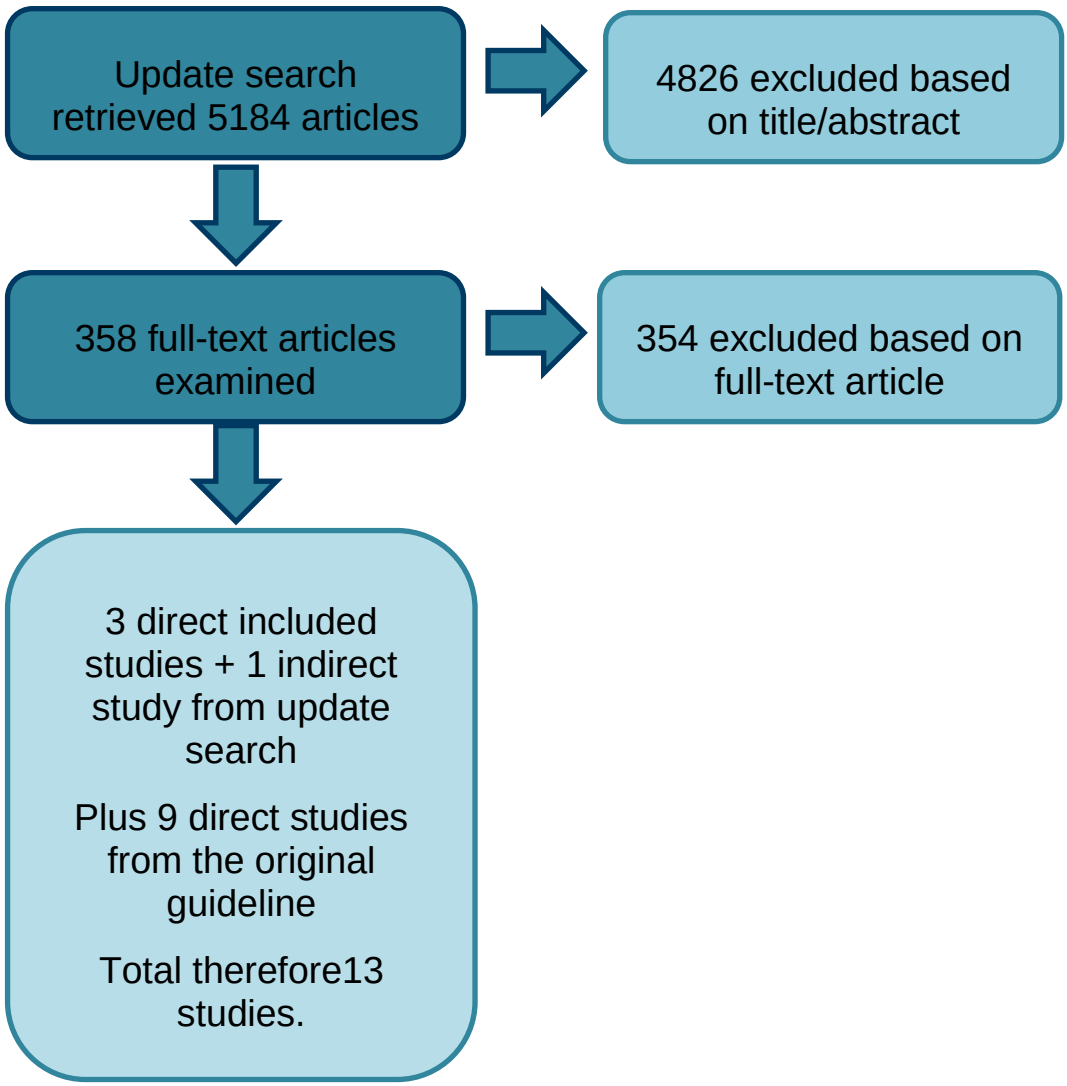
13 11 not 12

14 limit 13 to english language

15 limit 14 to ed=20120101-20151031

1

Appendix E: Review flowchart



1 Appendix F:Excluded studies

2

Study	Reason for Exclusion
Erratum to: Effects of switching from olanzapine to aripiprazole on the metabolic profiles of patients with schizophrenia and metabolic syndrome: A double-blind, randomized, open-label study (Neuropsychiatric Disease and Treatment, (2015), 11, 685-693), Neuropsychiatric Disease and Treatment.11 , 2015.Date of Publication: 2015., -, 2015	Study is in adults and no relevant data
Ader,M., Garvey,W.T., Phillips,L.S., Nemeroff,C.B., Gharabawi,G., Mahmoud,R., Greenspan,A., Berry,S.A., Musselman,D.L., Morein,J., Zhu,Y., Mao,L., Bergman,R.N., Ethnic heterogeneity in glucoregulatory function during treatment with atypical antipsychotics in patients with schizophrenia, Journal of psychiatric research, 42, 1076-1085, 2008	Study is in adults
Agarwal,V., Dhanasekaran,S., Metabolic syndrome in children and adolescents, Journal of Indian Association for Child and Adolescent Mental Health.8 (4) (pp 74-77), 2012.Date of Publication: October 2012., 74-77, 2012	Editorial
Agarwal,V., Sitholey,P., A preliminary open trial of olanzapine in paediatric acute and transient psychotic disorders, Indian journal of psychiatry, 48, 43-46, 2006	All subjects received olanzapine - no comparison against another SGA.
Agelink,M.W., Majewski,T., Wurthmann,C., Lukas,K., Ullrich,H., Linka,T., Klieser,E., Effects of newer atypical antipsychotics on autonomic neurocardiac function: a comparison between amisulpride, olanzapine, sertindole, and clozapine, Journal of clinical psychopharmacology, 21, 8-13, 2001	Study in adults
Aggarwal,S., Burnett,P., Tardive dyskinesia with atypical antipsychotics in youth, Australasian Psychiatry.21 (5) (pp 507-508), 2013.Date of Publication: October 2013., 507-508, 2013	Letter
Agid,O., Arenovich,T., Sajeev,G., Zipursky,R.B., Kapur,S., Foussias,G., Remington,G., An algorithm-based approach to first-episode schizophrenia: Response rates over 3 prospective antipsychotic trials with a retrospective data analysis, Journal of clinical psychiatry, 72, 1439-1444, 2011	No relevant results.
Agid,Ofer, Schulze,Laura, Arenovich,Tamara, Sajeev,Gautam, McDonald,Krysta, Foussias,George, Fervaha,Gagan, Remington,Gary, Antipsychotic response in first-episode schizophrenia: Efficacy of high doses and switching. [References], European neuropsychopharmacology, 23, 1017-1022, 2013	No relevant outcomes.
Ahn,Y.M., Kweon,Y.S., Kwon,J.S., Min,S.H.,	Cannot be sourced

Study	Reason for Exclusion
Park,D.B., Yang,M.J., The Study for Switching Methods to Olanzapine in Korean Schizophrenic Patients Treated with Other Antipsychotics (II): Comparison of Safety, Journal of Korean Neuropsychiatric Association, 41, 890-904, 2002	
Alfaro,C.L., Wudarsky,M., Nicolson,R., Gochman,P., Sporn,A., Lenane,M., Rapoport,J.L., Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine, Journal of child and adolescent psychopharmacology, 12, 83-91, 2002	Considered as part of the original 2012 review.
Almandil,N.B., Liu,Y., Murray,M.L., Besag,F.M.C., Aitchison,K.J., Wong,I.C.K., Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: A systematic review and meta-analysis, Pediatric DrugsPaediatr.Drugs, 15, 139-150, 2013	Meta-analysis of studies not meeting the review question's inclusion criteria - comparator is placebo not another second generation antipsychotic.
Alvarez,E., Ciudad,A., Olivares,J.M., Bousoño,M., Gómez,J.C., A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia, Journal of clinical psychopharmacology, 26, 238-249, 2006	Study in adults
Ardizzone,I., Nardecchia,F., Marconi,A., Carratelli,T.I., Ferrara,M., Antipsychotic medication in adolescents suffering from schizophrenia: a meta-analysis of randomized controlled trials. [Review], Psychopharmacology bulletin, 43, 45-66, 2010	Meta-analysis of studies not meeting the review question's inclusion criteria - comparator is not another SGA.
Argo,T., Carnahan,R., Barnett,M., Holman,T.L., Perry,P.J., Diabetes prevalence estimates in schizophrenia and risk factor assessment, Annals of Clinical Psychiatry.23 (2) (pp 117-124), 2011.Date of Publication: May 2011., 117-124, 2011	Study is in adults
Asmal,Laila, Flegar,Srnka J., Wang,Jikun, Rummel,Kluge Christine, Komossa,Katja, Leucht,Stefan, Quetiapine versus other atypical antipsychotics for schizophrenia, Cochrane Database of Systematic Reviews, -, 2013	No relevant studies in this review.
Atmaca,M., Kuloglu,M., Tezcan,E., Ustundag,B., Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics, Journal of clinical psychiatry, 64, 598-604, 2003	Study is in adults
Ayesa-Arriola,Rosa, Rodriguez-Sanchez,Jose Manuel, Perez-Iglesias,Rocio, Roiz-Santianez,Roberto, Martinez-Garcia,Obdulia, Sanchez-Moreno,Jose, Tabares-Seisdedos,Rafael, Vazquez-Barquero,Jose L., Crespo-Facorro,Benedicto, Long-term (3-year) neurocognitive effectiveness of antipsychotic medications in first-episode non-affective psychosis: A randomized comparison of haloperidol, olanzapine, and risperidone. [References], Psychopharmacology, 227, 615-	Study is in adults, mean >25 years

Study	Reason for Exclusion
625, 2013	
Bachmann,Christian J., Gebhardt,Stefan, Lehr,Dirk, Haberhausen,Michael, Kaiser,Christoph, Otto,Barbel, Theisen,Frank M., Subjective and biological weight-related parameters in adolescents and young adults with schizophrenia spectrum disorder under clozapine or olanzapine treatment. [References], Zeitschrift fur Kinder- und Jugendpsychiatrie und Psychotherapie, 40, 151-159, 2012	No relevant results by type of antipsychotic received.
Baeza,I., De La Serna,E., Calvo-Escalona,R., Morer,A., Merchan-Naranjo,J., Tapia,C., Martinez-Cantarero,M.C., Andres,P., Alda,J.A., Sanchez,B., Arango,C., Castro-Fornieles,J., Antipsychotic use in children and adolescents: A 1-year follow-up study, Journal of Clinical Psychopharmacology.34 (5) (pp 613-619), 2014.Date of Publication: October 2014., 613-619, 2014	No relevant results.
Barbui,C., Mule,S., Cipriani,A., Haloperidol, risperidone and olanzapine are similarly effective for first-episode non-affective psychosis but have differing side effects, Evidence-based mental health, 10, 74-, 2007	Commentary
Bartoli,F., Lax,A., Crocamo,C., Clerici,M., Carra,G., Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: A meta-analysis, Psychoneuroendocrinology.56 (pp 179-189), 2015.Date of Publication: 01 Jun 2015., -189, 2015	Meta-analysis of studies in adults
Ben Amor,Leila, Antipsychotics in pediatric and adolescent patients: A review of comparative safety data. [References], Journal of affective disorders, 138, S22-S30, 2012	Meta-analysis of pre-2012 studies; not all outcomes of interest are examined.
Bender,S., Dittmann-Balcar,A., Schall,U., Wolstein,J., Klimke,A., Riedel,M., Vorbach,E.U., Kühn,K.U., Lambert,M., Dittmann,R.W., Naber,D., Influence of atypical neuroleptics on executive functioning in patients with schizophrenia: a randomized, double-blind comparison of olanzapine vs. clozapine, International journal of neuropsychopharmacology, 9, 135-145, 2006	Study is in adults.
Berg,J., Stajich,G., Zdanowicz,M., Atypical antipsychotic-induced type 2 diabetes, Pharmacy Times.78 (3) , 2012.Date of Publication: March 2012., -, 2012	Narrative
Beuzen,J.N., Birkett,M., Kiesler,G., Wood,A., Olanzapine vs. Clozapine in resistant schizophrenic patients - results of an international double- blind randomised clinical trial, XXIst Collegium Internationale Neuro-psychopharmacologicum, Glasgow, Scotland.12th-16th July, 1998., -, 1998	Conference abstract
Bhowmick,S., Hazra,A., Ghosh,M., Amisulpride versus olanzapine in the treatment of	Study is in adults

Study	Reason for Exclusion
schizophrenia in Indian patients: randomized controlled trial, Australian and New Zealand journal of psychiatry, 44, 237-242, 2010	
Bitter,I., Dossenbach,M.R., Brook,S., Feldman,P.D., Metcalfe,S., Gagiano,C.A., Füredi,J., Bartko,G., Janka,Z., Banki,C.M., Kovacs,G., Breier,A., Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia, Progress in neuro-psychopharmacology & biological psychiatry, 28, 173-180, 2004	Study is in adults
Blonde,L., Kan,H.J., Gutterman,E.M., L'italien,G.J., Kim,M.S., Hanssens,L., McQuade,R.D., Predicted risk of diabetes and coronary heart disease in patients with schizophrenia: aripiprazole versus standard of care, Journal of clinical psychiatry, 69, 741-748, 2008	Study is in adults.
Bobo,W.V., Bonaccorso,S., Jayathilake,K., Meltzer,H.Y., Prediction of long-term metabolic effects of olanzapine and risperidone treatment from baseline body mass index in schizophrenia and bipolar disorder, Psychiatry research, 189, 200-207, 2011	Study is in adults
Boden,R., Edman,G., Reutfors,J., Ostenson,C., Osby,U., A comparison of cardiovascular risk factors for ten antipsychotic drugs in clinical practice, Neuropsychiatric Disease and Treatment.9 (pp 371-377), 2013.Date of Publication: 18 Mar 2013., -377, 2013	Study is in adults
Borkowska,J.K., The effect of treatment with risperidone, olanzapine or phenothiazines on cognitive functions in patients with schizophrenia, International journal of psychiatry in clinical practice, 5, 249-256, 2001	Study is in adults
Boter,H., Peuskens,J., Libiger,J., Fleischhacker,W.W., Davidson,M., Galderisi,S., Kahn,R.S., Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST), Schizophrenia research, 115, 97-103, 2009	Study is in adults
Bou,Khalil R., Rohayem,J., Abou,said N., El,Chammay R., Haddad,R., Richa,S., Metabolic syndrome (MetS) in Lebanese patients with schizophrenia receiving atypical antipsychotic drugs, Asian Journal of Psychiatry.6 (1) (pp 88-89), 2013.Date of Publication: February 2013., 88-89, 2013	Letter to the editor
Brecher,M., Risperidone versus olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder CONFERENCE ABSTRACT, 11th European College of Neuropsychopharmacology Congress.Paris, France.31st October - 4th November 1998., -, 1998	Conference abstract

Study	Reason for Exclusion
Breier,A., Berg,P.H., Thakore,J.H., Naber,D., Gattaz,W.F., Cavazzoni,P., Walker,D.J., Roychowdhury,S.M., Kane,J.M., Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia, American journal of psychiatry, 162, 1879-1887, 2005	Study is in adults
Broerse,A., Crawford,T.J., Boer,J.A., Differential effects of olanzapine and risperidone on cognition in schizophrenia? A saccadic eye movement study, Journal of neuropsychiatry and clinical neurosciences, 14, 454-460, 2002	Study is in adults and no relevant outcomes reported
Bruggen,J., Tijssen,J., Dingemans,P., Gersons,B., Linszen,D., Symptom response and side-effects of olanzapine and risperidone in young adults with recent onset schizophrenia, International clinical psychopharmacology, 18, 341-346, 2003	Study is in those aged 16 to 28 years and reports on no additional outcomes or comparisons not covered by the direct data.
Buchanan,R.W., Panagides,J., Zhao,J., Phiri,P., Hollander,W., Ha,X., Kouassi,A., Alphs,L., Schooler,N., Szegedi,A., Cazorla,P., Asenapine versus olanzapine in people with persistent negative symptoms of schizophrenia, Journal of clinical psychopharmacology, 32, 36-45, 2012	Study is in adults
Bushe,C., Sniadecki,J., Bradley,A.J., Poole,Hoffmann,V, Comparison of metabolic and prolactin variables from a six-month randomised trial of olanzapine and quetiapine in schizophrenia, Journal of psychopharmacology (Oxford, England), 24, 1001-1009, 2010	Study is in adults
Bushe,C.J., Slooff,C.J., Haddad,P.M., Karagianis,J.L., Weight change from 3-year observational data: Findings from the worldwide schizophrenia outpatient health outcomes database, Journal of Clinical Psychiatry.73 (6) (pp e749-e755), 2012.Date of Publication: June 2012., e749-e755, 2012	Study is in adults
Bushe,C.J., Slooff,C.J., Haddad,P.M., Karagianis,J.L., Weight change by baseline BMI from three-year observational data: Findings from the Worldwide Schizophrenia Outpatient Health Outcomes Database, Journal of Psychopharmacology.27 (4) (pp 358-365), 2013.Date of Publication: April 2013., 358-365, 2013	Study is in adults.
Cai,S., Lu,H., Bai,Z., Wu,R., Zhao,J., Paliperidone extended-release tablets in Chinese patients with schizophrenia: Meta-analysis of randomized controlled trials, Neuropsychiatric Disease and Treatment.11 (pp 1817-1834), 2015.Date of Publication: 23 Jul 2015., -1834, 2015	Meta-analysis of paliperidone versus 'other SGAs' as opposed to olanzapine specifically - also unclear if studies included are in adults or children.
Canive,J.M., Miller,G.A., Irwin,J.G., Moses,S.N., Thoma,R.J., Edgar,J.C., Sherwood,A., Torres,F., Lanoue,M., Lewis,S., Hanlon,F.M., Weisend,M.P., Mead,V., Tuason,V.B., Efficacy of olanzapine and risperidone in schizophrenia:	Unable to source

Study	Reason for Exclusion
a randomized double-blind crossover design, Psychopharmacology bulletin, 39, 105-116, 2006	
Casey,D.E., Daniel,D.G., Wassef,A.A., Tracy,K.A., Wozniak,P., Sommerville,K.W., Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia, Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 28, 182-192, 2003	Study is in adults and is looking at the effect of divalproex combined with olanzapine
Casey,D.E., L'italien,G.J., Cislo,P., Incidence of Metabolic Syndrome in Olanzapine and Aripiprazole Patients, 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, NY, NR338-, 2004	Original article of this conference abstract sourced but study is in adults
Chan,H.Y., Chang,C.J., Chiang,S.C., Chen,J.J., Chen,C.H., Sun,H.J., Hwu,H.G., Lai,M.S., A randomised controlled study of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced acute dystonia or parkinsonism, Journal of Psychopharmacology.24 (1) (pp 91-98), 2010.Date of Publication: 2010/01., 91-98, 2010	Study is in adults
Chan,H.Y., Chiang,S.C., Chang,C.J., Gau,S.S., Chen,J.J., Chen,C.H., Hwu,H.G., Lai,M.S., A randomized controlled trial of risperidone and olanzapine for schizophrenic patients with neuroleptic-induced tardive dyskinesia, The Journal of clinical psychiatry, 71, 1226-1233, 2010	Study is in adults
Chang,J.S., Hwang,S.S.-H., Yi,S.H., Kim,Y., Lee,Y.-S., Kim,Y.S., Jung,H.-Y., Evaluating subjective domains of antipsychotic-induced adverse effects using heart rate variability, Psychiatry and Clinical Neurosciences.69 (5) (pp 283-291), 2015.Date of Publication: 01 May 2015., 283-291, 2015	Study is in adults and no relevant results by anti-psychotic received
Chaves,K.M., Serrano-Blanco,A., Ribeiro,S.B., Soares,L.A.L., Guerra,G.C.B., Do Socorro Costa Feitosa Alves, De Araujo Junior,R.F., De Paula,Soares Rachetti,V, Filgueira,Junior A., De Araujo,A.A., Quality of life and adverse effects of olanzapine versus risperidone therapy in patients with schizophrenia, Psychiatric Quarterly.84 (1) (pp 125-135), 2013.Date of Publication: March 2013., 125-135, 2013	Study is in adults
Chen,J.-J., Chan,H.-Y., Chen,C.-H., Gau,S.S.-F., Hwu,H.-G., Risperidone and olanzapine versus another first generation antipsychotic in patients with schizophrenia inadequately responsive to first generation antipsychotics, Pharmacopsychiatry.45 (2) (pp 64-71), 2012.Date of Publication: 2012., 64-71, 2012	Study is in adults
Chiu,C.C., Chen,K.P., Liu,H.C., Lu,M.L., The early effect of olanzapine and risperidone on insulin secretion in atypical-naïve schizophrenic patients, Journal of clinical	Study is in adults

Study	Reason for Exclusion
psychopharmacology, 26, 504-507, 2006	
Choong,E., Bondolfi,G., Etter,M., Jermann,F., Aubry,J.-M., Bartolomei,J., Gholam-Rezaee,M., Eap,C.B., Psychotropic drug-induced weight gain and other metabolic complications in a Swiss psychiatric population, Journal of Psychiatric Research.46 (4) (pp 540-548), 2012.Date of Publication: April 2012., 540-548, 2012	Study is in adults.
Choure,B.K., Gosavi,D., Nanotkar,S., Comparative cardiovascular safety of risperidone and olanzapine, based on electrocardiographic parameters and blood pressure: a prospective open label observational study, Indian Journal of Pharmacology, 46, 493-497, 2014	Study is in adults
Chrzanowski,W.K., Marcus,R.N., Torbeyns,A., Nyilas,M., McQuade,R.D., Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine, Psychopharmacology, 189, 259-266, 2006	Study is in adults
Citrome,L., Volavka,J., Czobor,P., Sheitman,B., Lindenmayer,J.P., McEvoy,J., Cooper,T.B., Chakos,M., Lieberman,J.A., Effects of clozapine, olanzapine, risperidone, and haloperidol on hostility among patients with schizophrenia, Psychiatric services (Washington, D.C.), 52, 1510-1514, 2001	Study is in adults
Ciudad,A., Alvarez,E., Bousono,J., Cuesta,M., Olivares,J.M., Gomez,J.C., Efficacy of Olanzapine Versus Risperidone: One-Year Results in Schizophrenia, 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, NY, NR509-, 2004	Conference abstract.
Ciudad,A., Alvarez,E., Bousono,M., Olivares,J., Gomez,J.C., Olanzapine VERSUS Risperidone: One-Year Results in Positive Symptoms in Schizophrenia, 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA, NR239-, 2005	Abstract only
Ciudad,A., Alvarez,E., Bousoño,M., Olivares,J.M., Gómez,J.C., [Safety and tolerability of olanzapine versus risperidone: a one-year randomized study in outpatients with schizophrenia with prominent negative symptoms], Actas españolas de psiquiatría, 35, 105-114, 2007	Study is in adults
Ciudad,A., Gutiérrez,M., Cañas,F., Gibert,J., Gascón,J., Carrasco,J.L., Bobes,J., Gómez,J.C., Alvarez,E., Safety and effectiveness of olanzapine in monotherapy: a multivariate analysis of a naturalistic study, Progress in neuro-psychopharmacology & biological psychiatry, 29, 944-951, 2005	Study is in adults and comparator is any conventional antipsyshotic rather than a specific SGA.
Ciudad,A., Olivares,J.M., Bousoño,M., Gómez,J.C., Alvarez,E., Improvement in social	Study is in adults

Study	Reason for Exclusion
functioning in outpatients with schizophrenia with prominent negative symptoms treated with olanzapine or risperidone in a 1 year randomized, open-label trial, Progress in neuro-psychopharmacology & biological psychiatry, 30, 1515-1522, 2006	
Conley,R., Mahmoud,R., Efficacy of risperidone vs. Olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder, Journal of the European College of Neuropsychopharmacology (Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000), 10, S343-, 2000	Conference abstract
Conley,R., Mahmoud,R., Risperidone vs. Olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder: safety comparisons, Journal of the European College of Neuropsychopharmacology (Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000), 10, S342-, 2000	Conference abstract
Conley,R.R., Brecher,M.B., Risperidone versus olanzapine in the treatment of patients with schizophrenia or schizoaffective disorder, 152nd Annual Meeting of the American Psychiatric Association.Washington DC, USA.15-20th May, 1999., -, 1999	Conference abstract
Conley,R.R., Mahmoud,R., A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder, American journal of psychiatry, 158, 765-774, 2001	Study is in adults
Connolly,J.G., Toomey,T.J., Schneeweiss,M.C., Metabolic monitoring for youths initiating use of second-generation antipsychotics, 2003-2011, Psychiatric Services.66 (6) (pp 604-609), 2015.Date of Publication: 01 Jun 2015., 604-609, 2015	Population is users of SGAs - it is not specifically stated the population were schizophrenic nor are any relevant outcomes reported (numbers with a glucose test for each intervention reported but actual HbA1c levels eg: mean by group not reported).
Cornblatt,B., Kern,R.S., Carson,W.H., Ali,M.W., Luo,X., Green,M., Neurocognitive effects of aripiprazole versus olanzapine in stable psychosis, International Journal of Neuropsychopharmacology (Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum; June 23-27 2002, Montreal, Canada), 5, S185-, 2002	Conference abstract
Correll,C., Efficacy and safety of antipsychotics in early-onset schizophrenia: A meta-analysis of randomized controlled trials, Schizophrenia research, 136, S29-, 2012	Conference abstract
Correll,C.U., Robinson,D.G., Schooler,N.R., Brunette,M.F., Mueser,K.T., Rosenheck,R.A., Marcy,P., Addington,J., Estroff,S.E., Robinson,J., Penn,D.L., Azrin,S., Goldstein,A., Severe,J., Heinssen,R., Kane,J.M., Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders baseline results from the RAISE-ETP study, JAMA Psychiatry.71 (12) (pp 1350-1363),	Subjects aged 15 to 40 years, mean age by treatment arms not reported.

Study	Reason for Exclusion
2014.Date of Publication: 01 Dec 2014., 1350-1363, 2014	
Cortes,Benjamin, Becker,Joemir, Alvarez,Maria Teresa Mories, Marcos,Ana I.S., Molina,Vicente, Contribution of baseline body mass index and leptin serum level to the prediction of early weight gain with atypical antipsychotics in schizophrenia. [References], Psychiatry and clinical neurosciences, 68, 127-132, 2014	Study is in adults and no relevant results presented
Crespo-Facorro,B., Pérez-Iglesias,R., Mata,I., Caseiro,O., Martínez-Garcia,O., Pardo,G., Ramirez-Bonilla,M., Pelayo-Terán,J.M., Vázquez-Barquero,J.L., Relapse prevention and remission attainment in first-episode non-affective psychosis. A randomized, controlled 1-year follow-up comparison of haloperidol, risperidone and olanzapine, Journal of psychiatric research, 45, 763-769, 2011	Study is in adults
Crespo-Facorro,B., Pérez-Iglesias,R., Mata,I., Martínez-Garcia,O., Ortiz,V., Pelayo-Terán,J.M., Valdizan,E., Vazquez-Barquero,J.L., Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis, Psychopharmacology, 219, 225-233, 2012	Study is in adults.
Crespo-Facorro,B., Pérez-Iglesias,R., Mata,I., Ramirez-Bonilla,M., Martínez-Garcia,O., Pardo-Garcia,G., Caseiro,O., Pelayo-Terán,J.M., Vázquez-Barquero,J.L., Effectiveness of haloperidol, risperidone and olanzapine in the treatment of first-episode non-affective psychosis: results of a randomized, flexible-dose, open-label 1-year follow-up comparison, Journal of psychopharmacology (Oxford, England), 25, 744-754, 2011	Study is in adults
Crespo-Facorro,B., Pérez-Iglesias,R., Ramirez-Bonilla,M., Martínez-García,O., Llorca,J., Luis Vázquez-Barquero,J., A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis, Journal of clinical psychiatry, 67, 1511-1521, 2006	Study is in adults
Cuesta,M.J., Jalón,E.G., Campos,M.S., Peralta,V., Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis, British journal of psychiatry, 194, 439-445, 2009	Study is in adults
Czekalla,J., Beasley,C.M., Dellva,M.A., Berg,P.H., Grundy,S., Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis, Journal of clinical psychiatry, 62, 191-198, 2001	Study is in adults
Czobor,P., Volavka,J., Sheitman,B., Lindenmayer,J.P., Citrome,L., McEvoy,J., Cooper,T.B., Chakos,M., Lieberman,J.A., Antipsychotic-induced weight gain and therapeutic response: a differential association, Journal of clinical psychopharmacology, 22,	Study is in adults

Study	Reason for Exclusion
244-251, 2002	
Das,C., Mendez,G., Jagasia,S., Labbate,L.A., Second-generation antipsychotic use in schizophrenia and associated weight gain: A critical review and meta-analysis of behavioral and pharmacologic treatments, Annals of Clinical Psychiatry.24 (3) (pp 225-239), 2012.Date of Publication: August 2012., 225-239, 2012	Review of management for second generation antipsychotic induced weight gain.
Datta,S.S., Kumar,A., Wright,S.D., Furtado,V.A., Russell,P.S., Evidence base for using atypical antipsychotics for psychosis in adolescents, Schizophrenia Bulletin.40 (2) (pp 252-254), 2014.Date of Publication: March 2014., 252-254, 2014	Systematic review examining various comparisons: 3 RCTs for SGA vs another SGA but references of these individual RCTs not reported
David,S.R., Taylor,C.C., Kinon,B.J., Breier,A., The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia, Clinical therapeutics, 22, 1085-1096, 2000	Study is in adults
Davidson,M., Galderisi,S., Weiser,M., Werbeloff,N., Fleischhacker,W.W., Keefe,R.S., Boter,H., Keet,I.P., Prelipceanu,D., Rybakowski,J.K., Libiger,J., Hummer,M., Dollfus,S., López-Ibor,J.J., Hranov,L.G., Gaebel,W., Peuskens,J., Lindefors,N., Riecher-Rössler,A., Kahn,R.S., Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST), American journal of psychiatry, 166, 675-682, 2009	Study is in adults
De Araujo,A.A., Ribeiro,S.B., Dos Santos,A.C., Lemos,T.M., Medeiros,C.A., Guerra,G.C., De Araujo Junior,R.F., Serrano-Blanco,A., Rubio-Valera,M., Quality of Life and Hormonal, Biochemical, and Anthropometric Profile Between Olanzapine and Risperidone Users, Psychiatr.Q., -, 2015	Study is in adults
de Araujo,Aurigena Antunes, de Araujo Dantas,Diego, do Nascimento,Gemma Galgani, Ribeiro,Susana Barbosa, Chaves,Katarina Melo, de Lima Silva,Vanessa, de Araujo,Raimundo Fernandes Jr., de Souza,Dyego Leandro Bezerra, de Medeiros,Caroline Addison Carvalho Xavier, Quality of life in patients with schizophrenia: The impact of socio-economic factors and adverse effects of atypical antipsychotics drugs. [References], Psychiatric Quarterly, 85, 357-367, 2014	Study is in adults.
Deng,H.H., Zhen,H.B., He,Z.G., Zhou,L., A comparative trial of olanzapine versus clozopine in the treatment of schizophrenia, Journal of Shanghai Pschological Medicine, 12, 143-145, 2000	Study is not in English
Desamericq,G., Schurhoff,F., Meary,A., Szoke,A., Macquin-Mavier,I., Bachoud-Levi,A.C., Maison,P., Long-term neurocognitive	Meta-analysis of studies in adults

Study	Reason for Exclusion
effects of antipsychotics in schizophrenia: A network meta-analysis, European Journal of Clinical Pharmacology.70 (2) (pp 127-134), 2014.Date of Publication: February 2014., 127-134, 2014	
Devlin,A.M., Panagiotopoulos,C., Metabolic side effects and pharmacogenetics of second-generation antipsychotics in children, Pharmacogenomics.16 (9) (pp 981-996), 2015.Date of Publication: 01 Jun 2015., 981-996, 2015	Narrative review, results by type of antipsychotic not reported.
Dima,L., Vasile,D., Rogozea,L., Zia-Ul-Haq,M., Bukhari,S.A., Moga,M., Self-perception of quality of life in patients treated with antipsychotics, Turkish Journal of Medical Sciences.45 (4) (pp 782-788), 2015.Date of Publication: 27 Jun 2015., 782-788, 2015	Study is in adults
Dima,L., Vasile,D., Voicu,V.A., Comparative discontinuation rates in patients treated with antipsychotics, Therapeutics, Pharmacology and Clinical Toxicology.16 (3) (pp 181-189), 2012.Date of Publication: September 2012., 181-189, 2012	Study is in adults.
Dittmann-Balcar,A., Bender,S., Schall,U., Klimke,A., Mueller,N., Vorbach,U., Kuehn,K.U., Dittmann,R.W., Naber,D., Effects of olanzapine versus clozapine on executive functions in schizophrenia, Schizophrenia research, 60, 131-, 2003	Conference abstract
Divac,N., Prostran,M., Jakovcevski,I., Cerovac,N., Second-generation antipsychotics and extrapyramidal adverse effects, BioMed Research International.2014 , 2014.Article Number: 656370.Date of Publication: 2014., -, 2014	Narrative review
Dolnak,R., Rapaport,M.H., A prospective, randomized, doubleblind study examining functioning in schizophrenic patients treated with olanzapine and risperidone, Schizophrenia Research (Abstracts of the VIII International Congress on Schizophrenia Research; 2001 April 28-May 2; British Columbia, Canada), 49, 225-226, 2001	Conference abstract
Dossenbach,M., Slabber,M., Martenyi,F., Bartko,G., Bitter,I., Olanzapine vs. Clozapine in patients non-responsive or intolerant to standard acceptable treatment of schizophrenia, XI World Congress of Psychiatry , Hamburg, August 6-11, 1999, Abstracts Volume II, 148-, 1999	Study is in adults
Dossenbach,M.R.K., Beuzen,J.-N., Avnon,M., Belmaker,R.H., Elizur,A., Mark,M., Munitz,H., Schneidman,M., Shoshani,D., Kratky,P., Grundy,S.L., Tollefson,G.D., The effectiveness of olanzapine in treatment-refractory schizophrenia when patients are nonresponsive to or unable to tolerate clozapine, Clinical therapeutics, 22, 1021-1034, 2000	Study is in adults and has no comparator group

Study	Reason for Exclusion
Ebert,T., Midbari,Y., Shmilovitz,R., Kosov,I., Kotler,M., Weizman,A., Ram,A., Metabolic effects of antipsychotics in prepubertal children: A retrospective chart review, Journal of Child and Adolescent PsychopharmacologyJ.Child Adolesc.Psychopharmacol., 24, 218-222, 2014	Study compares adverse effects for a group of typical vs atypical antipsychotics - not specifically olanzapine
Edgell,E.T., Andersen,S.W., Grainger,D., Wang,J., Resource use and quality of life of olanzapine compared with risperidone: results from an international randomized clinical trial, XXIst Collegium Internationale Neuro-psychopharmacologicum, Glasgow, Scotland.12th-16th July, 1998., -, 1998	Abstract only
Edgell,E.T., Andersen,S.W., Johnstone,B.M., Dulisse,B., Revicki,D., Breier,A., Olanzapine versus risperidone. A prospective comparison of clinical and economic outcomes in schizophrenia, PharmacoEconomics, 18, 567-579, 2000	Study is in adults
Fawzi,M., Fawzi,J.M., Aripiprazole, olanzapine and olanzapineclomipramine combination in schizophrenia with obsessive-compulsive symptoms, World psychiatry, 8, 139-, 2009	Unable to source
Fervaha,G., Agid,O., Takeuchi,H., Foussias,G., Remington,G., Effect of antipsychotic medication on overall life satisfaction among individuals with chronic schizophrenia: Findings from the NIMH CATIE study, European neuropsychopharmacology, 24, 1078-1085, 2014	Study is in adults
Fervaha,G., Takeuchi,H., Lee,J., Foussias,G., Fletcher,P.J., Agid,O., Remington,G., Antipsychotics and amotivation, Neuropsychopharmacology, 40, 1539-1548, 2015	Study is in adults
Filakovi? P, Laufer,D., Radanovi?-Grguri? L, Koi? O, Fijacko,M., Durkovi? M, Newer antipsychotics and glucose metabolism: a comparison between olanzapine and risperidone, Psychiatria Danubina, 17, 63-66, 2005	Study is in adults
Findling,R.L., Johnson,J.L., McClellan,J., Frazier,J.A., Vitiello,B., Hamer,R.M., Lieberman,J.A., Ritz,L., McNamara,N.K., Lingler,J., Hlastala,S., Pierson,L., Puglia,M., Maloney,A.E., Kaufman,E.M., Noyes,N., Sikich,L., Double-blind maintenance safety and effectiveness findings from the Treatment of Early-Onset Schizophrenia Spectrum (TEOSS) study, Journal of the American Academy of Child and Adolescent Psychiatry, 49, 583-594, 2010	Greater than 50% attrition from one or more arms of the study
Fleischhacker,W.W., Keet,I.P., Kahn,R.S., The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial, Schizophrenia research, 78, 147-156, 2005	Protocol for the EUFEST trial (in adults)
Fleischhacker,W.W., McQuade,R.D.,	Study is in adults

Study	Reason for Exclusion
Marcus,R.N., Archibald,D., Swanink,R., Carson,W.H., A double-blind, randomized comparative study of aripiprazole and olanzapine in patients with schizophrenia, Biological psychiatry, 65, 510-517, 2009	
Fleischhacker,W.Wolfgang, Siu,Cynthia O., Boden,Robert, Pappadopulos,Elizabeth, Karayal,Onur N., Kahn,Rene S., Metabolic risk factors in first-episode schizophrenia: Baseline prevalence and course analysed from the European First-Episode Schizophrenia Trial. [References], International journal of neuropsychopharmacology, 16, 987-995, 2013	Study is mainly in adults (16-40 years), mean age around 26 years.
Fraguas,D., Llorente,C., Rapado-Castro,M., Parellada,M., Moreno,D., Ruiz-Sancho,A., Medina,O., Alvarez-Segura,M., de Castro,M.J., Arango,C., Attitude toward antipsychotic medication as a predictor of antipsychotic treatment discontinuation in first-episode early-onset psychosis, Revista de Psiquiatria y Salud Mental, 1, 10-17, 2008	No relevant outcomes.
Francesco,F., Cervone,A., Metabolic alterations associated with first and second generation antipsychotics: an twenty-years open study, Psychiatria Danubina, 26, Suppl-7, 2014	Study is in adults
Frazier,J.A., Giuliano,A.J., Johnson,J.L., Yakutis,L., Youngstrom,E.A., Breiger,D., Sikich,L., Findling,R.L., McClellan,J., Hamer,R.M., Vitiello,B., Lieberman,J.A., Hooper,S.R., Neurocognitive outcomes in the Treatment of Early-Onset Schizophrenia Spectrum Disorders study, Journal of the American Academy of Child and Adolescent Psychiatry, 51, 496-505, 2012	No relevant outcomes.
Fujii,K., Ozeki,Y., Okayasu,H., Takano,Y., Shinozaki,T., Hori,H., Orui,M., Horie,M., Kunugi,H., Shimoda,K., QT is longer in drug-free patients with schizophrenia compared with age-matched healthy subjects, PLoS ONE.9 (6) , 2014.Article Number: e98555.Date of Publication: 02 Jun 2014., -, 2014	Study is in adults
Fujimaki,K., Takahashi,T., Morinobu,S., Association of typical versus atypical antipsychotics with symptoms and quality of life in schizophrenia, PLoS ONE.7 (5) , 2012.Article Number: e37087.Date of Publication: 16 May 2012., -, 2012	Study is in adults
Gallego,J.A., Robinson,D.G., Sevy,S.M., Napolitano,B., McCormack,J., Lesser,M.L., Kane,J.M., Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months?, The Journal of clinical psychiatry, 72, 1691-1696, 2011	No relevant outcomes
Garcia-Ribera,C., Bennett,N., Naraine,M., Sevy,S., Robinson,D., Tardive dyskinesia among patients being treated for a first episode of schizophrenia, Neuropsychopharmacology,	Conference abstract

Study	Reason for Exclusion
35, S335-S336, 2010	
Gautam,S., Meena,P.S., Drug-emergent metabolic syndrome in patients with schizophrenia receiving atypical (second-generation) antipsychotics, Indian journal of psychiatry, 53, 128-133, 2011	Study is in adults
Gill,S.S., Stable monotherapy with clozapine or olanzapine increases the incidence of diabetes mellitus in people with schizophrenia, Evidence-based mental health, 8, 24-, 2005	Commentary
Gilmore,J., Kinon,B., Basson,B., Tollefson,G., Effect of long-term olanzapine treatment on weight change in schizophrenia, Journal of the European College of Neuropsychopharmacology (Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000), 10, S305-, 2000	Conference abstract
Gómez,J.C., Sacristán,J.A., Hernández,J., Breier,A., Ruiz,Carrasco P., Antón,Saiz C., Fontova,Carbonell E., The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO Study). Pharmacoepidemiologic Study of Olanzapine in Schizophrenia, Journal of clinical psychiatry, 61, 335-343, 2000	Study is in adults
Gothelf,D., Apter,A., Reidman,J., Brand-Gothelf,A., Bloch,Y., Gal,G., Kikinzon,L., Tyano,S., Weizman,R., Ratzoni,G., Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia, Journal of neural transmission (Vienna, Austria : 1996), 110, 545-560, 2003	Considered as part of the original 2012 review.
Grootens,K.P., Veelen,N.M., Peuskens,J., Sabbe,B.G., Thys,E., Buitelaar,J.K., Verkes,R.J., Kahn,R.S., Ziprasidone vs olanzapine in recent-onset schizophrenia and schizoaffective disorder: results of an 8-week double-blind randomized controlled trial, Schizophrenia bulletin, 37, 352-361, 2011	Comparator not met (ziprasidone which is not licensed for use in the UK)
Grunder,G., Heinze,M., Cordes,J., Ruther,E., Timm,J., The "neuroleptic strategy study" (NeSSy)-first vs. Second generation antipsychotics for the treatment of schizophrenia, Neuropsychopharmacology, 39, S370-S371, 2014	Conference abstract
Guelfucci,F., Watt,M., Vimont,A., Roiz,J., Cadi-Soussi,N., Comparative efficacy and metabolic side effects of lurasidone for the management of acute schizophrenia: A systematic literature review and mixed treatment comparison with first and second generation antipsychotics, Value in health, 16, A542-A543, 2013	Conference abstract
Guo,X., Zhai,J., Wei,Q., Twamley,E.W., Jin,H., Fang,M., Hu,M., Zhao,J., Early-stage Schizophrenia Outcome Study (ESOS) Investigators, Neurocognitive effects of first- and second-generation antipsychotic drugs in early-	Study is in adults

Study	Reason for Exclusion
stage schizophrenia: a naturalistic 12-month follow-up study, Neuroscience Letters, 503, 141-146, 2011	
Guo,X., Zhang,Z., Zhai,J., Fang,M., Hu,M., Wu,R., Liu,Z., Zhao,J., Effects of antipsychotic medications on quality of life and psychosocial functioning in patients with early-stage schizophrenia: 1-year follow-up naturalistic study, Comprehensive Psychiatry.53 (7) (pp 1006-1012), 2012.Date of Publication: October 2012., 1006-1012, 2012	Study is in adults
Gupta,A., Dadheech,G., Yadav,D., Sharma,P., Gautam,S., Metabolic issues in schizophrenic patients receiving antipsychotic treatment, Indian Journal of Clinical Biochemistry.29 (2) (pp 196-201), 2014.Date of Publication: April 2014., 196-201, 2014	Age group of participants not reported, study likely to be in adults as population is referred to as 'men and women'.
Gureje,O., Miles,W., Keks,N., Grainger,D., Lambert,T., McGrath,J., Tran,P., Catts,S., Fraser,A., Hustig,H., Andersen,S., Crawford,A.M., Olanzapine vs risperidone in the management of schizophrenia: a randomized double-blind trial in Australia and New Zealand, Schizophrenia research, 61, 303-314, 2003	Study is in adults
Gurpegui,M., Alvarez,E., Bousoño,M., Ciudad,A., Carlos,Gómez J., Olivares,J.M., Effect of olanzapine or risperidone treatment on some cognitive functions in a one-year follow-up of schizophrenia outpatients with prominent negative symptoms, European neuropsychopharmacology, 17, 725-734, 2007	Study is in adults
Gutiérrez,M., Miró,E., Chinchilla,A., Otero,A., Sala,J.M., López-Carrero,C., Gómez,J.C., Comparison between olanzapine and risperidone in the treatment of schizophrenia and other psycothic disorders: results of a double blind randomized study, Psiquiatría Biológica, 6, 49-54, 1999	Unable to source
Guz,H., Ozkan,A., Comparison of risperidone and olanzapine in schizophrenia. [Turkish], Ondokuz Mayis Universitesi Tip Dergisi, 19, 51-57, 2002	Study is not in English
Haan,L., Beuk,N., Hoogenboom,B., Dingemans,P., Linszen,D., Obsessive-compulsive symptoms during treatment with olanzapine and risperidone: a prospective study of 113 patients with recent-onset schizophrenia or related disorders, Journal of clinical psychiatry, 63, 104-107, 2002	No relevant outcomes.
Hardy,T.A., Henry,R.R., Forrester,T.D., Kryzhanovskaya,L.A., Campbell,G.M., Marks,D.M., Mudaliar,S., Impact of olanzapine or risperidone treatment on insulin sensitivity in schizophrenia or schizoaffective disorder, Diabetes, obesity & metabolism, 13, 726-735, 2011	Study is in adults
Harrigan,E.P., Miceli,J.J., Anziano,R.,	Study is in adults

Study	Reason for Exclusion
Watsky,E., Reeves,K.R., Cutler,N.R., Sramek,J., Shiovitz,T., Middle,M., A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition, Journal of clinical psychopharmacology, 24, 62-69, 2004	
Harvey,P.D., Green,M.F., McGurk,S.R., Meltzer,H.Y., Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study, Psychopharmacology, 169, 404-411, 2003	Study is in adults.
Harvey,P.D., Siu,C.O., Romano,S., Randomized, controlled, double-blind, multicenter comparison of the cognitive effects of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder, Psychopharmacology, 172, 324-332, 2004	Study is in adults and comparator not met.
Hashimoto,N., Toyomaki,A., Honda,M., Miyano,S., Nitta,N., Sawayama,H., Sugawara,Y., Uemura,K., Tsukamoto,N., Koyama,T., Kusumi,I., Long-term efficacy and tolerability of quetiapine in patients with schizophrenia who switched from other antipsychotics because of inadequate therapeutic response-a prospective open-label study, Annals of General Psychiatry.14 (1) , 2015.Article Number: 1.Date of Publication: January 22, 2015., -, 2015	Study is in adults
Hatta,K., Kawabata,T., Yoshida,K., Hamakawa,H., Wakejima,T., Furuta,K., Nakamura,M., Hirata,T., Usui,C., Nakamura,H., Sawa,Y., Olanzapine orally disintegrating tablet vs. risperidone oral solution in the treatment of acutely agitated psychotic patients, General hospital psychiatry, 30, 367-371, 2008	Study is in adults
Hatta,K., Otachi,T., Sudo,Y., Kuga,H., Takebayashi,H., Hayashi,H., Ishii,R., Kasuya,M., Hayakawa,T., Morikawa,F., Hata,K., Nakamura,M., Usui,C., Nakamura,H., Hirata,T., Sawa,Y., A comparison between augmentation with olanzapine and increased risperidone dose in acute schizophrenia patients showing early non-response to risperidone, Psychiatry research, 198, 194-201, 2012	Study is in adults
Hatta,Kotaro, Otachi,Taro, Fujita,Kiyoshi, Morikawa,Fumiyoshi, Ito,Shin, Tomiyama,Hirofumi, Abe,Takayuki, Sudo,Yasuhiko, Takebayashi,Hiroshi, Yamashita,Toru, Katayama,Shigemasa, Nakase,Reiko, Shirai,Yutaka, Usui,Chie, Nakamura,Hiroyuki, Ito,Hiroto, Hirata,Toyoaki, Sawa,Yutaka, Antipsychotic switching versus augmentation among early non-responders to risperidone or olanzapine in acute-phase schizophrenia. [References], Schizophrenia research, 158, 213-222, 2014	Study is in adults
Heres,S., Cirjaliu,D.M., Dehelean,L., Matei,V.P.,	Protocol for a trial in adults

Study	Reason for Exclusion
Podea,D.M., Sima,D., Stecher,L., Leucht,S., The SWITCH study: rationale and design of the trial, Eur.Arch.Psychiatry Clin.Neurosci., -, 2015	
Hermes,E., Nasrallah,H., Davis,V., Meyer,J., McEvoy,J., Goff,D., Davis,S., Stroup,T.S., Swartz,M., Lieberman,J., Rosenheck,R., The association between weight change and symptom reduction in the CATIE schizophrenia trial, Schizophrenia research, 128, 166-170, 2011	Age of subjects not reported.
Hermes,E., Rosenheck,R., Choice of randomization to clozapine versus other second generation antipsychotics in the CATIE schizophrenia trial, Journal of Psychopharmacology.26 (9) (pp 1194-1200), 2012.Date of Publication: September 2012., 1194-1200, 2012	Study is in adults
Hrdlicka,M., Dudova,I., Atypical antipsychotics in the treatment of early-onset schizophrenia, Neuropsychiatric Disease and Treatment.11 (pp 907-913), 2015.Date of Publication: 01 Apr 2015., -913, 2015	Narrative review
Hsu,W.Y., Huang,S.S., Lee,B.S., Chiu,N.Y., Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan, Journal of clinical psychopharmacology, 30, 230-234, 2010	Study is in adults
Hu,S., Yao,M., Peterson,B.S., Xu,D., Hu,J., Tang,J., Fan,B., Liao,Z., Yuan,T., Li,Y., Yue,W., Wei,N., Zhou,W., Huang,M., Xu,Y., A randomized, 12-week study of the effects of extended-release paliperidone (paliperidone ER) and olanzapine on metabolic profile, weight, insulin resistance, and beta-cell function in schizophrenic patients, Psychopharmacology, 230, 3-13, 2013	Study is in adults
Ingole,S., Belorkar,N.R., Waradkar,P., Shrivastava,M., Comparison of effects of olanzapine and risperidone on body mass index and blood sugar level in schizophrenic patients, Indian journal of physiology and pharmacology, 53, 47-54, 2009	Study is in adults
Iqbal,S.P., Khan,R.A., Ahmer,S., Antipsychotic treatment and weight gain: does risperidone behave differently in Pakistani psychiatric patients?, Journal of Ayub Medical College, Abbottabad: JAMC, 23, 66-69, 2011	Study is in adults
Jain,P., Singla,R.K., Gundamaraju,R., Dey,B., Varadaraj,Bhat G., Comparison of risperidon & olanzapine for extrapyramidal side effects on schizophrenic patients in Haryana, India, Indo Global Journal of Pharmaceutical Sciences.4 (2) (pp 91-99), 2014.Date of Publication: 2014., 91-99, 2014	Study is in adults

Study	Reason for Exclusion
Jarema,M., Olajossy,M., Chrzanowski,WI, Araszkiewicz,A., Landowski,J., Rybakowski,J., Bilikiewicz,A., Bomba,J., Debowska,G., Safety and efficacy of olanzapine versus perphenazine in patients with schizophrenia: Results of a multicenter, 18-week, double-blind clinical trial. [Polish], Psychiatria polska, 37, 641-655, 2003	Study not in English
Jayanthi,C.R., Divyashree,M., Sushma,M., Adverse drug reactions in psychiatry outpatients: Clinical spectrum, causality and avoidability, Journal of Chemical and Pharmaceutical Research.5 (8) (pp 128-135), 2013.Date of Publication: 2013., 128-135, 2013	Study is in adults
Jean-Noel,B., Wood,A.J., Kiesler,G.M., Birkett,M., Tollefson,G.D., Olanzapine vs. Clozapine: an international double-blind study in the treatment of resistant schizophrenia, XI World Congress of Psychiatry , Hamburg, August 6-11, 1999, Abstracts Volume II, 143-, 1999	Conference abstract
Jensen,J.B., Kumra,S., Leitten,W., Oberstar,J., Anjum,A., White,T., Wozniak,J., Lee,S.S., Schulz,S.C., A comparative pilot study of second-generation antipsychotics in children and adolescents with schizophrenia-spectrum disorders, Journal of child and adolescent psychopharmacology, 18, 317-326, 2008	Small sample size: n= 10 in all 3 study arms.
Jerrell,J.M., Cost-effectiveness of risperidone, olanzapine, and conventional antipsychotic medications, Schizophrenia bulletin, 28, 589-605, 2002	Study is in adults
Jesus,Mari J., Lima,M.S., Costa,A.N., Alexandrino,N., Rodrigues-Filho,S., Oliveira,I.R., Tollefson,G.D., The prevalence of tardive dyskinesia after a nine month naturalistic randomized trial comparing olanzapine with conventional treatment for schizophrenia and related disorders, European archives of psychiatry and clinical neuroscience, 254, 356-361, 2004	Study is in adults
Joel,J.J., Shastry,C.S., Rao,S., Evaluation of adverse drug reactions associated with the psychotropic drugs in the management of patients with schizophrenia, Der Pharmacia Lettre.6 (6) (pp 129-134), 2014.Date of Publication: 2014., 129-134, 2014	Study is in adults
Jones,B., Olanzapine versus risperidone and haloperidol in the treatment of schizophrenia, 151st Annual Meeting of the American Psychiatric Association.Toronto, Ontario, Canada.30th May-4th June 1998., -, 1998	Conference abstract
Kahn,R.S., Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomized clinical trial, World psychiatry, 8, 44-45, 2009	Study is in those aged 18-40, mean age >25 in relevant arms of the study.
Kane,J.M., Osuntokun,O., Kryzhanovskaya,L.A., Xu,W., Stauffer,V.L., Watson,S.B., Breier,A., A	Study is in adults

Study	Reason for Exclusion
28-week, randomized, double-blind study of olanzapine versus aripiprazole in the treatment of schizophrenia, Journal of clinical psychiatry, 70, 572-581, 2009	
Kang,S.H., Lee,J.I., Metabolic disturbances independent of body mass in patients with schizophrenia taking atypical antipsychotics, Psychiatry Investigation.12 (2) (pp 242-248), 2015.Date of Publication: 2015., 242-248, 2015	Study is in adults
Kaushal,J., Bhutani,G., Gupta,R., Comparison of fasting blood sugar and serum lipid profile changes after treatment with atypical antipsychotics olanzapine and risperidone, Singapore medical journal, 53, 488-492, 2012	Study is predominantly in adults - mean age >25.
Keefe,R.S., Sweeney,J.A., Gu,H., Hamer,R.M., Perkins,D.O., McEvoy,J.P., Lieberman,J.A., Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison, American journal of psychiatry, 164, 1061-1071, 2007	No relevant results.
Keefe,R.S., Young,C.A., Rock,S.L., Purdon,S.E., Gold,J.M., Breier,A., One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia, Schizophrenia research, 81, 1-15, 2006	Study is in adults
Kelly,A.C., Sheitman,B.B., Hamer,R.M., Rhyne,D.C., Reed,R.M., Graham,K.A., Rau,S.W., Gilmore,J.H., Perkins,D.O., Peebles,S.S., Vanderzwaag,C.J., Jarskog,L.F., A naturalistic comparison of the long-term metabolic adverse effects of clozapine versus other antipsychotics for patients with psychotic illnesses, Journal of Clinical Psychopharmacology.34 (4) (pp 441-445), 2014.Date of Publication: August 2014., 441-445, 2014	Study is in adults
Kelly,D.L., Conley,R.R., Love,R.C., Morrison,J.A., McMahon,R.P., Metabolic risk with second-generation antipsychotic treatment: a double-blind randomized 8-week trial of risperidone and olanzapine, Annals of clinical psychiatry, 20, 71-78, 2008	Study is in adults
Kelly,D.L., Conley,R.R., Richardson,C.M., Tamminga,C.A., Carpenter,W.T., Adverse effects and laboratory parameters of high-dose olanzapine vs. clozapine in treatment-resistant schizophrenia, Annals of clinical psychiatry, 15, 181-186, 2003	Study is predominantly in adults with a mean age <25 in one group (olanzapine) but >25 in the other (clozapine).
Kelly,D.L., Richardson,C.M., Yu,Y., Conley,R.R., Plasma concentrations of high-dose olanzapine in a double-blind crossover study, Human psychopharmacology, 21, 393-398, 2006	Study is in adults
Kern,R.S., Cornblatt,B., Carson,W.H., Dunbar,G., Ali,M., Ingenito,G., Green,M.F., An open-label comparison of the neurocognitive	Conference abstract

Study	Reason for Exclusion
effects of aripiprazole versus olanzapine in patients with stable psychosis, Schizophrenia Research (Abstracts of the VIII International Congress on Schizophrenia Research; 2001 April 28-May 2; British Columbia, Canada), 49, 234-, 2001	
Kern,R.S., Green,M.F., Cornblatt,B.A., Owen,J.R., McQuade,R.D., Carson,W.H., Ali,M., Marcus,R., The neurocognitive effects of aripiprazole: an open-label comparison with olanzapine, Psychopharmacology, 187, 312-320, 2006	Study is in adults
Kerwin,R., Millet,B., Herman,E., Banki,C.M., Lublin,H., Pans,M., Hanssens,L., L'Italien,G., McQuade,R.D., Beuzen,J.-N., A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients. Schizophrenic Trial of Aripiprazole: (STAR) study. [Polish], Wiadomosci Psychiatryczne, 11, 105-119, 2008	Study is in adults
Khanna,P., Suo,T., Komossa,K., Ma,H., Rummel-Kluge,C., El-Sayeh,H.G., Leucht,S., Xia,J., Aripiprazole versus other atypical antipsychotics for schizophrenia. [Review][Update of Cochrane Database Syst Rev. 2013;2:CD006569; PMID: 23450570], Cochrane Database of Systematic Reviews, 1, CD006569-, 2014	Cochrane review: No relevant new studies
Kim,E., Starr,H.L., Bossie,C., Mao,L., Alphs,L., Once-monthly paliperidone palmitate compared with oral atypical antipsychotic treatment in patients with schizophrenia, Schizophrenia bulletin, 41, S318-, 2015	Conference abstract
Kim,J.H., Yim,S.J., Nam,J.H., A 12-week, randomized, open-label, parallel-group trial of topiramate in limiting weight gain during olanzapine treatment in patients with schizophrenia, Schizophrenia research, 82, 115-117, 2006	Letter
Kim,K.S., Pae,C.U., Chae,J.H., Bahk,W.M., Jun,T.Y., Kim,D.J., Dickson,R.A., Effects of olanzapine on prolactin levels of female patients with schizophrenia treated with risperidone, Journal of clinical psychiatry, 63, 408-413, 2002	Study is in adults
Kinon,B.J., Chen,L., Ascher-Svanum,H., Stauffer,V.L., Kollack-Walker,S., Zhou,W., Kapur,S., Kane,J.M., Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia, Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 35, 581-590, 2010	Study is in adults
Kinon,B.J., Lipkovich,I., Edwards,S.B., Adams,D.H., Ascher-Svanum,H., Siris,S.G., A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with	Study is in adults

Study	Reason for Exclusion
prominent depressive symptoms, Journal of clinical psychopharmacology, 26, 157-162, 2006	
Kinon,B.J., Liu-Seifert,H., Ahl,J., Ahmed,S., Baker,R.W., Longitudinal effect of olanzapine on fasting serum lipids: a randomized, prospective, 4-month study, Annals of the New York Academy of Sciences, 1032, 295-296, 2004	Unclear what comparator is (conventional antipsychotics) and age group of participants not reported.
Kinon,B.J., Noordsy,D.L., Liu-Seifert,H., Gulliver,A.H., Ascher-Svanum,H., Kollack-Walker,S., Randomized, double-blind 6-month comparison of olanzapine and quetiapine in patients with schizophrenia or schizoaffective disorder with prominent negative symptoms and poor functioning, Journal of clinical psychopharmacology, 26, 453-461, 2006	Study is in adults
Kinon,B.J., Stauffer,V.L., Kollack-Walker,S., Chen,L., Sniadecki,J., Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia, Journal of clinical psychopharmacology, 28, 601-607, 2008	Study is in adults
Kiviniemi,M., Suvisaari,J., Koivumaa-Honkanen,H., Hakkinen,U., Isohanni,M., Hakko,H., Antipsychotics and mortality in first-onset schizophrenia: Prospective Finnish register study with 5-year follow-up, Schizophrenia Research.150 (1) (pp 274-280), 2013.Date of Publication: October 2013., 274-280, 2013	Study is in adults.
Kluge,M., Schuld,A., Himmerich,H., Dalal,M., Schacht,A., Wehmeier,P.M., Hinze-Selch,D., Kraus,T., Dittmann,R.W., Pollmächer,T., Clozapine and olanzapine are associated with food craving and binge eating: results from a randomized double-blind study, Journal of clinical psychopharmacology, 27, 662-666, 2007	Study is in adults
Kluge,M., Schuld,A., Schacht,A., Himmerich,H., Dalal,M.A., Wehmeier,P.M., Hinze-Selch,D., Kraus,T., Dittmann,R.W., Pollmächer,T., Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever, Psychoneuroendocrinology, 34, 118-128, 2009	Study is in adults
Komossa,Katja, Rummel,Kluge Christine, Hunger,Heike, Schmid,Franziska, Schwarz,Sandra, Duggan,Lorna, Kissling,Werner, Leucht,Stefan, Olanzapine versus other atypical antipsychotics for schizophrenia, SO: Cochrane Database of Systematic Reviews, -, 2010	Systematic review - relevant studies have been considered separately.
Konarzewska,B., Waszkiewicz,N., Galinska,B., Szulc,A., Fasting insulin serum levels and psychopathology profiles in male schizophrenic inpatients treated with olanzapine or risperidone, Neuroendocrinology Letters.34 (4) (pp 322-328), 2013.Date of Publication: 2013., 322-328, 2013	Study is in adults.
Krakowski,M., Czobor,P., Cholesterol and cognition in schizophrenia: a double-blind study	Study is in adults

Study	Reason for Exclusion
of patients randomized to clozapine, olanzapine and haloperidol, Schizophrenia research, 130, 27-33, 2011	
Krakowski,M., Czobor,P., Citrome,L., Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol, Schizophrenia research, 110, 95-102, 2009	Study is in adults
Krakowski,M.I., Czobor,P., A prospective longitudinal study of cholesterol and aggression in patients randomized to clozapine, olanzapine, and haloperidol, Journal of clinical psychopharmacology, 30, 198-199, 2010	Letter
Krakowski,M.I., Czobor,P., Citrome,L.L., Tremeau,F., Roy,B.B., Kline,L., Clozapine, olanzapine, and haloperidol treatment of violent patients with schizophrenia, 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA, No-, 2005	Conference abstract
Kranzler,H.N., Cohen,S.D., Psychopharmacologic Treatment of Psychosis in Children and Adolescents. Efficacy and Management, Child and Adolescent Psychiatric Clinics of North America.22 (4) (pp 727-744), 2013.Date of Publication: October 2013., 727-744, 2013	Narrative review
Kraus,J.E., Sheitman,B.B., Cook,A., Reviere,R., Lieberman,J.A., Olanzapine versus risperidone in newly admitted acutely ill psychotic patients, Journal of clinical psychiatry, 66, 1564-1568, 2005	Study is in adults
Kroken,R.A., Kjelby,E., Wentzel-Larsen,T., Mellesdal,L.S., Jorgensen,H.A., Johnsen,E., Time to discontinuation of antipsychotic drugs in a schizophrenia cohort: influence of current treatment strategies, Therapeutic Advances in Psychopharmacology.4 (6) (pp 228-239), 2014.Date of Publication: 10 Dec 2014., 228-239, 2014	Study is in adults
Kruse,G., Wong,B.J., Duh,M.S., Lefebvre,P., Lafeuille,M.H., Fastenau,J.M., Systematic Literature Review of the Methods Used to Compare Newer Second-Generation Agents for the Management of Schizophrenia: A focus on Health Technology Assessment, PharmacoEconomics, 33, 1049-1067, 2015	Systematic review of methods used to compare SGAs (RCTs vs cohort studies) - no relevant outcomes.
Kryzhanovskaya,L.A., Xu,W., Millen,B.A., Acharya,N., Jen,K.Y., Osuntokun,O., 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 (2) (pp 157-165), 2012.Date of Publication: 01 Apr 2012., 157-165, 2012	Studies included within this review article do not meet protocol inclusion criteria - comparator is either placebo and not another SGA or population is not as specified in protocol (eg: bipolar/personality disorder).

Study	Reason for Exclusion
Krzystanek,M., Krupka-Matuszczyk,I., An open, large, 6-month naturalistic study of outcome in schizophrenic outpatients, treated with olanzapine. [Review], Human psychopharmacology, 26, 81-85, 2011	Study is in adults and has no comparator group
Kumar,A., Datta,S.S., Wright,S.D., Furtado,V.A., Russell,P.S., Atypical antipsychotics for psychosis in adolescents. [Review], Cochrane Database of Systematic Reviews, 10, CD009582-, 2013	Systematic review, relevant studies have been considered separately.
Kumar,C.N., Thirthalli,J., Suresha,K.K., Arunachala,U., Gangadhar,B.N., Metabolic syndrome among schizophrenia patients: Study from a rural community of south India, Asian Journal of Psychiatry.6 (6) (pp 532-536), 2013.Date of Publication: December 2013., 532-536, 2013	Study is in adults
Kumar,H., Gupta,R., Metabolic syndrome in schizophrenia: How much is attributable to drug treatment?, Indian journal of psychiatry, 54, S102-, 2012	Study is in adults.
Kumra,S., Kranzler,H., Gerbino-Rosen,G., Kester,H.M., DeThomas,C., Cullen,K., Regan,J., Kane,J.M., Clozapine versus "high-dose" olanzapine in refractory early-onset schizophrenia: an open-label extension study, Journal of child and adolescent psychopharmacology, 18, 307-316, 2008	Considered as part of the original 2012 guideline.
Kunitomi,T., Hashiguchi,M., Mochizuki,M., Indirect comparison analysis of efficacy and safety between olanzapine and aripiprazole for schizophrenia, British Journal of Clinical Pharmacology.77 (5) (pp 767-776), 2014.Date of Publication: May 2014., 767-776, 2014	Review article - relevant studies have been reviewed individually by the NICE team.
Kwon,Jun Soo, Mittoux,Aurelia, Hwang,Jae Yeon, Ong,Adeline, Cai,Zhuo Ji, Su,Tung Ping, The efficacy and safety of 12 weeks of treatment with sertindole or olanzapine in patients with chronic schizophrenia who did not respond successfully to their previous treatments: A randomized, double-blind, parallel-group, flexible-dose study. [References], International clinical psychopharmacology, 27, 326-335, 2012	Study is in adults
Lahon,K., Shetty,H.M., Paramel,A., Sharma,G., A retrospective study of extrapyramidal syndromes with second generation antipsychotics in the psychiatric unit of a tertiary care teaching hospital, Journal of Pharmacology and Pharmacotherapeutics.3 (3) (pp 266-268), 2012.Date of Publication: July-September 2012., 266-268, 2012	Letter
Lambert,M., Conus,P., Naber,D., McGorry,P.D., Schimmelmann,B.G., Olanzapine in subjects with a first-episode psychosis non-responsive, intolerant or non-compliant to a first-line trial of risperidone, International journal of psychiatry in clinical practice, 9, 244-250, 2005	Subjects aged 15-29 years, mean age by study arm not reported.

Study	Reason for Exclusion
Landau,Z., Hadi-Cohen,R., Boaz,M., Krivoy,A., Amit,B.H., Zalsman,G., Levi,M., Shoval,G., Risk Factors for Weight Gain and Metabolic Syndrome in Adolescents with Psychiatric Disorders: A Historical Prospective Study, Journal of Child and Adolescent Psychopharmacology.25 (2) (pp 160-167), 2015.Date of Publication: 01 Mar 2015., 160-167, 2015	Only 20% of population had psychotic disorders and no relevant results by type of antipsychotic reported.
Lavalaye,J., Linszen,D.H., Booij,J., Reneman,L., Gersons,B.P., Royen,E.A., Dopamine D2 receptor occupancy by olanzapine or risperidone in young patients with schizophrenia, Psychiatry research, 92, 33-44, 1999	Age range 16 to 28 years, mean age by study arm not reported. Study reports on no additional outcomes or comparisons not covered by the direct data.
Law,S., Gudbrandsen,M., Magill,N., Sweetman,I., Rose,D., Landau,S., Flanagan,R.J., David,A.S., Patel,M.X., Olanzapine and risperidone plasma concentration therapeutic drug monitoring: A feasibility study, Journal of Psychopharmacology.29 (8) (pp 933-942), 2015.Date of Publication: 23 Aug 2015., 933-942, 2015	No relevant results.
Lecrubier,Y., Bouhassira,M., Olivier,V., Lancrenon,S., Crawford,A.M., Olanzapine versus amisulpride and placebo in the treatment of negative symptoms and deficit states of chronic schizophrenia, Journal of the European College of Neuropsychopharmacology, 9, S288-, 1999	Conference abstract
Lee,C., Wu,K.-H., Habil,H., Dyachkova,Y., Lee,P., Treatment with olanzapine, risperidone or typical antipsychotic drugs in Asian patients with schizophrenia, Australian and New Zealand journal of psychiatry, 40, 437-445, 2006	Study is in adults
Lee,E.H., Hui,C.L., Lin,J.J., Ching,E.Y., Chang,W.C., Chan,S.K., Chen,E.Y., Quality of life and functioning in first-episode psychosis Chinese patients with different antipsychotic medications, Early Interv.Psychiatry, -, 2015	Study is in adults.
Lee,M.-J., Lin,P.-Y., Chang,Y.-Y., Chong,M.-Y., Lee,Y., Antipsychotics-induced tardive syndrome: A retrospective epidemiological study, Clinical Neuropharmacology.37 (4) (pp 111-115), 2014.Date of Publication: July-August 2014., 111-115, 2014	Study is in adults
Lee,N.Y., Kim,S.H., Jung,D.C., Kim,E.Y., Yu,H.Y., Sung,K.H., Kang,U.G., Ahn,Y.M., Kim,Y.S., The prevalence of metabolic syndrome in Korean patients with schizophrenia receiving a monotherapy with aripiprazole, olanzapine or risperidone, Progress in neuro-psychopharmacology & biological psychiatry, 35, 1273-1278, 2011	Study is in adults
Lee,P., Eung,Kim C., Yoon,Kim C., Lin,W.W., Habil,H., Dyachkova,Y., Mcbride,M., Dossenbach,M., Long-term, naturalistic	Study is in adults

Study	Reason for Exclusion
treatment with olanzapine, risperidone, quetiapine, or haloperidol monotherapy: 24-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study, International journal of psychiatry in clinical practice, 12, 215-227, 2008	
Leucht,S., Cipriani,A., Spineli,L., Mavridis,D., Orey,D., Richter,F., Samara,M., Barbui,C., Engel,R.R., Geddes,J.R., Kissling,W., Stapf,M.P., Lassig,B., Salanti,G., Davis,J.M., Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. [Review][Erratum appears in Lancet. 2013 Sep 14;382(9896):940], Lancet, 382, 951-962, 2013	Meta-analysis of studies in adults, mean age 38.4 years and comparator is placebo.
Lin,C.-C., Chang,C.-M., Liu,C.-Y., Huang,T.-L., Increased high-sensitivity C-reactive protein levels in Taiwanese schizophrenic patients, Asia-Pacific Psychiatry.5 (2) (pp E58-E63), 2013.Date of Publication: June 2013., E58-E63, 2013	Study is in adults
Lin,L.A., Rosenheck,R., Sugar,C., Zbrozek,A., Comparing Antipsychotic Treatments for Schizophrenia: A Health State Approach, Psychiatric Quarterly.86 (1) (pp 107-121), 2015.Date of Publication: 2015., 107-121, 2015	Study is in adults.
Lindenmayer,J.-P., Czobor,P., Volavka,J., Lieberman,J.A., Citrome,L., Sheitman,B., Chakos,M., McEvoy,J.P., Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: An open-label switch study, Journal of clinical psychiatry, 63, 931-935, 2002	Study is in adults
Lindenmayer,J.P., Smith,R.C., Singh,A., Parker,B., Chou,E., Kotsaftis,A., Hyperglycemia in patients with schizophrenia who are treated with olanzapine, Journal of clinical psychopharmacology, 21, 351-353, 2001	Study is in adults
Ling Young,Su, Taylor,Mark, Lawrie,Stephen M., "First do no harm." A systematic review of the prevalence and management of antipsychotic adverse effects. [References], Journal of Psychopharmacology, 29, 353-362, 2015	Systematic review - adverse events by type of antipsychotic not reported.
Lohr,W.D., Chowning,R.T., Stevenson,M.D., Williams,P.G., Trends in Atypical Antipsychotics Prescribed to Children Six Years of Age or Less on Medicaid in Kentucky, Journal of Child and Adolescent Psychopharmacology.25 (5) (pp 440-443), 2015.Date of Publication: 01 Jun 2015., 440-443, 2015	No relevant results
Lu,M.-L., Wang,T.-N., Lin,T.-Y., Shao,W.-C., Chang,S.-H., Chou,J.-Y., Ho,Y.-F., Liao,Y.-T., Chen,V.C.H., Differential effects of olanzapine and clozapine on plasma levels of adipocytokines and total ghrelin, Progress in Neuro-Psychopharmacology and Biological Psychiatry.58 (pp 47-50), 2015.Date of	Study is in adults

Study	Reason for Exclusion
Publication: April 03, 2015., -50, 2015	
Ma,Q., Li,L.-X., Lian,H.-T., A controlled comparison study on paliperidone extended-release tablets and olanzapine in the treatment of schizophrenia. [Chinese], Chinese Journal of New Drugs, 21, 2658-2661, 2012	Study is not in English
Mahmoud,R., Harvey,P.D., Meltzer,H.Y., Green,M.F., Cognitive effects of risperidone and olanzapine in patients with schizophrenia or schizoaffective disorder, Schizophrenia Research (Abstracts of the VIII International Congress on Schizophrenia Research; 2001 April 28-May 2; British Columbia, Canada), 49, 236-237, 2001	Conference abstract
Mahmoud,R.A., Engelhart,L.M., Janagap,C., Awad,G., Assessment of symptoms affecting quality of life and patient satisfaction with antipsychotic drugs: new insights for a trial of, 152nd Annual Meeting of the American Psychiatric Association.Washington DC, USA.15-20th May, 1999., -, 1999	Conference abstract
Malhotra,A.K., Correll,C.U., Chowdhury,N.I., Muller,D.J., Gregersen,P.K., Lee,A.T., Tiwari,A.K., Kane,J.M., Fleischhacker,W.W., Kahn,R.S., Ophoff,R.A., Lieberman,J.A., Meltzer,H.Y., Lencz,T., Kennedy,J.L., Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug - Induced weight gain, Archives of General Psychiatry.69 (9) (pp 904-912), 2012.Date of Publication: September 2012., 904-912, 2012	Metabolic changes including triglycerides, cholesterol and glucose are not reported by type of antipsychotic received. Only potential results study refers for weight gain is in graphical format but exact numbers have already been extracted from the original study included in CG155 (Correll 2009).
Martin,S., L?o H, Peuskens,J., Thirumalai,S., Giudicelli,A., Fleurot,O., Rein,W., A double-blind, randomised comparative trial of amisulpride versus olanzapine in the treatment of schizophrenia: short-term results at two months, Current medical research and opinion, 18, 355-362, 2002	Study is in adults
Martinez-Ortega,J.M., Diaz-Atienza,F., Gutierrez-Rojas,L., Jurado,D., Gurpegui,M., Confounding by indication of a specific antipsychotic and the increase of body mass index among children and adolescents, European Child and Adolescent Psychiatry.20 (11-12) (pp 597-598), 2011.Date of Publication: December 2011., 597-598, 2011	Letter
Martinez-Ortega,J.M., Funes-Godoy,S., Diaz-Atienza,F., Gutierrez-Rojas,L., Perez-Costillas,L., Gurpegui,M., Weight gain and increase of body mass index among children and adolescents treated with antipsychotics: A critical review, European Child and Adolescent Psychiatry.22 (8) (pp 457-479), 2013.Date of Publication: August 2013., 457-479, 2013	2013 review article - all outcomes of interest haven't been assessed.
McClellan,J., Sikich,L., Findling,R.L., Frazier,J.A., Vitiello,B., Hlastala,S.A., Williams,E., Ambler,D., Hunt-Harrison,T.,	Rationale, design and methods of the TEOSS trial

Study	Reason for Exclusion
Maloney,A.E., Ritz,L., Anderson,R., Hamer,R.M., Lieberman,J.A., Treatment of early-onset schizophrenia spectrum disorders (TEOSS): rationale, design, and methods, Journal of the American Academy of Child and Adolescent Psychiatry, 46, 969-978, 2007	
McCue,R.E., Waheed,R., Urcuyo,L., Orendain,G., Joseph,M.D., Charles,R., Hasan,S.M., Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia, British journal of psychiatry, 189, 433-440, 2006	Study is in adults
McEvoy,J.P., Lieberman,J.A., Perkins,D.O., Hamer,R.M., Gu,H., Lazarus,A., Sweitzer,D., Olexy,C., Weiden,P., Strakowski,S.D., Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison, American journal of psychiatry, 164, 1050-1060, 2007	Study is in those aged 16-40 years. Mean age is >/=25 years in one or more of the study arms and no additional outcomes other than that covered by studies in subjects <18 years is reported.
McQuade,R.D., Stock,E., Marcus,R., Jody,D., Gharbia,N.A., Vanveggel,S., Archibald,D., Carson,W.H., A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study, Journal of clinical psychiatry, 65 Suppl 18, 47-56, 2004	Study is in adults
Meltzer,H.Y., Bobo,W.V., Roy,A., Jayathilake,K., Chen,Y., Ertugrul,A., Anil Ya?cio?lu AE, Small,J.G., A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia, Journal of clinical psychiatry, 69, 274-285, 2008	Study is in adults.
Meltzer,H.Y., Bonaccorso,S., Bobo,W.V., Chen,Y., Jayathilake,K., A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation, The Journal of clinical psychiatry, 72, 1602-1610, 2011	Study is in adults.
Meltzer,H.Y., Cucchiaro,J., Silva,R., Ogasa,M., Phillips,D., Xu,J., Kalali,A.H., Schweizer,E., Pikalov,A., Loebel,A., Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study, American journal of psychiatry, 168, 957-967, 2011	Study is in adults.
Meyer,J.M., Rosenblatt,L.C., Kim,E., Baker,R.A., Whitehead,R., The moderating impact of ethnicity on metabolic outcomes during treatment with olanzapine and aripiprazole in patients with schizophrenia, Journal of clinical psychiatry, 70, 318-325, 2009	Study is in adults
Midbari,Y., Ebert,T., Kosov,I., Kotler,M., Weizman,A., Ram,A., Hematological and Cardiometabolic safety of Clozapine in the treatment of very early onset schizophrenia: A	Study does not present results by type of antipsychotic received - groups are clozapine vs control group which includes children receiving

Study	Reason for Exclusion
retrospective chart review, Journal of Child and Adolescent Psychopharmacology.23 (8) (pp 516-521), 2013.Date of Publication: 01 Oct 2013., 516-521, 2013	various SGAs.
Miller,D.D., Caroff,S.N., Davis,S.M., Rosenheck,R.A., McEvoy,J.P., Saltz,B.L., Riggio,S., Chakos,M.H., Swartz,M.S., Keefe,R.S., Stroup,T.S., Lieberman,J.A., Extrapyramidal side-effects of antipsychotics in a randomised trial, British journal of psychiatry, 193, 279-288, 2008	Study is in adults
Moisan,J., Turgeon,M., Desjardins,O., Gregoire,J.P., Comparative safety of antipsychotics: another look at the risk of diabetes, Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 58, 218-224, 2013	Study is in adults
Monnelly,E.P., Fonda,J., Gagnon,D.R., Chittamooru,S., Lawler,E.V., Weight gain on antipsychotic medication is associated with sustained use among veterans with schizophrenia, Journal of Clinical Psychopharmacology.35 (1) (pp 57-62), 2015.Date of Publication: 01 Feb 2015., 57-62, 2015	Study is in adults.
Musil,R., Obermeier,M., Russ,P., Hamerle,M., Weight gain and antipsychotics: A drug safety review, Expert Opinion on Drug Safety.14 (1) (pp 73-96), 2015.Date of Publication: 01 Jan 2015., 73-96, 2015	Systematic review of studies in adults
Naber,D., Riedel,M., Klimke,A., Vorbach,E.U., Lambert,M., Kühn,K.U., Bender,S., Bandelow,B., Lemmer,W., Moritz,S., Dittmann,R.W., Randomized double blind comparison of olanzapine vs. clozapine on subjective well-being and clinical outcome in patients with schizophrenia, Acta psychiatrica Scandinavica, 111, 106-115, 2005	Study is in adults
Nagamine,T., Direct metabolic effects of risperidone and olanzapine in Japanese schizophrenic patients, Neuropsychiatric Disease & Treatment, 3, 177-179, 2007	Letter
Nagamine,T., Effects of risperidone and olanzapine on remnant-like lipoprotein particle cholesterol (RLP-C) in schizophrenic patients, Neuropsychiatric Disease & Treatment, 4, 481-486, 2008	Study is in adults
Nakajima,S., Takeuchi,H., Fervaha,G., Plitman,E., Chung,J.K., Caravaggio,F., Iwata,Y., Mihashi,Y., Gerretsen,P., Remington,G., Mulsant,B., Graff-Guerrero,A., Comparative efficacy between clozapine and other atypical antipsychotics on depressive symptoms in patients with schizophrenia: Analysis of the CATIE phase 2E data, Schizophrenia research, 161, 429-433, 2015	No relevant outcomes.
Nakamura,M., Nagamine,T., Metabolic effects of	Study is in adults

Study	Reason for Exclusion
sodium valproate on atypical antipsychotics in Japanese psychotic patients, Clinical Neuropsychopharmacology and Therapeutics.4 (pp 13-19), 2013.Date of Publication: 2013., -19, 2013	
Newcomer,J.W., Campos,J.A., Marcus,R.N., Breder,C., Berman,R.M., Kerselaers,W., L'italien,G.J., Nys,M., Carson,W.H., McQuade,R.D., A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine, Journal of clinical psychiatry, 69, 1046-1056, 2008	Study is in adults
Newcomer,J.W., Ratner,R.E., Eriksson,J.W., Emsley,R., Meulien,D., Miller,F., Leonova-Edlund,J., Leong,R.W., Brecher,M., A 24-week, multicenter, open-label, randomized study to compare changes in glucose metabolism in patients with schizophrenia receiving treatment with olanzapine, quetiapine, or risperidone, The Journal of clinical psychiatry, 70, 487-499, 2009	Study is in adults
Nielsen,R.E., Levander,S., Kjaersdam,Telleus G., Jensen,S.O.W., Ostergaard,Christensen T., Leucht,S., Second-generation antipsychotic effect on cognition in patients with schizophrenia-a meta-analysis of randomized clinical trials, Acta Psychiatrica Scandinavica.131 (3) (pp 185-196), 2015.Date of Publication: 01 Mar 2015., 185-196, 2015	Meta-analysis of studies in adults.
Nimwegen,L., Haan,L., Early withdrawal in a double-blind randomized clinical trial with olanzapine and risperidone performed in adolescents with first psychosis, Psychopathology, 39, 158-, 2006	Letter to the editor
Nimwegen,L., Haan,L., Beveren,N., Laan,W., Brink,W., Linszen,D., Obsessive-compulsive symptoms in a randomized, double-blind study with olanzapine or risperidone in young patients with early psychosis, Journal of clinical psychopharmacology, 28, 214-218, 2008	No relevant outcomes, mean age = 24.6 years.
Nussbaum,L.A., Dumitrascu,V., Tudor,A., Gradinaru,R., Andreescu,N., Puiu,M., Molecular study of weight gain related to atypical antipsychotics: clinical implications of the CYP2D6 genotype, Romanian Journal of Morphology & Embryology, 55, 877-884, 2014	No relevant results by type of antipsychotic received.
O'Donoghue,B., Schafer,M.R., Becker,J., Papageorgiou,K., Amminger,G.P., Metabolic changes in first-episode early-onset schizophrenia with second-generation antipsychotics, Early Intervention in Psychiatry.8 (3) (pp 276-280), 2014.Date of Publication: August 2014., 276-280, 2014	Sample size is less than 10 in intervention arm of the study.
Oh,G.H., Yu,J.-C., Choi,K.-S., Joo,E.-J., Jeong,S.-H., Simultaneous comparison of efficacy and tolerability of second-generation antipsychotics in schizophrenia: Mixed-treatment	Review article - unclear if studies included are in adults or children and all outcomes of interest are not assessed.

Study	Reason for Exclusion
comparison analysis based on head-to-head trial data, Psychiatry Investigation.12 (1) (pp 46-54), 2015.Date of Publication: 01 Jan 2015., 46-54, 2015	
Okruszek,L., Jernajczyk,W., Wierzbicka,A., Waliniowska,E., Jakubczyk,T., Jarema,M., Wichniak,A., Daytime sleepiness and EEG abnormalities in patients treated with second generation antipsychotic agents, Pharmacological Reports.66 (6) (pp 1077-1082), 2014.Date of Publication: 02 Aug 2014., 1077-1082, 2014	Study is in adults
Olfson,M., Gerhard,T., Huang,C., Lieberman,J.A., Bobo,W.V., Crystal,S., Comparative effectiveness of second-generation antipsychotic medications in early-onset schizophrenia, Schizophrenia Bulletin.38 (4) (pp 845-853), 2012.Date of Publication: June 2012., 845-853, 2012	No relevant outcomes
Ou,J.-J., Xu,Y., Chen,H.-H., Fan,X., Gao,K., Wang,J., Guo,X.-F., Wu,R.-R., Zhao,J.-P., Comparison of metabolic effects of ziprasidone versus olanzapine treatment in patients with first-episode schizophrenia, Psychopharmacology.225 (3) (pp 627-635), 2013.Date of Publication: February 2013., 627-635, 2013	Study is in adults
Pahari,N., Tripathi,S.K., Maity,T., Gupta,B.K., Bagchi,C., Mondal,D.K., Evaluation and analysis of adverse drug reactions of second generation antipsychotics in a psychiatry out-patient Department, International Journal of Pharmacy and Pharmaceutical Sciences.4 (SUPPL.5) (pp 158-162), 2012.Date of Publication: 2012., 158-162, 2012	Only 2% of the population are children - no subgroup analysis by age.
Parabiaghi,A., D'Avanzo,B., Tettamanti,M., Barbato,A., The GiSAS study: rationale and design of a pragmatic randomized controlled trial on aripiprazole, olanzapine and haloperidol in the long-term treatment of schizophrenia, Contemporary clinical trials, 32, 675-684, 2011	Protocol for a trial in adults
Parabiaghi,A., Tettamanti,M., D'Avanzo,B., Barbato,A., Metabolic syndrome and drug discontinuation in schizophrenia: a randomized trial comparing aripiprazole olanzapine and haloperidol, Acta psychiatrica Scandinavica, -, 2015	Study is in adults
Patel,J.K., Buckley,P.F., Woolson,S., Hamer,R.M., McEvoy,J.P., Perkins,D.O., Lieberman,J.A., Metabolic profiles of second-generation antipsychotics in early psychosis: findings from the CAFE study, Schizophrenia research, 111, 9-16, 2009	Age range is 16-40 years, mean age >/=25 in one or more study arms.
Pawar,G.R., Phadnis,P., Paliwal,A., Evaluation of efficacy, safety, and cognitive profile of amisulpride per se and its comparison with olanzapine in newly diagnosed schizophrenic patients in an 8-week, double-blind, single-	Study is in adults

Study	Reason for Exclusion
centre, prospective clinical trial, ISRN Psychiatry, 2012, 703751-, 2012	
Peluso,M.J., Lewis,S.W., Barnes,T.R.E., Jones,P.B., Non-neurological and metabolic side effects in the Cost Utility of the Latest Antipsychotics in Schizophrenia Randomised Controlled Trial (CUtLASS-1), Schizophrenia Research.144 (1-3) (pp 80-86), 2013.Date of Publication: March 2013., 80-86, 2013	Study is in adults
Peralta,Victor, de Jalon,Elena Garcia, Campos,Maria S., Cuesta,Manuel J., Phenomenological differences between spontaneous and drug-related extrapyramidal syndromes in patients with schizophrenia-spectrum disorders. [References], Journal of clinical psychopharmacology, 33, 438-440, 2013	Letter
Perez,R., Gonzalez-Blanch,C., Sierra-Biddle,D., Martinez,I., Vazquez-Barquero,J.L., Crespo-Facorro,B., Efficacy and safety of olanzapine, risperidone and haloperidol in acute treatment of patients with first episode psychosis, Schizophrenia research, 60, 298-299, 2003	Conference abstract
Perez-Iglesias,R., Crespo-Facorro,B., Amado,J.A., Garcia-Unzueta,M.T., Ramirez-Bonilla,M.L., Gonzalez-Blanch,C., Martinez-Garcia,O., Vazquez-Barquero,J.L., A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone, Journal of clinical psychiatry, 68, 1733-1740, 2007	Study is in subjects aged 15-50 years however mean age is greater than 25 years, no subgroup analysis by age.
Perez-Iglesias,R., Crespo-Facorro,B., Martinez-Garcia,O., Ramirez-Bonilla,M.L., Alvarez-Jimenez,M., Pelayo-Teran,J.M., Garcia-Unzueta,M.T., Amado,J.A., Vazquez-Barquero,J.L., Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naïve population, Schizophrenia research, 99, 13-22, 2008	Study is in adults
Pérez-Iglesias,R., Mata,I., Martínez-García,O., Garcia-Unzueta,M.T., Amado,J.A., Valdizán,E.M., Vázquez-Barquero,J.L., Crespo-Facorro,B., Long-term effect of haloperidol, olanzapine, and risperidone on plasma prolactin levels in patients with first-episode psychosis, Journal of clinical psychopharmacology, 32, 804-808, 2012	Study is in subjects aged 15-60 however mean age is >25 years (no subgroup analysis for adolescents).
Perez-Iglesias,R., Mata,I., Pelayo-Teran,J.M., Amado,J.A., Garcia-Unzueta,M.T., Berja,A., Martinez-Garcia,O., Vazquez-Barquero,J.L., Crespo-Facorro,B., Glucose and lipid disturbances after 1 year of antipsychotic treatment in a drug-naïve population, Schizophrenia research, 107, 115-121, 2009	Study is in adults
Perez-Iglesias,R., Vazquez-Barquero,J.L., Amado,J.A., Berja,A., Garcia-Unzueta,M.T., Pelayo-Terán,J.M., Carrasco-Marín,E., Mata,I.,	Study is in adults

Study	Reason for Exclusion
Crespo-Facorro,B., Effect of antipsychotics on peptides involved in energy balance in drug-naive psychotic patients after 1 year of treatment, Journal of clinical psychopharmacology, 28, 289-295, 2008	
Perkins,D.O., Gu,H., Weiden,P.J., McEvoy,J.P., Hamer,R.M., Lieberman,J.A., Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study, Journal of clinical psychiatry, 69, 106-113, 2008	No relevant outcomes, study compares those with discontinued treatment to completers.
Peuskens,J., Pani,L., Detraux,J., De,Hert M., The effects of novel and newly approved antipsychotics on serum prolactin levels: A comprehensive review, CNS Drugs.28 (5) (pp 421-453), 2014.Date of Publication: May 2014., 421-453, 2014	Narrative review
Phillips,G.A., Brunt,D.L., Roychowdhury,S.M., Xu,W., Naber,D., The relationship between quality of life and clinical efficacy from a randomized trial comparing olanzapine and ziprasidone, Journal of clinical psychiatry, 67, 1397-1403, 2006	Study is in adults
Pijnenborg,G.H.M., Timmerman,M.E., Derks,E.M., Fleischhacker,W.W., Kahn,R.S., Aleman,A., Differential effects of antipsychotic drugs on insight in first episode schizophrenia: Data from the European First-Episode Schizophrenia Trial (EUFEST), European Neuropsychopharmacology.25 (6) (pp 808-816), 2015.Date of Publication: 01 Jun 2015., 808-816, 2015	No relevant outcomes and mean age >25 years in most arms of the study.
Pikalov,A., Cucchiaro,J., Werner,P., Ogasa,M., Silva,R., Watabe,K., Loebel,A., Effect of lurasidone on weight and metabolic parameters: A comprehensive analysis of short-and long-term trials in schizophrenia, CNS spectrums, 18, 354-355, 2013	Meta-analysis of placebo controlled trials therefore comparator not met. Age of subjects not reported.
Piparva,K.G., Buch,J.G., Chandrani,K.V., Analysis of Adverse Drug Reactions of Atypical Antipsychotic Drugs in Psychiatry OPD, Indian Journal of Psychological Medicine, 33, 153-157, 2011	Study included subjects of any age, mean age of weight gain was 38 years.
Potvin,S., Zhornitsky,S., Stip,E., Antipsychotic-induced changes in blood levels of leptin in schizophrenia: a meta-analysis, Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 60, Suppl-34, 2015	Meta-analysis - comparator not met (before vs after treatment); age of included studies unclear
Pramyothin,P., Khaodhiar,L., Type 2 Diabetes in Children and Adolescents on Atypical Antipsychotics, Current Diabetes Reports.15 (8) , 2015.Article Number: 53.Date of Publication: 19 Aug 2015., -, 2015	Narrative review
Purdon,S.E., Jones,B.D., Stip,E., Labelle,A.,	Study is in adults.

Study	Reason for Exclusion
Addington,D., David,S.R., Breier,A., Tollefson,G.D., Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia, Archives of general psychiatry, 57, 249-258, 2000	
Purdon,S.E., Woodward,N., Lindborg,S.R., Stip,E., Procedural learning in schizophrenia after 6 months of double-blind treatment with olanzapine, risperidone, and haloperidol, Psychopharmacology, 169, 390-397, 2003	Study is in adults
Riedel,M., Müller,N., Spellmann,I., Engel,R.R., Musil,R., Valdevit,R., Dehning,S., Douhet,A., Cerovecki,A., Strassnig,M., Möller,H.J., Efficacy of olanzapine versus quetiapine on cognitive dysfunctions in patients with an acute episode of schizophrenia, European archives of psychiatry and clinical neuroscience, 257, 402-412, 2007	Study is in adults
Rittmannsberger,H., Fellinger,J., Foff,C., Walli,G., Zaunmller,T., Deterioration of metabolic parameters during short-term psychiatric inpatient treatment: A prospective naturalistic study, International Journal of Psychiatry in Clinical Practice.16 (1) (pp 8-17), 2012.Date of Publication: March 2012., 8-17, 2012	Study is in adults
Robinson,D.G., Woerner,M.G., Napolitano,B., Patel,R.C., Sevy,S.M., Gunduz-Bruce,H., Soto-Perello,J.M., Mendelowitz,A., Khadivi,A., Miller,R., McCormack,J., Lorell,B.S., Lesser,M.L., Schooler,N.R., Kane,J.M., Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia: 4-month outcomes, American journal of psychiatry, 163, 2096-2102, 2006	Mean age of all subjects is 23.3 years, age by study arms not reported. Study also does not report on any additional outcomes or comparisons not covered by the direct data.
Robles,O., Zabala,A., Bombín,I., Parellada,M., Moreno,D., Ruiz-Sancho,A., Arango,C., Cognitive efficacy of quetiapine and olanzapine in early-onset first-episode psychosis, Schizophrenia bulletin, 37, 405-415, 2011	No relevant outcomes
Rojas,P., Villar,M., Gonzalez,A., Poblete,C., Funez,F., Tong,A., Liberman,C., Increase in C-reactive protein and lipids in adolescents with psychiatric disease, Psychiatry Research.190 (2-3) (pp 372-374), 2011.Date of Publication: 30 December 2011., 372-374, 2011	No relevant results by type of antipsychotic received; study compares those with psychiatric disease against healthy controls for various outcomes.
Rojo,L.E., Gaspar,P.A., Silva,H., Risco,L., Arena,P., Cubillos-Robles,K., Jara,B., Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology, Pharmacol.Res., -, 2015	Narrative review
Roohafza,H., Khani,A., Garakyaraghi,M., Amirpour,A., Afshar,H., Ghodsi,B., Lipid profile in antipsychotic drug users: A comparative study, ARYA Atherosclerosis.9 (3) (pp 198-202),	Study is in adults.

Study	Reason for Exclusion
2013.Date of Publication: 2013., 198-202, 2013	
Rummel-Kluge,Christine, Komossa,Katja, Schwarz,Sandra, Hunger,Heike, Schmid,Franziska, Kissling,Werner, Davis,John M., Leucht,Stefan, A systematic review and meta-analysis of head-to-head comparisons. [References], Schizophrenia bulletin, 38, 167-177, 2012	Systematic review - mean age of participants in included studies is around mid 30s.
Rybakowski,J.K., Vansteelandt,K., Remlinger-Molenda,A., Fleischhacker,W.W., Kahn,R.S., Peuskens,J., Extrapyramidal symptoms during treatment of first schizophrenia episode: Results from EUFEST, European neuropsychopharmacology, 24, 1500-1505, 2014	Study is in adults
Ryu,S., Yoo,J.H., Kim,J.H., Choi,J.S., Baek,J.H., Ha,K., Kwon,J.S., Hong,K.S., Tardive dyskinesia and tardive dystonia with second-generation antipsychotics in non-elderly schizophrenic patients unexposed to first-generation antipsychotics a cross-sectional and retrospective study, Journal of Clinical Psychopharmacology.35 (1) (pp 13-21), 2015.Date of Publication: 01 Feb 2015., 13-21, 2015	Study is in adults, mean age >25 years.
Sacchetti,E., Valsecchi,P., Parrinello,G., A randomized, flexible-dose, quasi-naturalistic comparison of quetiapine, risperidone, and olanzapine in the short-term treatment of schizophrenia: the QUERISOLA trial, Schizophrenia research, 98, 55-65, 2008	Study is in adults
Saddichha,S., Ameen,S., Akhtar,S., Predictors of antipsychotic-induced weight gain in first-episode psychosis: conclusions from a randomized, double-blind, controlled prospective study of olanzapine, risperidone, and haloperidol, Journal of clinical psychopharmacology, 28, 27-31, 2008	Mean age is 26 years.
Saddichha,S., Manjunatha,N., Ameen,S., Akhtar,S., Metabolic syndrome in first episode schizophrenia - a randomized double-blind controlled, short-term prospective study, Schizophrenia research, 101, 266-272, 2008	Study is in adults
Saddichha,S., Manjunatha,N., Ameen,S., Akhtar,S., Diabetes and schizophrenia - effect of disease or drug? Results from a randomized, double-blind, controlled prospective study in first-episode schizophrenia, Acta psychiatrica Scandinavica, 117, 342-347, 2008	Study is in adults
Saddichha,S., Manjunatha,N., Ameen,S., Akhtar,S., Effect of olanzapine, risperidone, and haloperidol treatment on weight and body mass index in first-episode schizophrenia patients in India: a randomized, double-blind, controlled, prospective study, Journal of clinical psychiatry, 68, 1793-1798, 2007	Study is in adults
Safa,M., Sadr,S., Delfan,B., Saki,M.,	Study is in adults

Study	Reason for Exclusion
Javad,Tarrahi M., Metabolic effects of olanzapine and risperidone in patients with psychotic disorders, International journal of psychiatry in clinical practice, 12, 299-302, 2008	
Saljoughian,M., Atypical antipsychotics: Safety and use in pediatric patients, U.S.Pharmacist.40 (5) , 2015.Date of Publication: 2015., -, 2015	Narrative review
San,L., Arranz,B., Perez,V., Safont,G., Corripio,I., Ramirez,N., Dueñas,R., Alvarez,E., One-year, randomized, open trial comparing olanzapine, quetiapine, risperidone and ziprasidone effectiveness in antipsychotic-naive patients with a first-episode psychosis, Psychiatry research, 200, 693-701, 2012	Study is in adults
Sarkar,S., Grover,S., Antipsychotics in children and adolescents with schizophrenia: A systematic review and meta-analysis, Indian Journal of Pharmacology.45 (5) (pp 439-446), 2013.Date of Publication: September-October 2013., 439-446, 2013	Systematic review - relevant studies have been reviewed separately by the NICE team
Schoemaker,J., Naber,D., Vrijland,P., Panagides,J., Emsley,R., Long-Term Assessment of Asenapine vs. Olanzapine in Patients with Schizophrenia or Schizoaffective Disorder, Pharmacopsychiatry, 44, 343-, 2011	Study is in adults
Schoemaker,J., Stet,L., Vrijland,P., Naber,D., Panagides,J., Emsley,R., Long-term efficacy and safety of asenapine or olanzapine in patients with schizophrenia or schizoaffective disorder: an extension study, Pharmacopsychiatry, 45, 196-203, 2012	Study is in adults
Schreiner,A., Korcsog,P., Niehaus,D.J., Aadamsoo,K., Ucok,A., Franco,M., A prospective randomized controlled trial of paliperidone er versus oral olanzapine in patients with schizophrenia, International journal of neuropsychopharmacology, 13, 239-, 2010	Conference abstract
Schuster,J.P., Raucher-Chene,D., Lemogne,C., Rouillon,F., Gasquet,I., Leguay,D., Gierski,F., Azorin,J.M., Limosin,F., Impact of switching or initiating antipsychotic treatment on body weight during a 6-month follow-up in a cohort of patients with schizophrenia, Journal of clinical psychopharmacology, 32, 672-677, 2012	Study is in adults
Shafti,S.S., Jahromi,P.F., A comparative study between olanzapine and risperidone regarding drug-induced electrocardiographic changes, Cardiovascular Psychiatry and Neurology.2014 , 2014.Article Number: 637016.Date of Publication: 2014., -, 2014	Age range of participants not reported and mean age is not less than 25 years in both arms of the study
Shao,P., Ou,J., Wu,R., Fang,M., Chen,H., Xu,Y., Zhao,J., Effects of ziprasidone and olanzapine on glucose and lipid metabolism in first-episode schizophrenia. [Chinese], Journal of Central South University (Medical Sciences), 38, 365-369, 2013	Chinese study
Sharma,E., Venkatasubramanian,G.,	No relevant outcomes.

Study	Reason for Exclusion
Varambally,S., Sivakumar,P.T., Subbakrishna,D., Gangadhar,B.N., Antipsychotic induced metabolic changes & treatment response: A prospective study, Asian Journal of Psychiatry.11 (pp 39-44), 2014.Date of Publication: 01 Oct 2014., -44, 2014	
Shoja,Shafti S., Fallah,Jahromi P., Olanzapine induced Q-Tc shortening, Therapeutic Advances in Psychopharmacology, 4, 240-246, 2014	Includes subjects up to the age of 40 years, mean age is not less than 25 in one or more arms of the study.
Shoja,Shafti S., Gilanipoor,M., A Comparative Study between Olanzapine and Risperidone in the Management of Schizophrenia, Schizophrenia Research & Treatment Print, 2014, 307202-, 2014	Study is in adults
Shrivastava,A., Johnston,M., Terpstra,K., Stitt,L., Shah,N., Atypical antipsychotics usage in long-term follow-up of first episode schizophrenia, Indian Journal of Psychiatry.54 (3) (pp 248-252), 2012.Date of Publication: July-September 2012., 248-252, 2012	Study is in adults
Shulman,M., Miller,A., Misher,J., Tentler,A., Managing cardiovascular disease risk in patients treated with antipsychotics: A multidisciplinary approach, Journal of Multidisciplinary Healthcare.7 (pp 489-501), 2014.Date of Publication: 31 Oct 2014., -501, 2014	Narrative review
Sikich,L., Horrigan,J.P., Lieberman,J.A., Barnhill,L.J., Sheitman,B.B., Courvoisie,H.E., Comparative use of olanzapine and risperidone in psychotic youth, 154th Annual Meeting of the American Psychiatric Association; 2001 May 5-10; New Orleans, LA, No-, 2001	Conference abstract
Simpson,G.M., Glick,I.D., Weiden,P.J., Romano,S.J., Siu,C.O., Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder, American journal of psychiatry, 161, 1837-1847, 2004	Study is in adults
Simpson,G.M., O'Gorman,C.J., Loebel,A., Yang,R., Long-term improvement in efficacy and safety after switching to ziprasidone in stable outpatients with schizophrenia, CNS spectrums, 13, 898-905, 2008	Study is in adults.
Simpson,G.M., Weiden,P., Pigott,T., Murray,S., Siu,C.O., Romano,S.J., Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia, American journal of psychiatry, 162, 1535-1538, 2005	Age of population not reported therefore unclear if study is in children or adults.
Sirota,P., Pannet,I., Koren,A., Tchernichovsky,E., Quetiapine versus olanzapine for the treatment of negative symptoms in patients with schizophrenia, Human psychopharmacology, 21, 227-234, 2006	Study is in adults.
Smith,D.H., Atypical antipsychotics for psychosis	Commentary

Study	Reason for Exclusion
in adolescents, Paediatrics and Child Health (Canada).19 (8) (pp 405-406), 2014.Date of Publication: 01 Oct 2014., 405-406, 2014	
Smith,R.C., Kanellopoulou,I., Rachakonda,S., Lindenmayer,J.-P., Davis,J.M., Olanzapine vs. Risperidone effects on appetite and ghrelin in chronic schizophrenic patients, Neuropsychopharmacology, 35, S315-S316, 2010	Conference abstract
Smith,R.C., Lindenmayer,J.P., Hu,Q., Kelly,E., Viviano,T.F., Cornwell,J., Vaidhyanathaswamy,S., Marcovina,S., Davis,J.M., Effects of olanzapine and risperidone on lipid metabolism in chronic schizophrenic patients with long-term antipsychotic treatment: a randomized five month study, Schizophrenia research, 120, 204-209, 2010	Study is in adults.
Smith,R.C., Rachakonda,S., Dwivedi,S., Davis,J.M., Olanzapine and risperidone effects on appetite and ghrelin in chronic schizophrenic patients, Psychiatry research, 199, 159-163, 2012	Study is in adults.
Stafford,M.R., Mayo-Wilson,E., Loucas,C.E., James,A., Hollis,C., Birchwood,M., Kendall,T., Efficacy and safety of pharmacological and psychological interventions for the treatment of psychosis and schizophrenia in children, adolescents and young adults: A systematic review and meta-analysis, PLoS ONE.10 (2) , 2015.Article Number: e0117166.Date of Publication: 11 Feb 2015., -, 2015	Systematic review - studies from relevant comparison in this review have been reviewed separately by the updates team
Stargardt,T., Edel,M.-A., Ebert,A., Busse,R., Juckel,G., Gericke,C.A., Effectiveness and cost of atypical versus typical antipsychotic treatment in a nationwide cohort of patients with schizophrenia in Germany, Journal of Clinical Psychopharmacology.32 (5) (pp 602-607), 2012.Date of Publication: October 2012., 602-607, 2012	Study is in those aged 16 to 92 years, no outcomes of interest have been reported by age.
Stentebjerg-Olesen,M., Jeppesen,P., Pagsberg,A.K., Fink-Jensen,A., Kapoor,S., Chekuri,R., Carbon,M., Al-Jadiri,A., Kishimoto,T., Kane,J.M., Correll,C.U., Early nonresponse determined by the clinical global impressions scale predicts poorer outcomes in youth with schizophrenia spectrum disorders naturalistically treated with second-generation antipsychotics, Journal of Child and Adolescent Psychopharmacology.23 (10) (pp 665-675), 2013.Date of Publication: 01 Dec 2013., 665-675, 2013	No relevant results by type of antipsychotic received.
Stroup,T.S., Lieberman,J.A., McEvoy,J.P., Davis,S.M., Swartz,M.S., Keefe,R.S., Miller,A.L., Rosenheck,R.A., Hsiao,J.K., Results of phase 3 of the CATIE schizophrenia trial, Schizophrenia research, 107, 1-12, 2009	Study is in adults.

Study	Reason for Exclusion
Sugai,T., Suzuki,Y., Fukui,N., Ono,S., Watanabe,J., Tsuneyama,N., Someya,T., Dysregulation of adipocytokines related to second-generation antipsychotics in normal fasting glucose patients with schizophrenia, Journal of Clinical Psychopharmacology.32 (3) (pp 390-393), 2012.Date of Publication: June 2012., 390-393, 2012	Study is in adults.
Suzuki,Y., Ono,S., Tsuneyama,N., Sawamura,K., Sugai,T., Fukui,N., Watanabe,J., Someya,T., Effects of olanzapine on the PR and QT intervals in patients with schizophrenia, Schizophrenia Research.152 (1) (pp 313-314), 2014.Date of Publication: 2014., 313-314, 2014	Letter
Suzuki,Y., Sugai,T., Fukui,N., Watanabe,J., Ono,S., Tsuneyama,N., Saito,M., Someya,T., Sex differences in the effect of four second-generation antipsychotics on QTc interval in patients with schizophrenia, Human psychopharmacology, 28, 215-219, 2013	Study is in adults.
Suzuki,Y., Sugai,T., Fukui,N., Watanabe,J., Ono,S., Tsuneyama,N., Saito,M., Someya,T., Changes in QT interval after switching to quetiapine in Japanese patients with schizophrenia, Human Psychopharmacology.28 (1) (pp 94-96), 2013.Date of Publication: January 2013., 94-96, 2013	Study is in adults.
Suzuki,Y., Sugai,T., Fukui,N., Watanabe,J., Ono,S., Tsuneyama,N., Saito,M., Someya,T., Differences in plasma prolactin levels in patients with schizophrenia treated on monotherapy with five second-generation antipsychotics, Schizophrenia Research.145 (1-3) (pp 116-119), 2013.Date of Publication: April 2013., 116-119, 2013	Study is in adults.
Suzuki,Y., Sugai,T., Ono,S., Sawamura,K., Fukui,N., Watanabe,J., Tsuneyama,N., Saito,M., Someya,T., Changes in PR and QTc intervals after switching from olanzapine to risperidone in patients with stable schizophrenia, Psychiatry & Clinical Neurosciences, 68, 353-356, 2014	Study is in adults
Suzuki,Y., Sugai,T., Ono,S., Sawamura,K., Fukui,N., Watanabe,J., Tsuneyama,N., Someya,T., Changes in the metabolic parameters and QTc interval after switching from olanzapine to aripiprazole in Japanese patients with stable schizophrenia, Journal of clinical psychopharmacology, 31, 526-528, 2011	Letter
Swartz,M.S., Perkins,D.O., Stroup,T.S., Davis,S.M., Capuano,G., Rosenheck,R.A., Reimherr,F., McGee,M.F., Keefe,R.S., McEvoy,J.P., Hsiao,J.K., Lieberman,J.A., Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study, American journal of psychiatry, 164, 428-436, 2007	Study is in adults

Study	Reason for Exclusion
Swartz,M.S., Stroup,T.S., McEvoy,J.P., Davis,S.M., Rosenheck,R.A., Keefe,R.S., Hsiao,J.K., Lieberman,J.A., What CATIE found: results from the schizophrenia trial, Psychiatric services (Washington, D.C.), 59, 500-506, 2008	Study is in adults - overview of the CATIE trial
Takeuchi,H., Suzuki,T., Remington,G., Watanabe,K., Mimura,M., Uchida,H., Lack of effect of risperidone or olanzapine dose reduction on metabolic parameters, prolactin, and corrected QT interval in stable patients with schizophrenia, Journal of Clinical Psychopharmacology.34 (4) (pp 517-520), 2014.Date of Publication: August 2014., 517-520, 2014	Letter
Takeuchi,Hiroyoshi, Fervaha,Gagan, Lee,Jimmy, Agid,Ofer, Remington,Gary, Effectiveness of different dosing regimens of risperidone and olanzapine in schizophrenia. [References], European neuropsychopharmacology, 25, 295-302, 2015	Study is in adults
Tek,C., Kucukgoncu,S., Guloksuz,S., Woods,S.W., Srihari,V.H., Annamalai,A., Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications, Early Interv.Psychiatry, -, 2015	Meta-analysis of various antipsychotics versus placebo (comparator therefore not met)
Tollefson,G.D., Birkett,M.A., Kiesler,G.M., Wood,A.J., Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine, Biological psychiatry, 49, 52-63, 2001	Study is in adults
Tran,P.V., Hamilton,S.H., Kuntz,A.J., Potvin,J.H., Andersen,S.W., Beasley,C., Tollefson,G.D., Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders, Journal of clinical psychopharmacology, 17, 407-418, 1997	Study is in adults
Tran,P.V., Tollefson,G.D., Hamilton,S., Kuntz,A., Olanzapine vs. risperidone in the treatment of psychosis, Sixth World Congress of Biological Psychiatry, Nice, France.June 22-27, 1997., -, 1997	Conference abstract
Treuer,T., Hoffmann,V.P., Chen,A.K., Irimia,V., Ocampo,M., Wang,G., Singh,P., Holt,S., Factors associated with weight gain during olanzapine treatment in patients with schizophrenia or bipolar disorder: results from a six-month prospective, multinational, observational study, World journal of biological psychiatry, 10, 729-740, 2009	Study is in adults
Unsal,C., Albayrak,Y., Albayrak,N., Kuloglu,M., Hashimoto,K., Reduced serum paraoxonase 1 (PON1) activity in patients with schizophrenia treated with olanzapine but not quetiapine, Neuropsychiatric Disease and Treatment.9 (pp 1545-1552), 2013.Date of Publication: 10 Oct	Study is in adults

Study	Reason for Exclusion
2013., -1552, 2013	
Veelen,N.M., Grootens,K.P., Peuskens,J., Sabbe,B.G., Salden,M.E., Verkes,R.J., Kahn,R.S., Sitskoorn,M.M., Short term neurocognitive effects of treatment with ziprasidone and olanzapine in recent onset schizophrenia, Schizophrenia research, 120, 191-198, 2010	No relevant results
Vernal,D.L., Kapoor,S., Al-Jadiri,A., Sheridan,E.M., Borenstein,Y., Mormando,C., David,L., Singh,S., Seidman,A.J., Carbon,M., Gerstenberg,M., Saito,E., Kane,J.M., Steinhausen,H.-C., Correll,C.U., Outcome of Youth with Early-Phase Schizophrenia-Spectrum Disorders and Psychosis Not Otherwise Specified Treated with Second-Generation Antipsychotics: 12 Week Results from a Prospective, Naturalistic Cohort Study, Journal of Child and Adolescent Psychopharmacology.25 (7) (pp 535-547), 2015.Date of Publication: 01 Sep 2015., 535-547, 2015	No relevant results by type of antipsychotic received.
Villari,V., Rocca,P., Fonzo,V., Montemagni,C., Pandullo,P., Bogetto,F., Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation, Progress in neuro-psychopharmacology & biological psychiatry, 32, 405-413, 2008	Study is in adults
Volavka,J., Czobor,P., Cooper,T.B., Sheitman,B., Lindenmayer,J.P., Citrome,L., McEvoy,J.P., Lieberman,J.A., Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol, Journal of clinical psychiatry, 65, 57-61, 2004	Age of study subjects not reported but are referred to as men and women so study likely to be in adults. Also, relevant results are in graphical form without accompanying numbers.
Volavka,J., Czobor,P., Nolan,K., Sheitman,B., Lindenmayer,J.P., Citrome,L., McEvoy,J.P., Cooper,T.B., Lieberman,J.A., Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol, Journal of clinical psychopharmacology, 24, 225-228, 2004	No relevant outcomes.
Volavka,J., Czobor,P., Sheitman,B., Lindenmayer,J.P., Citrome,L., McEvoy,J.P., Cooper,T.B., Chakos,M., Lieberman,J.A., Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder, American journal of psychiatry, 159, 255-262, 2002	Study is in adults
Volpato,A.M., Zugno,A.I., Quevedo,J., Recent evidence and potential mechanisms underlying weight gain and insulin resistance due to atypical antipsychotics, Revista Brasileira de PsiquiatriaRev.Bras.Psiquiatr., 35, 295-304, 2013	Narrative review.

Study	Reason for Exclusion
Wang,J., Hu,M., Guo,X., Wu,R., Li,L., Zhao,J., Cognitive effects of atypical antipsychotic drugs in first-episode drug-naive schizophrenic patients, Neural Regeneration Research, 8, 277-286, 2013	No relevant outcomes.
Washida,K., Takeda,T., Habara,T., Sato,S., Oka,T., Tanaka,M., Yoshimura,Y., Aoki,S., Efficacy of second-generation antipsychotics in patients at ultra-high risk and those with first-episode or multi-episode schizophrenia, Neuropsychiatric Disease and Treatment.9 (pp 861-868), 2013.Date of Publication: 2013., -868, 2013	No relevant results by type of antipsychotic received.
Watanabe,J., Suzuki,Y., Fukui,N., Ono,S., Sugai,T., Tsuneyama,N., Someya,T., Increased risk of antipsychotic-related QT prolongation during nighttime: a 24-hour holter electrocardiogram recording study, Journal of clinical psychopharmacology, 32, 18-22, 2012	Study is in adults
Weiser,M., Shneider-Beeri,M., Nakash,N., Brill,N., Bawnik,O., Reiss,S., Hocherman,S., Davidson,M., Improvement in cognition associated with novel antipsychotic drugs: A direct drug effect or reduction of EPS?, Schizophrenia Research, 46, 81-89, 2000	Study is in adults.
Werner,F.-M., Covenas,R., Safety of antipsychotic drugs: Focus on therapeutic and adverse effects, Expert Opinion on Drug Safety.13 (8) (pp 1031-1042), 2014.Date of Publication: August 2014., 1031-1042, 2014	Narrative review
Wiguna,T., Guerrero,A.P.S., Honjo,S., Ismail,I., Noorhana,S.W.R., Kaligis,F., Executive dysfunction among children with antipsychotic treated schizophrenia, Clinical Psychopharmacology and Neuroscience.12 (3) (pp 203-208), 2014.Date of Publication: 01 Dec 2014., 203-208, 2014	Study does not present an analysis by type of antipsychotic received
Wong,M.M., Extent of weight gain in patients with first-episode psychotic disorders after one year of antipsychotic treatment in Hong Kong, East Asian Archives of Psychiatry, 20, 57-61, 2010	Subjects aged 14-59 years, mean >25, no subgroup analysis by age.
Wu,R.R., Zhao,J.P., Liu,Z.N., Zhai,J.G., Guo,X.F., Guo,W.B., Tang,J.S., Effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia, Psychopharmacology, 186, 572-578, 2006	Study is in adults
Wu,R.R., Zhao,J.P., Zhai,J.G., Guo,X.F., Guo,W.B., Sex difference in effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia, Journal of clinical psychopharmacology, 27, 374-379, 2007	Study is in adults.
Wu,X.L., Wang,J.H., Hu,S.H., Tao,J., Serum prolactin levels and the acute-phase efficacy in drug-naive schizophrenia treated with	Comparator not met (ziprasidone which is not licensed for use in the UK)

Study	Reason for Exclusion
ziprasidone and olanzapine (translated version). [Chinese, English], East Asian Archives of Psychiatry.22 (1) (pp 3-11), 2012.Date of Publication: March 2012., 3-11, 2012	
Wudarsky,M., Nicolson,R., Hamburger,S.D., Spechler,L., Gochman,P., Bedwell,J., Lenane,M.C., Rapoport,J.L., Elevated prolactin in pediatric patients on typical and atypical antipsychotics, Journal of child and adolescent psychopharmacology, 9, 239-245, 1999	Considered as part of the original 2012 review and small sample size - both study arms have only 10 subjects each
Xiang,Y.-T., Chiu,H.F.K., Ungvari,G.S., Correll,C.U., Lai,K.Y.C., Wang,C.-Y., Si,T.-M., Lee,E.H.M., He,Y.-L., Yang,S.-Y., Chong,M.-Y., Kua,E.-H., Fujii,S., Sim,K., Yong,M.K.H., Trivedi,J.K., Chung,E.-K., Udomratn,P., Chee,K.-Y., Sartorius,N., Tan,C.-H., Shinfuku,N., QTc prolongation in schizophrenia patients in Asia: Clinical correlates and trends between 2004 and 2008/2009, Human Psychopharmacology.30 (2) (pp 94-99), 2015.Date of Publication: March 2015., 94-99, 2015	Study is in adults
Yeh,C.-B., Huang,Y.-S., Tang,C.-S., Wang,L.-J., Chou,W.-J., Chou,M.-C., Chen,C.-K., Neurocognitive effects of aripiprazole in adolescents and young adults with schizophrenia, Nordic Journal of Psychiatry.68 (3) (pp 219-224), 2014.Date of Publication: April 2014., 219-224, 2014	Intervention not as specified in protocol.
Zhang,H.-X., Shen,X.-L., Zhou,H., Yang,X.-M., Wang,H.-F., Jiang,K.-D., Predictors of response to second generation antipsychotics in drug naive patients with schizophrenia: A 1 year follow-up study in Shanghai, Psychiatry Research.215 (1) (pp 20-25), 2014.Date of Publication: 30 Jan 2014., 20-25, 2014	Study is in adults.
Zhang,S., Lan,G., Prospective 8-week trial on the effect of olanzapine, quetiapine, and aripiprazole on blood glucose and lipids among individuals with first-onset schizophrenia, Shanghai Jingshen Yixue, 26, 339-346, 2014	Study is in adults

Appendix G: Evidence tables

Hyperlink to template

G.1 Evidence tables for studies included from update search - direct studies i.e. age ≤18 years

Bibliographic reference	**Authors: Noguera et al 2013** **Title: Twenty-Four Months of Antipsychotic Treatment in Children and Adolescents with Fisst Psychotic Episode**
Study type	Prospective cohort study
Aim	To describe the naturalistic psychopharmacological treatment administered during a 24-month follow up period, as well as discontinuation rates, reasons for discontinuation and adverse effects.
Patient characteristics	• Diagnosis: at baseline were schizophrenia (n=8), schizoaffective disorder (n=5), schizophreniform disorder (n=30), psychotic disorder not otherwise specified (n=42), major depressive disorder with psychotic symptoms (n=12) and bipolar disorder (n=13). At 24 months, the diagnoses of the 83 patients in follow-up were schizophrenia (n=43), schizoaffective disorder (n=5), psychotic disorder not otherwise specified (n=5), major depressive disorder with psychotic symptoms (n=4) and bipolar disorder (n=19). • Diagnostic tool: diagnosis of schizophrenia made based on negative or affective symptoms of more than 6 months duration **Inclusion criteria** • Age between 7 and 17 years at the time of initial evaluation • Presence of positive psychotic symptoms (within a psychotic episode) such as delusions or hallucinations of less than 6 months duration (this short duration of positive psychotic symptoms was established to increase the homogeneity of the sample and to avoid the influence of variables such as prolonged psychopharmacological treatment or extended admission periods). **Exclusion criteria** • Presence of a concomitant Axis I disorder at the time of evaluation that might account for the psychotic symptoms (for instance, substance abuse*, autism spectrum disorders, posttraumatic stress disorder, or acute

Bibliographic reference	Authors: Noguera et al 2013 Title: Twenty-Four Months of Antipsychotic Treatment in Children and Adolescents with Fisst Psychotic Episode

stress disorder)

- Mental retardation according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria including not only an IQ below 70 but also impaired functioning, pervasive developmental disorder, neurological disorders, history of head trauma with loss of consciousness and pregnancy

*****Occasional substance use was not an exclusion criterion if positive symptoms persisted for more than 2 weeks after a negative urine drug test.

Baseline characteristics

	Quetiapine	Risperidone	Olanzapine
Gender, % male	69%	65%	78%
Age in years at time of trial, mean (SD)	16.4 (1.6)	15.2 (2)	15.6 (1.2)
Ethnicity	Not reported	Not reported	Not reported
Mean duration of disorder	Not reported	Not reported	Not reported
Mean age of onset	Not reported	Not reported	Not reported
Prior antipsychotic use	Subjects were assigned to various treatments arms according to the treatment they were receiving at the time of enrolment (n=56). Remaining were drug naïve and decision to intiate treatment taken by physician.		
Concomitant treatment % with antidepressants % with anxiolytics % with mood stabilisers	 25 31 25	 12 35 2	 17 50 11
Substance misuse % with tobacco use % with cannabis % with cannabis and other drugs % with alcohol % with alcohol and lysergic acid diethylamide	Percentages are across all groups 31 19 9 4.5 0.9		

Number of Patients	Total of 110 patients at baseline, 83 at 24 months follow up

Bibliographic reference	**Authors: Noguera et al 2013** **Title: Twenty-Four Months of Antipsychotic Treatment in Children and Adolescents with Fisst Psychotic Episode**
	At baseline Quetiapine: n=16; Risperidone: n= 51; Olanzapine: n=18 (16 further subjects received combined antipsychotics and 6 received 'others') At 6 months* Quetiapine: n=20; Risperidone: n= 36; Olanzapine: n=16 *Numbers have increased in certain arms of the study as subjects were allowed to change treatment during the course of the study.
Intervention	**Olanzapine,** mean (SD)**:** at 6 months 11.7mg/d (7.6), at 12 months 9.7mg/d (6), at 24 months 11.4mg/d (7.2)
Comparison	**Quetiapine,** mean (SD): at 6 months 614.5 (454.2), at 12 months 567.9 (327.9), at 24 months 400 (305.5) **Risperidone,** mean (SD): at 6 months 3.1 (1.3), at 12 months 2.9 (1.5), at 24 months 3 (2.3) * Subjects were assigned to various treatments arms according to the treatment they were receiving at the time of enrolment (n=56). Remaining patients were drug naïve and the decision to initiate treatment was taken by the physician. Median dose (SD) at baseline for those already on treatment: Olanzapine: median dose – at baseline 10mg/d (SD: 5.07), Quetiapine: median dose – at baseline 245.94mg/d (SD: 195.44), Risperidone: median dose – 3.57mg/d (SD: 1.60),
Length of follow up	24 months
Location	Spain
Outcomes measures and effect size	**1) Metabolic side effects** <u>BMI increase at 6 months, mean (SD)</u> Quetiapine: 2.5 (2.1), n=20 Risperidone: 1.8 (2.3), n=36 Olanzapine: 4.3 (1.9), n=16 **2) Neurological side effects**

Bibliographic reference	Authors: Noguera et al 2013 Title: Twenty-Four Months of Antipsychotic Treatment in Children and Adolescents with Fisst Psychotic Episode
	- Assessed by the UKU scale in this study At 6 months, mean (SD) Quetiapine: 0.5 (0.7), n=20 Risperidone: 1.2 (2.1), n=36 Olanzapine: 0.3 (0.8), n=16 **3) Hormonal side effects** Not reported **4) Cardiac side effects** Not reported **5) Leaving the study early for any reason including mortality** At 6 months, n/N (%) Quetiapine: 4/16 (25) – reasons included adverse reaction (n=1), insufficient response (n=1), Not available (n=1), Lost to follow up (n=1) Risperidone: 22/51 (43.1) – reasons included adverse reaction (n=5), insufficient response (n=11), Other (n=1), Not available (n=1), Lost to follow up (n=4) Olanzapine: 8/18 (44.4) – reasons included adverse reaction (n=2), insufficient response (n=5), Lost to follow up (n=1) **6) Quality of life** Not reported **7) Developmental progress eg; school performance** Not reported

Bibliographic reference	**Authors: Noguera et al 2013** **Title: Twenty-Four Months of Antipsychotic Treatment in Children and Adolescents with Fisst Psychotic Episode**
Source of funding	Grant from the Carlos III Institute of Health, Spanish Department of Health, Cooperative Research Thematic Network and from the Spanish Ministry of Science and Innovation
Comments	**Allocation to treatment groups:** participants were assigned to various treatment arms according to the treatment they were receiving at the time of enrolment (n=56). The remaining patients were drug naïve and the decision to initiate treatment was taken by the physician. **Blinding:** not described **Evaluation of adverse effects:** UKU effect rating scale administered, weight measured in kilograms, BMI calculated in kilograms per meter squared. **Other:** heterogeneous sample of diagnoses (not reported by treatment arms), occasional substance use, concomitant medications allowed, subjects were allowed to change treatment during the course of the study. Unclear whether doses stated are medians or means as text says medians but table states means. Data at 12 and 24 months not extracted as >50% attrition from one or more arms.

1

Bibliographic reference	**Authors: Carbon 2015** **Title: Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 'second generation' antipsychotics**
Study type	Prospective cohort study
Aim	To quantify extrapyramidal side effects (EPS) and to identify risk profiles for treatment emergent EPS in youth treated with 'second generation' antipsychotics (SGAs)
Patient characteristics	• Diagnosis

	Aripiprazole	Olanzapine	Quetiapine	Risperidone
Mood spectrum disorders (MDD, BD, Mood disorder NOS), %	40.9	50	60.61	42.34
Schizophrenia spectrum disorders (schizophrenia, schizophreniform, schizoaffective disorder, psychotic disorder NOS), %	25.76	27.59	15.15	30.66

Bibliographic reference	Authors: Carbon 2015 Title: Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 'second generation' antipsychotics

Aggression spectrum disorder (ASD, OCD, CD), %	33.33	22.41	24.24	27.01

- Diagnostic tool: not reported

Inclusion criteria

- Children and adolescents aged 4 to 19 years who were initiating antipsychotic treatment based on clinician/family choice provided that baseline assessments occurred within 7 days of the current antipsychotic treatment

Exclusion criteria

- Baseline use of anticholinergic medication
- Tourette syndrome/tic disorder
- Catatonia
- Antipsychotic switch explicitly because of EPS
- Data from patients with sequential antipsychotic treatment trials were restricted to the first one

Baseline characteristics

	Aripiprazole	**Olanzapine**	**Quetiapine**	**Risperidone**
Gender, % male	66.7	67.24	42.42	59.85
Age in years at time of trial, mean (SD)	12.97 (3.41)	14.21 (3.26)	13.3 (3.15)	13.71 (3.74)
Ethnicity, % non-white	50	58.62	59.09	54.01
Mean duration of disorder	Not reported	Not reported	Not reported	Not reported
Mean age of onset	Not reported	Not reported	Not reported	Not reported
Antipsychotic naïve, %	55.55	70.69	53.03	81.75

Bibliographic reference	**Authors: Carbon 2015** **Title: Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 'second generation' antipsychotics**

Antipsychotic history ≥1 month of SGA, %	19.7	20.69	18.18	12.41
Antipsychotic switch, %	25.76	8.62	28.79	5.84
Comedications, %				
Psychostimulants	21.21	15.52	28.79	21.32
Antidepressants	25.76	17.24	33.33	30.66
Mood stabiliser	21.21	43.10	46.97	25.55
Cormorbidities, %				
ADHD	40.91	43.94	43.94	41.61
OCD	4.55	5.17	6.06	5.11
SUD	9.09	22.41	12.12	18.25
Substance use, %	Not reported	Not reported	Not reported	Not reported
Inpatients, %	51.52	86.21	68.18	67.88

Number of Patients	N=342 in total across 5 study arms (only 4 arms relevant to this question): Aripiprazole: n=66 Olanzapine: n= 58 Quetiapine: n=66 Risperidone: n=137
Intervention	**Olanzapine** Dose at week 12, mean (SD): 9.68 (6.85)
Comparison	**Aripiprazole** Dose at week 12, mean (SD): 11.76 (7.39) **Quetiapine** Dose at week 12, mean (SD): 231.9 (184.3) **Risperidone:** Dose at week 12, mean (SD): 1.38 (1.17)

Bibliographic reference	**Authors: Carbon 2015** **Title: Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 'second generation' antipsychotics**
Length of follow up	12 weeks
Location	USA
Outcomes measures and effect size	**1) Metabolic side effects** Not reported **2) Neurological side effects** a) parkinsonism – defined as patients fulfilling 1 or more of the following criteria: mean Simpson Angus Scale (SAS) score >0.33 in patients with baseline mean SAS ≤0.33; start of anticholinergic medication; or marked increase of total SAS ratings of ≥2 in patients with baseline positive rating for EPS At baseline Aripiprazole, n/N (%): 6/66 (9.09) Olanzapine, n/N (%): 0/58 (0) Quetiapine, n/N (%): 3/66 (4.55) Risperidone, n/N (%): 5/137 (3.65) At 12 weeks – drug induced parkinsonism Aripiprazole, n/N (%): 13/49 (26.53) Olanzapine, n/N (%): 4/51 (7.85) Quetiapine, n/N (%): 1/50 (2) Risperidone, n/N (%): 7/101 (6.93) b) Dyskinesia – defined as treatment emergent dyskinesia in patients without dyskinesia in a prior rating, or as an increase of ≥2 on AIMS (the abnormal involuntary movement scale) total rating in patients with dyskinesia at baseline At baseline Aripiprazole, n/N (%): 7/66 (10.77) Olanzapine, n/N (%): 4/58 (6.90) Quetiapine, n/N (%): 6/66 (9.38) Risperidone, n/N (%): 6/137 (9.38) At 12 weeks

Bibliographic reference	Authors: Carbon 2015 Title: Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 'second generation' antipsychotics
	Aripiprazole, n/N (%): 0/49 (0) Olanzapine, n/N (%): 3/51 (5.88) Quetiapine, n/N (%): 2/50 (4) Risperidone, n/N (%): 1/101 (0.98) c) Akathisia – defined as a rating of >1 on the BARNES Akathisia Rating Scale (BARS) <u>At baseline</u> Aripiprazole, n/N (%): 0/66 (0) Olanzapine, n/N (%): 0/58 (0) Quetiapine, n/N (%): 0/66 (0) Risperidone, n/N (%): 2/137 (1.46) <u>At 12 weeks</u> Aripiprazole, n/N (%): 3/49 (6.25) Olanzapine, n/N (%): 2/51 (4) Quetiapine, n/N (%):0/50 (0) Risperidone, n/N (%): 2/101 (2.06) **3) Hormonal side effects** Not reported **4) Cardiac side effects** Not reported **5) Leaving the study early for any reason including mortality** Reported as discontinuation due to extrapyridamal side effect, n (%) Aripiprazole: 4/66 (6.15) Olanzapine: 1/58 (1.72) Quetiapine: 0/66 (0) Risperidone: 6/137 (4.48)

Bibliographic reference	**Authors: Carbon 2015** **Title: Neuromotor adverse effects in 342 youth during 12 weeks of naturalistic treatment with 5 'second generation' antipsychotics**
	6) Quality of life Not reported **7) Developmental progress eg; school performance** Not reported
Source of funding	Not reported
Comments	**Allocation to treatment groups:** subjects initiated antipsychotics based on clinical decisions made by their treating physicians unrelated to the study team. **Blinding:** described as not blinded **Evaluation of adverse effects:** Simpson Angus Scale, Abnormal Involuntary movement scale and the Barnes Akathisia Rating scale used to assess neuromotor adverse effects. **Other:** Heterogeneous sample of diagnoses, cormorbidities, comedications. 50% or more subjects from each treatment arm were inpatients. Unbalanced groups at baseline in terms of neurological side effects.

1

Bibliographic reference	**Authors: Arango 2014** **Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients**
Study type	Prospective cohort study
Aim	To assess weight gain and metabolic effects of 6 months of treatment with 'second generation' antipsychotics in naïve/quasi-naïve youths
Patient characteristics	• Diagnosis: psychiatric diagnosis other than a primary eating disorder

	Risperidone	**Olanzapine**	**Quetiapine**
Schizophrenia spectrum, %	31.37	34.88	46.67
Mood spectrum disorders, %	22.22	39.53	46.67
Behavioural disorders, %	27.45	11.63	0
Other diagnoses, %	18.95	13.95	6.67

Bibliographic reference	Authors: Arango 2014 Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients

- Diagnostic tool: DSM-IV

Inclusion criteria

- 4 to 17 years
- ≤30 days of lifetime exposure to SGAs
- DSM-IV psychiatric diagnosis other than a primary eating disorder

Exclusion criteria

- Not completing a post-baseline visit

Baseline characteristics

	Risperidone	Olanzapine	Quetiapine
% male	64.33	63.64	53.19
Age in years at time of trial, mean (SD)	14.03 (3.25)	15.36 (1.81)	15.74 (1.63)
Ethnicity, % white	84.71	93.18	89.36
Mean duration of disorder	Not reported	Not reported	Not reported
Mean age of onset	Not reported	Not reported	Not reported
Antipsychotic naïve, %	50.96	31.82	51.06
Prior antipsychotic use in quasi-naïve patients, mean number of days (SD)	9.67 (7.22)	10.37 (6.18)	9.38 (6.63)
Concomitant treatment % with antidepressants % with benzodiazepines % with mood stabilizers % with stimulants	 8.92 25.48 12.10 5.00	 31.82 40.91 15.91 0.00	 23.91 26.09 15.22 0.00
Substance misuse			

Bibliographic reference	**Authors: Arango 2014** **Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients**
	Tobacco use, % 36.31 37.14 35 Alcohol use, % 29.30 27.91 29.8 Cannabis use % 32.05 29.55 44.68 Inpatients, % Overall, 72% hospitalised and 28% outpatients.
Number of Patients	N=328 eligible; 303 consented to take part; 9 did not complete a post-baseline visit therefore data for 279 subjects were analysed Of the 279 subjects, treatment arms at baseline was as follows: Risperidone: n=157 Olanzapine: n=44 Quetiapine: n=47 Other: n=31
Intervention	**Olanzapine** Mean cumulative dose (SD), mg/day: 143.52 (137.77)
Comparison	**Risperidone** Mean cumulative dose (SD), mg/day: 91.5 (140.44), **Quetiapine** Mean cumulative dose (SD), mg/day: 78 (133.92)
Length of follow up	6 months
Location	Spain
Outcomes measures and effect size	**1) Metabolic side effects** a) Glucose changes i. Hyperglycemia (≥100-125mg/dl), n(%) Risperidone – 3 months: 10 (8*); N=118 Olanzapine – 3 months: 6 (17*), N=35 Quetiapine – 3 months: 2 (6*), N=32 ii. Diabetes (≥126mg/dl), n (%)

Bibliographic reference	Authors: Arango 2014 Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients
	Risperidone – 3 months: 2 (2*); N=118 Olanzapine – 3 months:0 (0*); N=35 Quetiapine – 3 months: 0 (0*); N=32 iii) Mean change in fasting glucose, mg/dl (95%CI) Risperidone – baseline to 3 months: 4.93 (1.94 to 7.92); SD**: 16.4; N=118 Olanzapine – baseline to 3 months: 3.47 (-1.60 to 8.53); SD**: 14.74; N=35 Quetiapine – baseline to 3 months: -4.36 (-10.19 to 1.47); SD**: 16.17; N=32 *percentages re-calculated by analyst as those reported in study do not match up with N reported in study **CIs converted into SDs by analyst b) Mean change in fasting cholesterol changes i. Hypercholesterolemia (≥170mg/dl), n(%) Risperidone – 3 months: 45 (38*); N=118 Olanzapine – 3 months: 18 (51*); N=35 Quetiapine – 3 months: 12 (38*); N=32 ii. Mean total fasting cholesterol, mg/dl (95%CI) Risperidone – baseline to 3 months: 8.30 (2.90 to 13.70); SD**: 29.62; N=118 Olanzapine – baseline to 3 months: 12.04 (2.89 to 21.19); SD**: 26.64; N=35 Quetiapine – baseline to 3 months: 9.63 (-0.88 to 20.15); SD**: 29.16; N=32 *percentages re-calculated by analyst as those reported in study do not match up with N reported in study **CIs converted into SDs by analyst c) Fasting triglycerides changes i. Hypertriglyceridemia (≥110mg/dl) Risperidone – 3 months: 18 (15*); N=118 Olanzapine – 3 months: 12 (34*); N=35 Quetiapine – 3 months: 7 (22*); N=32

Bibliographic reference	Authors: Arango 2014 Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients
	ii.) Mean fasting triglycerides, mg/dl (95%CI) Risperidone – baseline to 3 months: 5 (-3.40 to 13.20); SD**: 45.53; N=118 Olanzapine – baseline to 3 months: 20.99 (6.89 to 35.08); SD**: 41.03; N=35 Quetiapine – baseline to 3 months: 0.14 (-5.40 to 15.69); SD**; 29.25; N=32 *percentages re-calculated by analyst as those reported in study do not match up with N reported in study **CIs converted into SDs by analyst d) Weight changes i. ≥7% weight increase, n (%) Risperidone – baseline to 3 months: 74 (63*); N=118 Olanzapine – baseline to 3 months: 28 (80*); N=35 Quetiapine – baseline to 3 months: 22 (69*); N=32 ii. Mean change in BMI (95%CI) Risperidone – baseline to 3 months: 1.80 (1.44 to 2.15); SD**: 1.95; N=118 Olanzapine – baseline to 3 months: 2.96 (2.32 to 3.60); SD**: 1.86; N=35 Quetiapine – baseline to 3 months: 1.81 (1.08 to 2.53); SD**: 2.01; N=32 *percentages re-calculated by analyst as those reported in study do not match up with N reported in study **CIs converted into SDs by analyst **2) Neurological side effects** Not reported **3) Hormonal side effects** Not reported **4) Cardiac side effects** a) Blood pressure changes

Bibliographic reference	Authors: Arango 2014 Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients
	i. Systolic blood pressure >90th percentile, n (%) Risperidone – 3 months: 28 (24*); N=118 Olanzapine – 3 months: 4 (11*); N=35 Quetiapine – 3 months: 3 (9*); N=32 ii. Mean change in diastolic blood pressure, mmHg (95%CI) Risperidone – baseline to 3 months: 1.45 (-0.44 to 3.35); SD**: 10.39; N=118 Olanzapine – baseline to 3 months: -4.25 (-8.34 to -0.15); SD**: 11.92; N=35 Quetiapine – baseline to 3 months: -5.31 (-9.71 to -0.91); SD**: 12.2; N=32 iii. Mean change in systolic blood pressure, mmHg (95%CI) Risperidone – baseline to 3 months: 2.29 (-0.46 to 5.05); SD**: 15.11; N=118 Olanzapine – baseline to 3 months: 0.20 (-5.73 to 6.13); SD**: 17.26; N=35 Quetiapine – baseline to 3 months: -3.87 (-10.24 to 2.50); SD**: 17.67; N=32 *percentages re-calculated by analyst as those reported in study do not match up with N reported in study **CIs converted into SDs by analyst **5) Leaving the study early for any reason including mortality** Risperidone Up to 3 months: n/N=39/157 (lost to follow up n=17, drug withdrawal n=4, nonadherence n=2, lack of efficacy n=1, symptom remission n=2, change of treatment n=8, other reasons n=5) Between 3 to 6 months: n/N=36/118 (lost to follow up n=18, drug withdrawal n=3, nonadherence n=2, lack of efficacy n=1, symptom remission n=6, change of treatment n=6) Olanzapine Up to 3 months: n/N=9/44 (lost to follow up n=2, symptom remission n=5, change of treatment n=1, intolerance n=1) Between 3 to 6 months: n/N=14/35 (lost to follow up n=6, symptom remission n=4, change of treatment n=1, drug withdrawal n=3) Quetiapine Up to 3 months: n/N=15/47 (lost to follow up n=7, nonadherence n=1, symptom remission n=2, change of treatment

Bibliographic reference	**Authors: Arango 2014** **Title: 'second generation' antipsychotic use in children and adolescents: a six month prospective cohort study in drug naïve patients**
	n=4, drug withdrawal n=1) Between 3 to 6 months: n/N=6/32 (lost to follow up n=6) **6) Quality of life** Not reported **7) Developmental progress eg; school performance** Not reported
Source of funding	Not reported
Comments	**Allocation to treatment groups:** unclear, it seems subjects carried on with treatment they were receiving at baseline. If a patient was switched to a different antipsychotic or another was added, only the previous visits were included in the analysis. **Blinding:** described as not blinded **Evaluation of adverse effects:** Fasting blood drawn for metabolic factors, BMI calculated as weight in kilograms divided by height in metres squared. **Other:** Heterogeneous sample of diagnoses, comedications and substances use. Percentages and numbers reported in study do not match in all cases as denominators are not clearly reported – these have therefore been re-calculated by analyst based on N reported in figure 1 of study at different time points. **Reported but not extracted:** data at 6 months as greater than 50% attrition from one or more arms.

G.2 Evidence tables for studies included from original guideline - direct studies i.e. age ≤18 years

1

Bibliographic reference	**Authors: Sikich et al 2004** **Title: A pilot study of risperisone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial**
Study type	RCT Randomisation stratified by age
Aim	To estimate the acute antipsychotic effect size and side effects of risperidone and olanzapine in the paediatric population, in comparison with haloperidol
Patient characteristics	Recruited from in-patient and outpatients throughout North Carolina, November 1997 to May 2001 • Diagnosis: - Entire sample - schizophrenia spectrum 52%, affective disorders 48% - Risperidone – schizophrenia spectrum 68%, affective disorders 32% - Olanzapine – schizophrenia spectrum 31%, affective disorders 69%. • Diagnostic tool: based on medical record review, detailed clinical examination by a child psychiatrist and a structured diagnostic interview administered by social workers or a psychiatric nurse specialist, all with extensive child psychiatry experience **Inclusion criteria** • ≥1 positive psychiatric symptom of moderate or greater severity on the Brief Psychiatric Rating Scale for Children (BPRS-C) present throughout the past 2weeks • Full scale IQ greater than 69 **Exclusion criteria** • Psychotic symptoms that appeared to result from acute substance intoxication or withdrawal, history of serious adverse reactions or nonresponse to an adequate trial of any of the study medications during this psychotic episode • Prior diagnosis of a pervasive developmental disorder, serious medical or neurological disorder, pregnancy or refusal to practice contraception, imminent risk of harm to self or others **Baseline characteristics**

	Risperidone	**Olanzapine**
Gender, n (%)	13 (68)	9 (56)
Age in years at time of trial, mean	14.6 (2.9)	14.6 (3.1)

Bibliographic reference	**Authors: Sikich et al 2004** **Title: A pilot study of risperisone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial**

(SD)		
Ethnicity, n Caucasian (%)	9 (47)	10 (63)
Mean duration of disorder	Not reported	Not reported
Mean age of onset	Not reported	Not reported
Prior antipsychotic use, n (%) Classical antipsychotic Atypical antipsychotic Prior antidepressant Prior mood stabiliser	 5 (26) 12 (63) 9 (47) 5 (26)	 1 (6) 7 (44) 8 (50) 4 (25)
Substance use, %	Not reported	Not reported
Concomitant medication, n (%) Benztropine Amantadine Propranolol Lorazepam Initial antidepressant Mood stabiliser at trial's end	 4 (21) 2 (11) 1 (5) 2 (11) 5 (26) 3 (16)	 5 (31) 0 (0) 2 (13) 1 (7) 5 (31) 1 (6)
Comorbidities*	Not reported	Not reported

*Comorbidities: numbers not reported however individuals with comorbid diagnoses of post-traumatic stress disorder were permitted only of majority of psychotic symptoms appeared unrelated to the to the PTSD. Individuals with current or recent diagnosis of ADHD, Tourette's syndrome, or OCD or past history of substance abuse or dependence were allowed if their psychotic symptoms were not better accounted for by the comorbid disorder.

Number of Patients			
		Olanzapine	**Risperidone**
	Number randomised	16	19

Intervention	Olanzapine 2.5 to 12.5mg in 2.5mg increments Doses titrated to a moderate target dose, over 1 to 2weeks (slower titration used if participants had significant side effects). Psychoeducation and supportive psychotherapy provided to all subjects and their families during the course of the study (in-patients also received routine group, recreational and occupational therapies)

<table>
<tr><td>Bibliographic reference</td><td>Authors: Sikich et al 2004
Title: A pilot study of risperisone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial</td></tr>
<tr><td>Comparison</td><td>Risperidone 0.5 to 3mg in 0.5mg increments

Doses titrated to a moderate target dose, over 1 to 2weeks (slower titration used if participants had significant side effects).</td></tr>
<tr><td>Length of follow up</td><td>Treatment period 8weeks, weekly visits (those who responded were eligible to continue for an additional 12weeks)</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Outcomes as specified in review protocol:

1) Metabolic side effects, mean (SD)

Risperidone (n=19)
<table>
<tr><th>Measure</th><th>Baseline</th><th>Week 8 or end point</th></tr>
<tr><td>Weight (kg)</td><td>61.3 (23)</td><td>66.2 (23.4)</td></tr>
<tr><td>BMI (kg/m2)</td><td>22.9 (7.3)</td><td>24.5 (6.9)</td></tr>
<tr><td>Glucose (mg/dL) – random glucose test not fasting</td><td>86.9 (17.8)</td><td>79.0 (19.8)</td></tr>
<tr><td>HDL (mg/dL)</td><td>49.0 (10.3)</td><td>49.7 (15.2)</td></tr>
<tr><td>LDL (mg/dL)</td><td>96.0 (21.1)</td><td>98.9 (26.5)</td></tr>
<tr><td>Triglycerides (mg/dL)</td><td>116 (68)</td><td>114 (70)</td></tr>
</table>

Olanzapine (n=16)
<table>
<tr><th>Measure</th><th>Baseline</th><th>Week 8 or end point</th></tr>
<tr><td>Weight (kg)</td><td>66.7 (26.1)</td><td>73.9 (26.2)</td></tr>
<tr><td>BMI (kg/m2)</td><td>23.5 (6.1)</td><td>25.9 (6.0)</td></tr>
<tr><td>Glucose (mg/dL)</td><td>87.2 (10.8)</td><td>97.2 (14.4)</td></tr>
<tr><td>HDL (mg/dL)</td><td>52.0 (13.7)</td><td>44.5 (13.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Authors: Sikich et al 2004 Title: A pilot study of risperisone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial

LDL (mg/dL)	78.7 (34.0)	86.3 (27.7)
Triglycerides (mg/dL)	116 (75)	142 (62)

2) Neurological side effects, mean (SD) unless otherwise stated

Risperidone (n=19)

Measure	Baseline	Week 8 or end point
Simpson- angus EPS	2.8 (4.1)	2.1 (2.2)
Akathisia, n (%)	4 (21)	0 (0)

Olanzapine (n=16)

Measure	Baseline	Week 8 or end point
Simpson- angus EPS	1.6 (2.0)	1.9 (2.4)
Akathisia, n (%)	5 (31)	2 (14)

3) Hormonal side effects, mean (SD)

Risperidone (n=19)

Measure	Baseline	Week 8 or end point
Prolactin (ng/mL)	34.1 (21.1)	37.2 (19.8)

Olanzapine (n=16)

Measure	Baseline	Week 8 or end point
Prolactin (ng/mL)	31.5 (25.8)	30.0 (12.9)

Bibliographic reference	Authors: Sikich et al 2004 Title: A pilot study of risperisone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial

4) Cardiac side effects, mean (SD)

Risperidone (n=19)

Measure	Baseline	Week 8 or end point
QTc (ms)	399 (29)	402 (25)

Olanzapine (n=16)

Measure	Baseline	Week 8 or end point
QTc	408 (20)	402 (23)

5) Leaving the study early for any reason including mortality

	Risperidone (n=19) (week of withdrawal)	Olanzapine (n=16) (week of withdrawal)
Insufficient response	2 (3,7)	2 *(1,5)
EPS	1 (1)	0
Weight gain	3 (4,6,7)	0
Other side effects	1 (3)	0
Noncompliance	2 (4,6)	0
Moved to remote site	1 (4)	0
Total withdrawals	9 – 47%	2 *(1,5) – 13%

*= subject withdrew because of insufficient response and intolerable side effects.

6) Quality of life

Not reported

7) Developmental progress eg; school performance

Not reported

Source of funding	NIMH grant, UNC-Mental Health and Neuroscience Clinical Research Centre, NIH grant from the General Clinical

Bibliographic reference	**Authors: Sikich et al 2004** **Title: A pilot study of risperisone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial**
	Research Centres, Janssen Pharmaceutica, Eli Lilly Company, the Foundation of Hope
Comments	**Randomisation:** Computer generated randomisation stratified by age (8-11 years or ≥12 years) to ensure younger children who might have different metabolism or adverse reactions were equally represented in all treatment groups. **Allocation concealment:** Not described **Blinding:** Described as 'double blind' – further details not specified. **Evaluation of adverse effects:** Acute EPS evaluated using a modification of the Simpson Angus Extrapyramidal Symptoms Scale. Tardive dyskinesia assessed at baseline and termination using the Abnormal Involuntary Movement Scale. BMI calculated as weight in kg/height in m^2. Metabolic factors, prolactin ad cardiac rhythm assessed at baseline and termination. It was not possible to consistently obtain labs at the same time of the day or in a fasting state. **Other:** Differences in the diagnoses of participants in the different treatment groups, use of concomitant medications and fewer than intended sample due to recruitment issues **Reported but not extracted the following subjective side effects**: sedation, blurry vision, dry mouth, urinary retention, nervousness, headache, drooling, irregular menses, light headedness, nausea, weakness, constipation, chest pain, decreased coordination, dysuria, itching, musculoskeletal pain, rash, sweats/chills, vomiting.

1

2

3

Bibliographic reference	**Authors: Shaw et al 2006** **Title: Childhood-onset schizophrenia: a double blind randomised clozapine-olanzapine comparison**
Study type	RCT, double-blind (randomisation via random-number charts, in blocks of 4; allocation concealed until study number assignment)
Aim	To compare and examine the efficacy and safety of olanzapine and clozapine among children and adolescents with childhood-onset schizophrenia
Patient characteristics	Recruited nationally, January 1998 to June 2005 • Diagnosis: schizophrenia • Diagnostic tool: on the basis of review of medical and school records, interview with child and parents, administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children

Bibliographic reference	**Authors: Shaw et al 2006** **Title: Childhood-onset schizophrenia: a double blind randomised clozapine-olanzapine comparison**

Inclusion criteria

- 7 to 16years, meeting unmodified DSM-IV criteria for schizophrenia, onset before 13years
- Resistant to treatment with ≥2 antipsychotics
- IQ >70, no history of progressive neurological or medical disorders, failure to respond to 2 antipsychotic medications

Exclusion criteria

- Non-response to an adequate trial of clozapine or olanzapine,

Baseline characteristics

	Clozapine (n=12)	**Olanzapine (n=13)**
Gender, n male (%)	8/12	7/13
Age in years at time of trial, mean (SD)	11.7 (2.3)	12.8 (2.4)
Ethnicity, n White Black Other	 7 3 2	 7 4 2
Age at onset of symptoms, mean (SD)	8.6 (2.7)	9.5 (2.2)
Duration of psychosis in years before trial entry, mean (SD)	3.1 (1.9)	3.3 (3.0)
Prior antipsychotic use, mean (SD) Typical Atypical	 1.25 (1.2) 2.75 (1.3)	 1.15 (1.1) 2.31 (0.9)
Past exposure to olanzapine, n (%)	9 (75)	6 (46)
Past exposure to clozapine, n (%)	3 (25)	4 (31)
Comorbid ADHD, ODD, CD, n (%)	4 (33)	3 (23)
Comorbid anxiety disorders	6 (50)	1 (8)
Concomitant medications, n		

Bibliographic reference	**Authors: Shaw et al 2006** **Title: Childhood-onset schizophrenia: a double blind randomised clozapine-olanzapine comparison**

Valproate sodium	0	2
Clomipramine hydrochloride	0	1
Guanfacine hydrochloride	1	0
Lorazepam	2	3
Diphenydramine hydrochloride	4	6
Substance use, %	Not reported	Not reported
Inpatients, %	100	

Number of Patients

	Clozapine	**Olanzapine**
Number randomised	12	13

Intervention

On admission all medication dosages were tapered during a 1 to 4week period, then medication free for up to 3weeks

Olanzapine 5mg increased to 15mg

Further increases guided by clinical judgement to a maximum of olanzapine 20mg and clozapine 300mg
After the double-blind trial patients were offered an open trial of second medication if nonresponse to trial medication was evident .

Children received up to 4hours/per of specialised education and recreational and occupational therapy in addition to nursing care.

Comparison

Clozapine 12.5mg increased to 150mg

Length of follow up

8week trial, 2year open-label follow-up

Location

USA

Outcomes measures and effect size

Outcomes as specified in review protocol:

1) Metabolic side effects

Measure	**Clozapine**	**Olanzapine**
Weight gain (kg) mean (SD)	+3.8 (6.0), n=12	+3.6 (4.0), n=13

Bibliographic reference	**Authors: Shaw et al 2006** **Title: Childhood-onset schizophrenia: a double blind randomised clozapine-olanzapine comparison**

Change in BMI in kg/m^2, mean (SD)	+1.6 (2.5), n=12	+1.4 (1.6), n=13

2) Neurological side effects

Not extracted as medians (ranges) presented without means, standard deviations, or 95% confidence intervals, so no effect sizes could be extracted or calculated.

3) Hormonal side effects

Not reported

4) Cardiac side effects

Measure	Clozapine	Olanzapine
Hypertension, n/N	7/11	1/11
Tachycardia (>100 bpm (supine), n/N	7/10	2/12
Tachycardia (>120 bpm (supine), n/N	1/10	0/12

5) Leaving the study early for any reason including mortality

Unclear how many subjects dropped out during 8 week trial, at 2 year follow up – 8/10 subjects in olanzapine arm for who follow up data were obtained dropped out and changed to clozapine due to treatment resistance. 1/10 subjects in clozapine arm discontinued due to extreme weight gain.

6) Quality of life

Not reported

7) Developmental progress eg; school performance

Not reported

Source of funding	Not reported
Comments	**Randomisation:** Random allocation using a random number chart in blocks of 4 **Allocation concealment:** Numbered containers were used to implement the random allocation sequence which were concealed until study subject number assignment

Bibliographic reference	Authors: Shaw et al 2006 Title: Childhood-onset schizophrenia: a double blind randomised clozapine-olanzapine comparison
	Blinding: Double blind – participants and those administering and assessing intervention and assessing outcomes were blind to the randomisation scheme. **Evaluation of adverse effects:** All observed or volunteered adverse events were collected on a weekly basis by a physician blind to treatment status using the Subjective Treatment Emergent Symptoms scale. Extrapyramidal adverse effects and other abnormal movements were recorded using the Abnormal Involuntary Movements Scale and the Simpson Angus Scale. BMI calculated before study entry and at completion. Cardiac parameters included the development of hypertension defined as 3 readings above the 95% percentile for systolic or diastolic blood pressure for the same age and height percentile group and tachycardia (mild defined as >100 and moderate as >120 beats/min on 3 readings). **Other:** Use of concomitant medications and comorbidities present. Study powered to detect differential treatment effect sizes of 1.2 with 80% power and α of 0.05 (with 12 patients in each treatment arm) **Reported but not extracted the following subjective side effects**: enuresis, increased appetite, hypersalivation, constipation, difficulty concentrating, somnolence, insomnia. Hypertriglyceridemia, hypercholesterolemia and hyperprolactinemia also reported but not extracted as only means (without SDs) reported.

1

2

Bibliographic reference	Authors: Arango 2009 et al Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode
Study type	RCT
Aim	To compare the efficacy, safety and tolerability of olanzapine and quetiapine in adolescents with first episode psychosis
Patient characteristics	• Diagnosis - Olanzapine: schizophrenia (n=9, 34.6%), bipolar disorder (n=5, 19.2%), psychosis NOS (n=4, 33.3%), schizoaffective disorder (n=3, 25%), schizophreniform disorder (n=2, 16.6%), major depressive disorder (n=3, 25%) - Quetiapine: schizophrenia (n=8, 33.3%), bipolar disorder (n=8, 33.3%), psychosis NOS (n=2, 25%), schizoaffective disorder (n=2, 25%), schizophreniform disorder (n=2, 25%), major depressive disorder (n=2, 25%) • Diagnostic tool: K-SADS-PL; DSM-IV **Inclusion criteria** • First episode of psychosis before 18 years, lasting less than 1 year after onset of first symptom

Bibliographic reference	Authors: Arango 2009 et al Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode

- 12 to 18 years old

Exclusion criteria

- Psychotic symptoms appeared to result from acute intoxication or withdrawal
- Meeting DSM-IV criteria for any substance abuse, learning disabilities, or pervasive developmental disorder
- Suffered from any organic central nervous system disorder
- History of traumatic brain injury with loss of consciousness
- Pregnant or breast feeding
- Taking olanzapine or quetiapine before enrolment (use of other antipsychotic drugs other than olanzapine or quetiapine before enrolment was allowed).

Baseline characteristics

	Olanzapine (n=26)	Quetiapine (n=24)
Gender, % male	76	79.2
Age in years, mean (SD)	15.7 (1.4)	16.3 (1.1)
Ethnicity, n (%) Caucasian	20 (76.9)	21 (87.5)
Mean duration of disorder	Not reported	Not reported
Mean age of onset	Not reported	Not reported
Prior Antipsychotic Use, %	30.8	16.7
Antipsychotic naïve prior to inclusion, %	38	63
Comorbidities	Not reported	Not reported
Adjunctive treatment, n (%) Anticholinergics Beta-blockers Benzodiazepines Antidepressants Antiepileptic Lithium	 3 (12.5) 2 (8.3) 14 (58.3) 8 (33.3) 7 (29.2) 6 (25)	 8 (30.8) 1 (3.8) 17 (65.4) 10 (38.5) 7 (26.9) 2 (7.7)

Bibliographic reference	**Authors: Arango 2009 et al** **Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode**

Analgesics	2 (8.3)	0 (0)
Iron compounds	1 (4.2)	0 (0)
Non-steroidal anti-inflammatory drugs	1 (4.2)	0 (0)
Cough medications	1 (4.2)	0 (0)
Substance use, %	Not reported	Not reported
Inpatients, %	100	100

All patients were prescribed risperidone 2-6mg (flexible dose at discretion of clinician)

Number of Patients

	Olanzapine	**Quetiapine**
Number randomised	26	24

Intervention

Olanzapine, mean dose 12.11mg/day (variable dose*), over 6 months.

*Doses were administered at the discretion of the clinician. Mean treatment time for olanzapine was 144.1(62.5) days.

Comparison

Quetiapine, mean dose 438.8mg/day (variable dose*), over 6 months.

*Doses were administered at the discretion of the clinician. Mean treatment time for quetiapine was 143.75(68) days.

Length of follow up

6 months

Location

Madrid Spain

Outcomes measures and effect size

1. Metabolic side effects

n (%) with weight gain

At any point in the study

Olanzapine: 20 (77*) N=26

Quetiapine: 13 (54*) N=24

Bibliographic reference	Authors: Arango 2009 et al Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode
	At end point in the study Olanzapine: 15 (58*) N=26 Quetiapine: 8 (33*) N=24 *percentages and N reported in study do not match up therefore the number randomised has been used as the denominator **2. Neurological side effects as measured with the UKU scale** n (%) with concentration difficulties **At any point in the study** Olanzapine: 18 (69*) N=26 Quetiapine:16 (67*) N=24 **At end point in the study** Olanzapine: 9 (35*) N=26 Quetiapine: 6 (25*) N=24 n (%) with hypokinesia/akinesia **At any point in the study** Olanzapine: 14 (54*) N=26 Quetiapine: 11 (46*) N=24 **At end point in the study** Olanzapine: 4 (15*) N=26 Quetiapine: 2 (8*) N=24 n (%) with tremor **At any point in the study** Olanzapine: 13 (50*) N=26 Quetiapine: 7 (29*) N=24 **At end point in the study**

Bibliographic reference	Authors: Arango 2009 et al Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode
	Olanzapine: 4 (15*) N=26 Quetiapine: 4 (17*) N=24 n (%) with akathisia **At any point in the study** Olanzapine: 8 (31*) N=26 Quetiapine: 6 (25*) N=24 **At end point in the study** Olanzapine: 3 (12*) N=26 Quetiapine: 0 (0*) N=24 *percentages and N reported in study do not match up therefore the number randomised has been used as the denominator **3. Hormonal side effects** n (%) with increased tendency to sweat **At any point in the study** Olanzapine: 7 (27*) N=26 Quetiapine: 8 (33*) N=24 **At end point in the study** Olanzapine: 5 (19*) N=26 Quetiapine: 1 (4*) N=24 *percentages and N reported in study do not match up therefore the number randomised has been used as the denominator **4. Cardiac side effects** n (%) with palpitations/tachycardia **At any point in the study** Olanzapine: 8 (31*) N=26

Bibliographic reference	Authors: Arango 2009 et al Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode
	Quetiapine: 11 (46*) N=24 **At end point in the study** Olanzapine: 1 (4*) N=26 Quetiapine: 1 (4*) N=24 *percentages and N reported in study do not match up therefore the number randomised has been used as the denominator **5. Leaving the study early for any reason, n/N (%)** Olanzapine: 10/26 (38.5) – reasons included loss to follow up (n=4), symptom remission (n=1), poor response (n=2), change to treatment (n=2), adverse events (n=0) Quetiapine: 8/24 (33.3) – reasons included loss to follow up (n=3), poor compliance (n=1), poor response (n=4), adverse events (n=0) **6. Quality of life** Not reported **7. Developmental progress** Not reported
Source of funding	AstraZeneca
Comments	**Randomisation:** Stratified random sampling conducted by age and gender. **Allocation concealment:** Not described **Blinding:** Open label trial (neither participants or researchers blinded to treatment received) **Evaluation of adverse effects:** Weight change measured as increase in kilograms and body mass index. Other measures included the UKU scale of adverse reactions, Barnes Akathisia Scale and Simpson Neurological Rating Scale for extrapyramidal side effects. Blood cell counts, metabolic measures and prolactin performed at baseline and at each visit. All blood tests were performed in a fasting state. **Other:** heterogeneous sample of diagnoses, concomitant medications, all patients were prescribed risperidone 2-6mg (flexible dose at discretion of clinician) 3-5 days prior to randomisation. Poor reporting of data - *percentages and N reported in study do not match up for a number of outcomes, therefore the number randomised has been used as the denominator.

Bibliographic reference	**Authors: Arango 2009 et al** **Title: Olanzapine compared to quetiapine in adolescents with a first psychotic episode**
	Reported but not extracted the following side effects: asthenia/lassitude/increased fatigability, sleepiness/sedation, failing memory, depression, tension/inner unrest, increased duration of sleep, reduced duration of sleep, increased dream activity, emotional indifference, rigidity, accommodation disturbances, increased salivation, reduced salivation, constipation, polyuria/polydipsia, orthostatic dizziness, amenorrhea, increased sexual desire, dry vagina, tension headache. Also not extracted BMI increase, total cholesterol and thyroid hormone as only p values reported (no means/SDs).

1

Bibliographic reference	**Authors: Mozes et al 2006** **Title: An open label trial of randomised comparison of olanzapine versus risperidone in the treatment of childhood onset schizophrenia**
Study type	RCT
Aim	To compare the effectiveness and tolerability of risperidone versus olanzapine in the treatment of childhood onset schizophrenia
Patient characteristics	• Diagnosis: Schizophrenic disorder – 10 patients with schizophreniform disorder, 7 with disorganised schizophrenia, 6 with paranoid schizophrenia and 2 patients with unspecified schizophrenia • Diagnostic tool: K-SADS-PL, DSM-IV **Inclusion criteria:** NR **Exclusion criteria:** Learning disabilities **Baseline characteristics**

	Olanzapine (n=12)	**Risperidone (n=13)**
Gender, n male (%)	5 (42)	5 (38)
Age in years, mean (SD)	11.5 (1.64)	10.71 (1.43)
Ethnicity	Not reported	Not reported
Mean duration of disorder	Not reported	Not reported
Mean age of onset	Not reported	Not reported
Prior antipsychotic use, %	% not reported but permitted	% not reported but permitted

Bibliographic reference	**Authors: Mozes et al 2006** **Title: An open label trial of randomised comparison of olanzapine versus risperidone in the treatment of childhood onset schizophrenia**

Comorbidities, n		
OCD	0	3
Epilepsy	0	2
ADHD	2	1
Familial Mediterranean Fever	1	0
Neurofibromatosis	0	1
Tic disorder	1	0
Concomitant medications, n		
Valproic acid	1	1
Phenytoin	0	1
Carbamazepine	2	0
Biperiden	2	4
Promethizine	2	1
Methylphenidate	2	0
Colchicine	1	0
Citalopram	1	2
Fluoxetine	1	0
Inpatients, %	100	100
Substance use, %	Not reported	Not reported

Number of Patients

	Olanzapine	**Risperidone**
Number randomised	12	13

Intervention

Olanzapine, mean (range) 8.18 (2.5-20) mg/day, over 12 weeks

Notes about the intervention/comparator:
Dosing of either intervention was determined according to clinical response and side effects

Comparison

Risperidone, mean (range) 1.62 (0.25-4.5) mg/day, over 12 weeks

Bibliographic reference	**Authors: Mozes et al 2006** **Title: An open label trial of randomised comparison of olanzapine versus risperidone in the treatment of childhood onset schizophrenia**
Length of follow up	12 weeks
Location	Israel
Outcomes measures and effect size	**1. Metabolic side effects** Weight gain in kg, mean (SD) Olanzapine: 5.78 (3.11) n=11 Risperidone: 4.45 (2.87) n= 9 **2. Neurological side effects** Extrapyramidal side effects as assed by the Simpson Angus scale (SAS) and Barnes Akathisia Rating scale (BAS) Gait, n/N (%) Olanzapine: 3/12 (25) Risperidone: 5/13 (38.5) Arm dropping, n/N (%) Olanzapine: 0/12 (0) Risperidone: 4/13 (30.8) Shoulder shaking, n/N (%) Olanzapine: 0/12 (0) Risperidone: 3/13 (23.1) Elbow rigidity, n/N (%) Olanzapine: 1/12 (8.3) Risperidone: 4/13 (30.8) Wrist rigidity, n/N (%) Olanzapine: 0/12 (0) Risperidone: 4/13 (30.8) Leg pendulousness, n/N (%) Olanzapine: 1/12 (8.3)

Bibliographic reference	Authors: Mozes et al 2006 Title: An open label trial of randomised comparison of olanzapine versus risperidone in the treatment of childhood onset schizophrenia
	Risperidone: 2/13 (16.7) Head dropping, n/N (%) Olanzapine: 1/12 (8.3) Risperidone: 2/13 (15.4) Glabellar tap Olanzapine: 4/12 (33.3) Risperidone: 9/13 (69.2) Tremor Olanzapine: 6/12 (50) Risperidone: 9/13 (69.2) Salivation Olanzapine: 4/12 (33.3) Risperidone: 5/13 (38.5) Akathisia objective Olanzapine: 2/12 (16.7) Risperidone: 1/13 (7.7) Akathisia subjective Olanzapine: 2/12 (16.7) Risperidone: 2/13 (15.4) Distress related to restlessness Olanzapine: 2/12 (16.7) Risperidone: 0/13 (0) Global clinical assessment of akathisia

Bibliographic reference	Authors: Mozes et al 2006 Title: An open label trial of randomised comparison of olanzapine versus risperidone in the treatment of childhood onset schizophrenia
	Olanzapine: 2/12 (16.7) Risperidone: 1/13 (7.7) **3. Hormonal side effects** Not reported **4. Cardiac side effects** Not reported **5. Leaving the study early for any reason including mortality, n/N (%)** Olanzapine – 1/12 (8.3) – contact was lost Risperidone – 4/13 (30.8) – 3 dropped out due to lack of improvement, and 1 due to severe hyperprolactinemia and reduction of growth hormone level **6. Quality of life** Not reported **7. Developmental progress: eg: school performance** Not reported
Source of funding	Not reported
Comments	**Randomisation:** 'randomised allocation' but method not described. **Allocation concealment:** Not described **Blinding:** Open-label: neither subjects nor researchers blinded **Evaluation of adverse effects:** Weight, pulse and blood pressure monitored once weekly. Treatment emergent adverse events monitored by the Barnes Akathisia Rating scale and the Simpson Angus scale. **Other:** Use of concomitant medications, comorbidities and small sample size. Inclusion criteria not reported.

1

Bibliographic reference	Authors: Kumra et al, 2008 Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison

<table>
<tr><td>Bibliographic reference</td><td>Authors: Kumra et al, 2008
Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison</td></tr>
<tr><td>Study type</td><td>RCT</td></tr>
<tr><td>Aim</td><td>To evaluate the effectiveness and safety of clozapine versus high dose olanzapine in treatment refractory adolescents with schizophrenia</td></tr>
<tr><td>Patient characteristics</td><td>

Diagnosis

Olanzapine: Schizophrenia n=14, schizoaffective disorder n=7
Clozapine: Schizophrenia n=11, schizoaffective disorder n=7

Diagnostic tool: K-SADS-PL DSM-IV

Inclusion criteria:

Aged between 10 and 18 years
Diagnosis of schizophrenia or schizoaffective disorder based on a structured interview (K-SADS-PL)
Meet study criteria for treatment-refractoriness that was defined as a documented treatment failure of at least two prior adequate antipsychotic trials and a baseline BPRS total score of at least 35 and a score of at least “moderate” on one or more psychotic item(s) on the BPRS (e.g., conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content)

Exclusion criteria:

Premorbid diagnosis of learning disabilities (IQ<70)
History of serious adverse reactions to the proposed treatments (For females) pregnancy
Serious and unstable medical condition
Failed an adequate trial of clozapine (at least 12 weeks) at adequate doses (300 mg/day or higher) and/or had failed an adequate trial of olanzapine (at least 8 weeks) at high doses (20 mg/day or higher).

Baseline characteristics
<table>
<tr><th></th><th>Clozapine (n=18)</th><th>Olanzapine (n=21)</th></tr>
<tr><td>Gender, n male (%)</td><td>8 (44)</td><td>13 (62)</td></tr>
<tr><td>Age in years, mean (SD)</td><td>15.8 (2.2)</td><td>15.5 (2.1)</td></tr>
<tr><td>Ethnicity, n Caucasian</td><td>2</td><td>6</td></tr>
<tr><td>Mean age of onset in years, mean (SD)</td><td>12.7 (2.4)</td><td>11.7 (3.2)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Authors: Kumra et al, 2008
Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison</td></tr>
<tr><td></td><td>
<table>
<tr><td>Comorbidities</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Substance use</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Concomitant medication</td><td colspan="2">Not reported by study arms however 11 olanzapine patients and 6 clozapine medication continued to receive the following medications because the safety officer judged these medications could not be safely removed (lithium n=7, depakoate n=3, other mood stabiliser n=6, antidepressant n=4, stimulant n=1 and naltrexone n=1)</td></tr>
<tr><td>Prior antipsychotic use</td><td colspan="2">Not reported by study arms however all patients were being treated with antipsychotic medications: risperidone (n=5), olanzapine (n=16), ziprasidone (n=4), aripiprazole (n=3), quetiapine (n=9), haloperidol (n=9) and thorazine (n=7). Simultaneously as study medications were being titrated, current medication therapies were tapered as tolerated over the first 4 weeks of the trial to allow patients to achieve a therapeutic dosage of study medications.</td></tr>
<tr><td>Inpatients, %</td><td colspan="2">90% of all subjects began as inpatients.</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>Olanzapine</td><td>Clozapine</td></tr>
<tr><td>Number randomised</td><td>21</td><td>18</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Olanzapine, mean (range) dose: 26.2 (5-30) mg/day, over 12 weeks

Olanzapine therapy was started at a dose of 5 mg/day up and could be increased in 5-mg increments every 3 days to a maximum of 30 mg/day As study medications were being titrated, current medication therapies were tapered, as tolerated over the first 4 weeks of the trial to allow patients to achieve a therapeutic dosage of study medications. Patients never received less than the same dosage of antipsychotic medication (in terms of chlorpromazine equivalents) than they had at study entry</td></tr>
<tr><td>Comparison</td><td>Clozapine, mean (range) dose: 403.1 (25-900) mg/day, over 12 weeks

Clozapine therapy started at a dose of 25 mg/day and could be increased in 25-mg or 50-mg increments every 3 days to a maximum dose of 900 mg/day</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>USA</td></tr>
</table>

Bibliographic reference	**Authors: Kumra et al, 2008** **Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison**
Outcomes measures and effect size	**1. Metabolic side effects** a) Fasting glucose in mg/dl, mean (SD) Olanzapine At baseline: 80.4 (9.1), n=21 At week 12: 84 (7.7), n=21 Clozapine At baseline: 89.6 (16.4), n=18 At week 12: 94.1 (16.8), n=17 b) Fasting triglycerides, mean (SD) Olanzapine At baseline: 122 (73.3), n=21 At week 12: 133.4 (67.2), n=21 Clozapine At baseline: 136.8 (49.9), n=18 At week 12: 153.6 (76.6), n=17 c) Fasting cholesterol, mean (SD) Olanzapine At baseline: 161.0 (28), n=21 At week 12: 178.2 (33.8), n=21 Clozapine At baseline: 171.3 (29.5), n=18 At week 12: 167.8 (32.6), n=17 d) BMI, mean (SD) Olanzapine At baseline: 28.5 (5.5), n=21

Bibliographic reference	Authors: Kumra et al, 2008 Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison
	At week 12: 29.2 (5.5), n=21 Clozapinesk At baseline: 28 (3.4), n=18 At week 12: 28.7 (3.4), n=17 e) At healthy weight (BMI percentile ≥5 to <85), n/N (%) Olanzapine At baseline: 3/21 (14.3) At week 12: 4/21 (19) Clozapine At baseline: 2/18 (11.1) At week 12: 1/17 (5.9) f) Overweight (BMI percentile ≥85 to <95), n/N (%) Olanzapine At baseline: 9/21 (42.9) At week 12: 5/21 (23.9) Clozapine At baseline: 10/18 (55.6) At week 12: 9/17 (52.9) g) Obese (BMI ≥95 percentile), n/N(%) Olanzapine At baseline: 7/21 (41.4) At week 12: 12/21 (57.1) Clozapine At baseline: 6/18 (33.3)

Bibliographic reference	**Authors: Kumra et al, 2008** **Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison**
	At week 12: 9/17 (42.9) h) Gaining>7% of baseline body weight by study end point, n/N (%) Olanzapine: 2/21 (10) Clozapine: 3/18 (17) **2. Neurological side effects** Not reported **3. Hormonal side effects** Not reported **4. Cardiac side effects** Not reported **5. Leaving the study early for any reason** Olanzapine: 7/21 (33) – nonresponse (n=6), treatment emergent neutropenia (n=1) Clozapine: 4/18 (22) – excessive weight gain (n=2), treatment non-response (n=1), withdrawal of consent (n=1) **6. Quality of life** Not reported **7. Developmental progress** Not reported
Source of funding	Not reported
Comments	**Randomisation:** Computer generated randomisation **Allocation concealment:** Not described **Blinding:** Described as 'double blind' – further details not specified. **Evaluation of adverse effects:** this included weekly subjective treatment emergent symptoms scale, a complete blood count, fasting blood glucose, lipid serum levels, weight and BMI measurements. **Other:** Use of concomitant medications, units for many outcomes not reported.

Bibliographic reference	**Authors: Kumra et al, 2008** **Title: Clozapine and high dose olanzapine in refractory early onset Schizophrenia: a 12 week randomised and double blind comparison**
	Reported but not extracted the following subjective side effects: insomnia, drowsiness, nasal congestion, constipation, dry mouth, increased appetite, enuresis, increased salivation, sweating.

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Bibliographic reference	**Authors: Sikich et al, 2008** **Title: Double-blind comparison of first and 'second generation' antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders study**
Study type	RCT
Aim	To compare the efficacy and safety of two 'second generation' antipsychotics (olanzapine and risperidone) with a first generation antipsychotic (molindone) in the treatment of early-onset schizophrenia and schizoaffective disorder.
Patient characteristics	• Diagnosis - Schizophrenia: Olanzapine (63%), Risperidone (68%) - Schizoaffective disorders: Olanzapine (37%), Risperidone (32%) • Diagnostic tool: SCID DSM-IV **Inclusion criteria** • 8 to 19 years old (no more than 30% of subjects 16 to 19 years) • Score of at least moderate severity on 1 of the positive psychotic symptom ratings of the PANSS or BPRS-C • Met DSM-IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder • No depot antipsychotic medication for at least six months • Good physical health • Able to provide informed consent/assent for the study and have a guardian who gives informed written consent **Exclusion criteria** • History of an adequate trial of risperidone, olanzapine, or molindone (defined as at least 8 weeks of treatment with the dose during the final 2 weeks of treatment >risperidone 6 mg/day, olanzapine 20 mg/day, or molindone 140 mg/day) during current psychotic episode

Bibliographic reference	**Authors: Sikich et al, 2008** **Title: Double-blind comparison of first and 'second generation' antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders study**

- History of non-response to an adequate trial of study drug during a prior episode
- History of intolerance to risperidone, olanzapine, or molindone
- Bipolar disorder, primary posttraumatic stress disorder, primary personality disorder, or psychosis NOS diagnosed by clinician and confirmed by KID-SCID
- Current major depressive episode: Active substance abuse or dependence, Premorbid diagnosis of learning disabilities, Endocrinological or neurological conditions that confound the diagnosis or are a contraindication to treatment, Pregnancy or refusal to practice contraception during the study.

Baseline characteristics

	Olanzapine (n=35)	Risperidone (n=41)
Gender, %	71	66
Age in years, % 8 to 11: 12 to 15: 16 to 19:	 20 57 23	 15 54 32
Ethnicity, % white	60	61
Mean duration of disorder	Not reported	Not reported
Mean age of onset	Not reported	Not reported
Antipsychotic-naïve, %	37	22
Baseline antipsychotic use*, % Olanzapine Risperidone Other 'second generation' antipsychotics First generation antipsychotics	 6 37 23 0	 15 37 22 2
Baseline medications*, % Antidepressants Mood stabilisers	 11 6	 12 10

<table>
<tr><td>Bibliographic reference</td><td>Authors: Sikich et al, 2008
Title: Double-blind comparison of first and ‘second generation’ antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders study</td></tr>
<tr><td></td><td>
<table>
<tr><td>Antidepressants and mood stabilisers
Benzodiazepine</td><td>0

9</td><td>2

15</td></tr>
<tr><td>Inpatient at baseline, %</td><td>6</td><td>15</td></tr>
<tr><td>Prior substance use, %</td><td>6</td><td>5</td></tr>
</table>
*Antipsychotics and side effect medications in use at the time of the random assignment were cross-tapered during the first 2 weeks of study treatment. Individuals whose mood symptoms had been well controlled on a stable dose of antidepressants or nonantipsychotics mood stabilisers for at least 4 weeks prior to study entry were allowed to continue treatments during the study. Concomitant treatments with anticholinergic agents, propranolol and benzodiazepines were guided by algorithms.
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Olanzapine</th><th>Risperidone</th></tr>
<tr><td>Number randomised</td><td>36 (1 withdrew before treatment therefore n=35, however ITT analysis used)</td><td>41 (1 withdrew before treatment therefore n=40, however ITT analysis used)</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Olanzapine, mean (range) 11.4 (2.5-20) mg/day, over 8 weeks

Notes about the intervention and comparator: Dose schedules were variable. Medications were initiated at the lowest dose within the range and typically increased to the middle of the dose range within 10 days for those participants aged 12 years and older and within 14 days for those participants aged 8 to 11 years according to age specific schedules.</td></tr>
<tr><td>Comparison</td><td>Risperidone, mean (range) 2.8 (0.5-6.0) mg/day, over 8 weeks</td></tr>
<tr><td>Length of follow up</td><td>8 weeks
Plus 44-week double-blind maintenance phase for responders (separate study)</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1. Metabolic side effects
a) Weight change in kg, mean (SD)
Olanzapine: 6.1 (3.6); n=35
Risperidone: 3.6 (4.0); n=41

b) BMI change in kg/m^2, mean (SD)</td></tr>
</table>

Bibliographic reference	Authors: Sikich et al, 2008 Title: Double-blind comparison of first and 'second generation' antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders study
	Olanzapine: 2.2 (1.2), n=35 Risperidone: 1.3 (1.5); n=41 c) Total cholesterol change in mg/dl, mean (SD) - fasting Olanzapine: 19.9 (23.9), n=12 Risperidone: -10.2 (26.7), n=22 d) HDL cholesterol change in mg/dl, mean (SD) – fasting Olanzapine: 1.1 (8.3), n=12 Risperidone: -4 (9.4), n=21 e) LDL cholesterol change in mg/dl, mean (SD)- fasting Olanzapine: 14.7 (18.7), n=12 Risperidone: -9.6 (22.2), n=20 f) Triglycerides change in mg/dl, mean (SD) - fasting Olanzapine: 21.6 (65.3), n=12 Risperidone: 7.1 (33.3), n=21 g) Glucose change in mg/dl, mean (SD) – fasting Olanzapine: 0.6 (15.7), n=12 Risperidone: 1.2 (7.3), n=22 **2. Neurological side effects – extrapyramidal symptoms** a) Simpson-Angus Rating Scale change, mean (SD) Olanzapine: 0.4 (1.9), n=35 Risperidone: 0.6 (2.5), n=41 b) Barnes Rating Scale for Drug Induced Akathisia change, mean (SD) Olanzapine: 0.2 (2.1), n=35

Bibliographic reference	**Authors: Sikich et al, 2008** **Title: Double-blind comparison of first and 'second generation' antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders study**
	Risperidone: 0.4 (2.4), n=41 c) AIMS change, mean (SD) Olanzapine: -0.2 (2.3), n=35 Risperidone: -0.2 (1.8), n=41 **3. Hormonal side effects (prolactin levels, thyroid stimulating hormone levels)** a) Prolactin change in ug/l, mean (SD) Olanzapine: -1.5 (20.2), n=35 Risperidone: 19.5 (21.5), n=41 **4. Cardiac side effects (blood pressure, QTc interval)** a) QT_c change in msec, mean (SD) Olanzapine: 11.2 (16.8), n=35 Risperidone: 0.5 (29.5), n=41 **5. Leaving the study early for any reason including mortality** Olanzapine: 18/35 (51) – lost to follow (n=2), noncompliance (n=7), inadequate efficacy (n=3), weight gain (n=2), insomnia (n=2), sedation (n=1) Risperidone: 13/41 (32) – noncompliance (n=4), inadequate efficacy (n=4), parkinsonian symptoms (n=3), akathisia (n=1), sedation (n=1) **6. Quality of life** Not reported **7. Developmental progress eg; school performance** Not reported
Source of funding	Funding source: Non-industry sponsors
Comments	**Randomisation:** method not described **Allocation concealment:** method not described

Bibliographic reference	**Authors: Sikich et al, 2008** **Title: Double-blind comparison of first and 'second generation' antipsychotics in early onset schizophrenia and schizoaffective disorder: findings from the treatment of early onset schizophrenia spectrum disorders study**
	Blinding: described as 'double blind' **Evaluation of adverse effects:** The Simpson-Angus Rating Scale, Barnes Rating Scale and Abnormal Involuntary Movement Scale (AIMS) were employed to monitor extrapyramidal symptoms. Fasting metabolic parameters, prolactin levels and routine blood and urine chemistries were monitored at weeks 0, 4 and 8. **Other:** Use of concomitant medications, 285 not enrolled in study (reasons not provided). Random assignment to olanzapine was discontinued towards the end of the recruitment phase by NIMH's data and safety monitoring board following their review of the interim data, which showed a greater increase in weight with olanzapine than molidone or risperidone, without evidence of greater efficacy. Participants being treated with olanzapine continued their participation and the integrity of the study blind was maintained.

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Bibliographic reference	**CROCQ 2007**
Study type	Prospective cohort
Aim	To compare the changes in weight and body mass index in 52 hospitalised adolescents between baseline and after 12 weeks of monotherapy
Patient characteristics	• Diagnosis: Schizophreniform disorder • Diagnostic tool: DSM-IV **Inclusion criteria:** Not reported **Exclusion criteria**: Not reported **Baseline characteristics**

	Olanzapine (n=16)	**Risperidone (n=26)**
Gender, % male	31	58
Age in years, mean (SD)	16.5 (1.7)	15.2 (1.4)
Caucasian, %	100	100
Mean duration of disorder	Not reported	Not reported
Mean age of onset	Not reported	Not reported

Bibliographic reference	**CROCQ 2007**
	<table><tr><td>Prior Antipsychotic Use, %</td><td colspan="2">75% of all subjects antipsychotic naïve</td></tr><tr><td>Concomitant medications, %</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Substance use, %</td><td>Not reported</td><td>Not reported</td></tr><tr><td>Inpatients, %</td><td>100</td><td>100</td></tr></table>
Number of Patients	Number of people screened, excluded and reasons not reported. Data available for 52 hospitalised adolescents across 3 arms in the study, only 2 study arms relevant to this question: Olanzapine, n=16 Risperidone, n=26
Intervention	**Olanzapine orally disintegrating tablet** (mean dose 16.6 mg/day), over 12 weeks Notes about the interventions: Subjects were hospitalized during the study period. Consequently, medication compliance was verified; also, all participants took part in the same sports activities and they were served the same meals. However, the quantity of food that was effectively eaten was not kept constant and depended on individual appetites.
Comparison	**Risperidone (mean dose 2.8 mg/day), over 12 weeks**
Length of follow up	12 weeks
Location	France
Outcomes measures and effect size	**1. Metabolic side effects** a) Weight gain in kg, mean (SD) Olanzapine: 3.0 (2.1), n=16 Risperidone: 1.0 (1.8), n=26 b) BMI change in kg/m^2, mean (SD) Olanzapine: 1.1 (0.8), n=16 Risperidone: 0.4 (0.7), n=26 **2. Neurological side effects** Not reported

Bibliographic reference	CROCQ 2007
	3. Hormonal side effects (prolactin levels, thyroid stimulating hormone levels) Not reported **4. Cardiac side effects (blood pressure, QTc interval)** Not reported **5. Leaving the study early for any reason including mortality** Not reported **6. Quality of life** Not reported **7. Developmental progress eg; school performance** Not reported
Source of funding	Not reported
Comments	**Allocation to treatment groups:** not reported **Blinding:** described as 'open=label' **Evaluation of adverse effects:** baseline BMI and change along with weight gain in kg's was measured for all subjects. **Other:** concomitant meds not reported, inclusion and exclusion criteria not reported. Olanzapine standard tablet arm has not been extracted given there are only 10 subjects in this group – this is one of the exclusion criteria in the protocol.

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Bibliographic reference	**Authors: Castroforniles et al 2008** **Title: Antipsychotic Treatment in Child and Adolescent First Episode Psychosis: a longitudinal naturalistic approach**
Study type	Multi centre (6 university hospitals) prospective cohort
Aim	To describe the antipsychotic treatment during the first year of early onset first psychotic episodes and to compare

<table>
<tr><td>Bibliographic reference</td><td>Authors: Castroforniles et al 2008
Title: Antipsychotic Treatment in Child and Adolescent First Episode Psychosis: a longitudinal naturalistic approach</td></tr>
<tr><td></td><td>the most frequently used agents after 6 months.</td></tr>
<tr><td>Patient characteristics</td><td>

Diagnosis: Schizophrenia type disorder: 39.1%, Psychotic disorder NOS: 38.2%, Depressive disorder with psychotic symptoms: 11.8%, bipolar disorder, manic episode with psychotic symptoms: 10.9% (breakdown of diagnoses by study arms not reported).
Diagnostic tool: DSM-IV

Inclusion criteria:

Age between 7 and 17 years at the time of first evaluation
Presence of positive psychotic symptoms (within a psychotic episode) such as delusions or hallucinations of less than 6 months’ duration.

Exclusion criteria:

Presence of a concomitant Axis I disorder at the time of evaluation that might account for the psychotic symptoms (such as substance abuse, autistic spectrum disorders, post traumatic stress disorder, or acute stress disorder)
Mental retardation according to DSM-IV criteria including not only an intelligence quotient (IQ) below 70 but also impaired functioning
Pervasive developmental disorder
Neurological disorders
History of head trauma with loss of consciousness
Pregnancy
Occasional substance use was not an exclusion criterion if positive symptoms persisted for more than 2 weeks after a negative urine drug test.

Baseline characteristics
<table>
<tr><th></th><th>Risperidone (n=31)</th><th>Quetiapine (n=15)</th><th>Olanzapine (n=14)</th></tr>
<tr><td>Gender, % male</td><td>67.7</td><td>66.7</td><td>71.4</td></tr>
<tr><td>Age in years, mean (SD)</td><td>15.1 (2.1)</td><td>16.4 (1.1)</td><td>15.7 (1.2)</td></tr>
<tr><td>Ethnicity, % Caucasian</td><td colspan="3">86% overall</td></tr>
<tr><td>Mean duration of disorder</td><td colspan="3">Not reported</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Authors: Castroforniles et al 2008** **Title: Antipsychotic Treatment in Child and Adolescent First Episode Psychosis: a longitudinal naturalistic approach**

Mean age of onset	Not reported
Prior antipsychotic use	51% antipsychotic naïve
Concomitant medication at baseline, % Anxiolytics Antidepressants Mood stabilisers Anticholinergic drugs No psychopharmacological treatment	 47.3 across all groups 16.4 across all groups 12.7 across all groups 7.3 across all groups 1.8 across all groups
Concomitant medication at 6 months, % Anxiolytics Antidepressants Mood stabilisers Anticholinergic drugs No psychopharmacological treatment	 18.8 across all groups 15.8 across all groups 14.9 across all groups 15.8 across all groups 5.9 across all groups
Substance use, %	Not reported
Inaptient, %	At baseline, 84% were hospitalised, 16% were outpatients.

Number of Patients

Number of people screened, excluded and reasons: 116 individuals met the inclusion criteria. Six patients were excluded, three due to mental retardation and 3 due to parents' refusal to participate. The final sample comprised 110 children and adolescents. Only patients receiving the same and only one antipsychotic from baseline until 6 months follow up were included in the analysis. Sample therefore = 60 subjects.

Risperidone	**Quetiapine**	**Olanzapine**
n=31	n=15	n=14

Intervention

Olanzapine (mean dose 11.6 mg/day)

Comparison

Quetiapine (mean dose 405.1 mg/day)
Risperidone (mean dose 3.3 mg/day)

Bibliographic reference	**Authors: Castroforniles et al 2008** **Title: Antipsychotic Treatment in Child and Adolescent First Episode Psychosis: a longitudinal naturalistic approach**
Length of follow up	6 months
Location	Spain
Outcomes measures and effect size	**1. Metabolic side effects** a) Weight increase in kg, mean (SD) Olanzapine – 11.7 (6.1), n=14 Quetiapine – 6 (5.5), n=15 Risperidone – 6.1 (4.8), n=31 b) Body mass index increase, mean (SD) Olanzapine – 3.9 (2.8), n=14 Quetiapine – 1.4 (3.2), n=15 Risperidone – 1.9 (1.7), n=31 **2. Neurological side effects** a) As measured on the UKU scale, mean (SD) Olanzapine: 0.4 (0.9), n=14 Quetiapine: 0.6 (0.7), n=15 Risperidone: 1.4 (2.2), n=31 **3. Hormonal side effects** Not reported **4. Cardiac side effects (blood pressure, QTc interval)** Not reported **5. Leaving the study early for any reason including mortality** 5 patients treated with risperidone and one with olanzapine had stopped the initial treatment due to side effects- details not reported. **6. Quality of life** Not reported

Bibliographic reference	**Authors: Castroforniles et al 2008** **Title: Antipsychotic Treatment in Child and Adolescent First Episode Psychosis: a longitudinal naturalistic approach**
	7. Developmental progress eg; school performance Not reported
Source of funding	Carlos III Institute of Health, Spanish Department of Health, Cooperative Research Thematic Network and from the Spanish Ministry of Health, Instituto de Salud Carlos III, CIBERSAM Network.
Comments	**Allocation to treatment groups:** not explicitly stated but 50.9% were already receiving psychopharmacological treatment at the time of enrolment, the rest were drug naïve. Unclear whether those already receiving antipsychotic carried on with same treatment or not. Subjects were allowed to shift medications at different time points in the study (at discretion of clinician?) but only patients receiving the same and only one antipsychotic from baseline until 6 months were included in the analysis. **Blinding:** described as 'not double blind'. **Evaluation of adverse effects:** UKU side effects rating scale administered by the clinician at 6 months. Breakdown of neurological side effects measured by the UKU scale have not been extracted due to poor reporting of data – numbers and percentages reported do not match up, number available for analysis unclear. **Other:** Heterogeneous sample of diagnoses, authors state % of patients with diagnosis of depression with psychotic symptoms, bipolar, or schizoaffective disorder significantly higher in patients treated with quetiapine and olanzapine than risperidone. Small samples sizes, concomitant medications used.

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Bibliographic reference	**Authors: Correll 2009** **Title: Cardiometabolic risk of second-generation antipsychotic medications during first time use in children and adolescents**
Study type	Prospective cohort study
Aim	To study the association of 'second generation' antipsychotic medications with body composition and metabolic parameters in patients without prior antipsychotic medication exposure.
Patient characteristics	• Diagnosis:

	Aripiprazole	Olanzapine	Quetiapine	Risperidone
Schizophrenia spectrum disorder, %	31.1	35.6	16.7	34.1

Bibliographic reference	Authors: Correll 2009 Title: Cardiometabolic risk of second-generation antipsychotic medications during first time use in children and adolescents

Mood disorder spectrum disorder, %	27.5	35.6	25	40.7
Disruptive or aggressive behaviour spectrum disorder, %	22.2	20.0	16.7	25.2

- Diagnostic tool: assessed with the diagnostic and statistical manual of mental disorders

Inclusion criteria:

- Age 4 to 19 years and 1 week or less of lifetime antipsychotic treatment
- Psychiatric illness prompting antipsychotic medication initiation
- Consent or baseline anthropometric and biochemical assessments obtained within 7 days of antipsychotic medication initiation

Exclusion criteria:

- Treatment with more than 1 antipsychotic medication
- Active or past eating disorder
- Biochemical evidence of thyroid dysfunction
- Acute medical disorders
- Pregnancy or breastfeeding
- Wards of the state (because research consent by a public agency representative within 1 week was unlikely)
- Leaving the catchment area within 4 weeks

Baseline characteristics

	Aripiprazole	Olanzapine	Quetiapine	Risperidone
Gender, % male	56.1	64.4	36.1	62.2
Age in years, mean (SD)	13.4 (3.1)	14.7 (3.2)	14.0 (3.1)	13.6 (4.0)
Ethnicity, %	62.5	46.7	50	46.3

<table>
<tr><td>Bibliographic reference</td><td>Authors: Correll 2009
Title: Cardiometabolic risk of second-generation antipsychotic medications during first time use in children and adolescents</td></tr>
<tr><td></td><td>
<table>
<tr><td>Caucasian</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean duration of disorder</td><td colspan="4">Not reported</td></tr>
<tr><td>Mean age of onset</td><td colspan="4">Not reported</td></tr>
<tr><td>Prior antipsychotic use</td><td colspan="4">Only included those with 1 week or less of lifetime antipsychotic treatment</td></tr>
<tr><td>Concomitant medication, %</td><td colspan="4">Permitted based on clinical necessity, numbers not reported</td></tr>
<tr><td>Substance use, %</td><td colspan="4">Not reported</td></tr>
<tr><td>Inpatient, %</td><td colspan="4">%s not reported but inpatients and outpatients included</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><td></td><td>Aripiprazole</td><td>Olanzapine</td><td>Quetiapine</td><td>Risperidone</td></tr>
<tr><td>Number analysed</td><td>41</td><td>45</td><td>36</td><td>135</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Olanzapine, dosing based on clinical necessity</td></tr>
<tr><td>Comparison</td><td>Arpiprazole
Quetiapine
Risperidone

Dosing based on clinical necessity</td></tr>
<tr><td>Length of follow up</td><td>12 weeks</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect size</td><td>1. Metabolic side effects
a) Weight change at 12 weeks in kg, mean (95%CI); SD*
Aripiprazole: 4.44 (3.71 to 5.18); 2.33, n=41
Olanzapine: 8.54 (7.38 to 9.69); 3.84, n=45
Quetiapine: 6.06 (4.90 to 7.21); 3.41, n=36
Risperidone: 5.34 (4.81 to 5.87); 3.11, n=135</td></tr>
</table>

Bibliographic reference	Authors: Correll 2009 Title: Cardiometabolic risk of second-generation antipsychotic medications during first time use in children and adolescents
	SD calculated by analyst based on data reported in the article b) BMI change at 12 weeks, mean (95%CI); SD Aripiprazole: 1.67 (1.36 to 1.98); 0.98, n=41 Olanzapine: 3.01 (2.60 to 3.42); 1.36, n=45 Quetiapine: 2.12 (1.71 to 2.53); 1.21, n=36 Risperidone: 1.92 (1.72 to 2.12); 1.17, n=135 *SD calculated by analyst based on data reported in the article c) Glucose change at 12 weeks in mg/dl, mean (95%CI); SD* Aripiprazole: 0.54 (-2.85 to 3.93); 10.74; n=41 Olanzapine: 3.14 (0.69 to 5.59); 8.15; n=45 Quetiapine: 2.64 (-0.65 to 5.93); 9.72; n=36 Risperidone: 1.14 (-0.84 to 3.12); 11.63; n=135 *SD calculated by analyst based on data reported in the article d) Total cholesterol change at 12 weeks in mg/dl, mean (95%CI); SD* Aripiprazole: 3.75 (-3.85 to 11.35); 24.08; n=41 Olanzapine: 15.58 (6.88 to 24.28); 28.96; n=45 Quetiapine: 9.05 (0.41 to 17.69); 25.54; n=36 Risperidone: 3.46 (-1.44 to 8.36); 28.79; n=135 *SD calculated by analyst based on data reported in the article e) LDL cholesterol change at 12 weeks in mg/dl, mean (95%CI); SD* Aripiprazole: 7.38 (0.77 to 13.99); 20.94; n=41 Olanzapine: 11.54 (3.97 to 19.11); 25.20; n=45 Quetiapine: 3.88 (-3.37 to 11.13); 21.43; n=36 Risperidone: 0.21 (-4.14 to 4.56); 25.55; n=135

Bibliographic reference	Authors: Correll 2009 Title: Cardiometabolic risk of second-generation antipsychotic medications during first time use in children and adolescents
	SD calculated by analyst based on data reported in the article f) HDL cholesterol change at 12 weeks in mg/dl, mean (95%CI); SD Aripiprazole: 0.29 (-2.32 to 2.90); 8.27; n=41 Olanzapine: -1.27 (-3.80 to 1.26); 8.42; n=45 Quetiapine: -1.47 (-5.06 to 2.12); 10.61; n=36 Risperidone: 0.33 (-1.26 to 1.92); 9.34; n=135 *SD calculated by analyst based on data reported in the article g) Triglycerides change at 12 weeks in mg/dl, mean (95%CI); SD* Aripiprazole: -2.40 (-19.71 to 14.91); 54.84; n=41 Olanzapine: 24.34 (9.80 to 38.88); 48.40; n=45 Quetiapine: 36.96 (10.13 to 63.79); 79.30; n=36 Risperidone: 9.74 (0.45 to 19.03); 54.58; n=135 *SD calculated by analyst based on data reported in the article **2. Neurological side effects** Not reported **3. Hormonal side effects** Not reported **4. Cardiac side effects (blood pressure, QTc interval)** Not reported **5. Leaving the study early for any reason including mortality** Not reported

Bibliographic reference	**Authors: Correll 2009** **Title: Cardiometabolic risk of second-generation antipsychotic medications during first time use in children and adolescents**
	6. Quality of life Not reported **7. Developmental progress eg; school performance** Not reported
Source of funding	Supported by grant from the National institutes of health, a national alliance for research in schizophrenia and depression independent investigator award, Feinstein institute for medical research, national centre for research resources.
Comments	**Allocation to treatment groups:** patients received antipsychotic treatment based on the clinician's choice. **Blinding:** not described **Evaluation of adverse effects:** BMI calculated as weight in kilograms divided by height in meters squared, weight measured with patients clothed, with emptied pockets and without socks or shoes using the following subtraction schedule: -1.3kg for those taller than 150cm, wearing long trousers, and long sleeve shirts or sweatshirts; -1.1kg for those wearing 1 of the 2 items with short sleeves, -0.7kg for those wearing short pants or short sleeve or light shirts; and -0.5kg for those wearing just underwear. For individuals measuring less than 150cm but 120cm or more, an additional 0.2kg was subtracted from the above formula. For individuals measuring less than 120cm, an additional 0.45kg was subtracted. Fasting blood was drawn between 7 and 11am prior to taking morning antipsychotic medications. **Other:** heterogeneous sample of diagnoses, comedications permitted but numbers not reported.

G.3 Evidence table for studies included from update search - indirect studies i.e. mean age <25 years

<table>
<tr><td>Bibliographic reference</td><td>Authors: Montes 2003
Title: Safety, effectiveness and quality of life of olanzapine in first episode schizophrenia: a naturalistic study</td></tr>
<tr><td>Study type</td><td>Prospective cohort study</td></tr>
<tr><td>Aim</td><td>To determine the safety and effectiveness of olanzapine in routine clinical conditions versus other antipsychotic drugs in treating an outpatient population with first episode schizophrenia and to determine patients' subjective satisfaction with treatment and quality of life following 6 months of treatment.</td></tr>
<tr><td>Patient characteristics</td><td>
Diagnosis: Schizophrenia
<table>
<tr><td></td><td>Olanzapine</td><td>Risperidone</td></tr>
<tr><td>Paranoid schizophrenia, %</td><td>71.9</td><td>71</td></tr>
<tr><td>Undifferentiated schizophrenia, %</td><td>14.9</td><td>19.4</td></tr>
<tr><td>Disorganised schizophrenia, %</td><td>12.3</td><td>9.7</td></tr>
<tr><td>Catatonic schizophrenia, %</td><td>0.9</td><td>0.0</td></tr>
</table>
Diagnostic tool: ICD-10 criteria
Inclusion criteria
Confirmed diagnosis of schizophrenia according to ICD-10 criteria
Requiring antipsychotic treatment for a first episode of schizophrenia with olanzapine or another antipsychotic except clozapine
Not over the age of 40 years
Exclusion criteria
Those in whom treatment with antipsychotic medication was contraindicated
Already participating in a clinical trial
Those in whom treatment with clozapine was indicated
Baseline characteristics
</td></tr>
</table>

<table>
<tr><td>Bibliographic reference</td><td>Authors: Montes 2003
Title: Safety, effectiveness and quality of life of olanzapine in first episode schizophrenia: a naturalistic study</td></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Olanzapine</th><th>Risperidone</th></tr>
<tr><td>Gender, % male</td><td>63.2</td><td>67.7</td></tr>
<tr><td>Age in years at time of trial, mean (SD)</td><td>24 (5.2)</td><td>22.6 (4.6)</td></tr>
<tr><td>Ethnicity</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Mean duration of disorder</td><td>Less than one year</td><td>Less than one year</td></tr>
<tr><td>Mean age of onset</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Prior antipsychotic use</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Concomitant treatment, %
High potency antipsychotics
Low potency antipsychotics
Benzodiazepines
Anticholinergics
Antidepressants
Mood stabilisers</td><td>
3.5
2.6
30.7
3.5
1.8
0.0</td><td>
9.7
0.0
38.7
16.1
3.2
3.2</td></tr>
<tr><td>Substance misuse</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>Inpatient, %</td><td>All outpatients</td><td>All outpatients</td></tr>
</table>
</td></tr>
<tr><td>Number of Patients</td><td>
<table>
<tr><th></th><th>Olanzapine</th><th>Risperidone</th></tr>
<tr><td>Number analysed</td><td>114</td><td>31</td></tr>
</table>
</td></tr>
<tr><td>Intervention</td><td>Olanzapine, initial mean dose 12.9mg/day (SD: 5.3). Mean dose throughout the study period 13.5mg/day (SD:5.2) over 6 months</td></tr>
<tr><td>Comparison</td><td>Risperidone, initial mean dose 5.2mg/day (SD: 2.2). Mean dose throughout the study period 5.4mg/day (SD: 2.2) over 6 months</td></tr>
<tr><td>Length of follow up</td><td>6 months</td></tr>
<tr><td>Location</td><td>Spain</td></tr>
<tr><td>Outcomes measures and effect size</td><td>Note: given the age range of this study (up to 40 years), only outcomes not covered by the direct studies (i.e. those in subjects <18 years) have been extracted.</td></tr>
</table>

Bibliographic reference	**Authors: Montes 2003** **Title: Safety, effectiveness and quality of life of olanzapine in first episode schizophrenia: a naturalistic study**
	1) Quality of life – EuroQoL-1 change from baseline to endpoint at 6 months, mean (SD) Olanzapine: 0.35 (0.3); n=114 Risperidone: 0.36 (0.3), n=31
Source of funding	Not reported
Comments	**Allocation to treatment groups:** based on clinical criteria, no further details reported **Blinding:** described as open label **Evaluation of adverse effects:** quality of life assessed by means of the Spanish version of the EuroQol (EQ-5D). It is a self-administered instrument. The first part of the instrument describes the health status itself in terms of 5 dimensions (mobility, personal care, daily activities, pain/discomfort and anxiety/depression) each of which includes three degrees of severity (1=no problem, 2=some/moderate problems, 3=many problems). Points are assigned to each of these possible states of health for their quantification. The second part is a visual analog scale (VAS) consisting of a 20cm long vertical graph, with ends labelled 'worst state of health possible' and 'best state of health possible', and with scores of 0 to 100 respectively. Subjects make a mark indicating their state of health. **Other:** concomitant medications permitted, indirect age group.

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Appendix H: GRADE profiles

H.1 GRADE profiles for evidence from observational studies - direct studies i.e. age ≤18 years

Table 4: GRADE profile for Olanzapine versus Aripiprazole - dichotmous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Aripiprazole	Relative (95% CI)	Absolute	
Outcome: neurological side effects											
Drug induced parkinsonism at 12 weeks[1]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Serious[5]	None	4/51 (8%)	13/49 (27%)	RR: 0.30 (0.10 to 0.84)	-	VERY LOW
Dyskinesia at 12 weeks[6]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[7]	None	3/51 (6%)	0/49 (0%)	RR: 6.73 (0.36 to 127.02)	-	VERY LOW
Akathisia at 12 weeks[8]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[7]	None	2/51 (4%)	3/49 (6%)	RR: 0.64 (0.11 to 3.67)	-	VERY LOW
Outcome: leaving the study early for any reason[9]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[7]	None	1/58 (2%)	4/66 (6%)	RR: 0.28 (0.03 to 2.47)	-	VERY LOW

[1] *Drug induced parkinsonism defined as patients fulfilling 1 or more of the following criteria: mean Simpson Angus Scale (SAS) score >0.33 in patients with baseline mean SAS ≤0.33; start of anticholinergic medication; or marked increase of total SAS ratings of ≥2 in patients with baseline positive rating for EPS.*

[2] *Serious risk of bias: described as not blinded – downgraded 1 level*

[3] *Serious risk of indirectness: 1) heterogeneous sample of diagnoses –28% of olanzapine arm and 26% of aripiprazole arm had schizophrenia spectrum disorders,(rest of the population were a mix of mood spectrum disorders (50% in olanzapine arm vs 41% in aripiprazole arm) and aggression spectrum disorder (22% in olanzapine arm vs 33% in aripiprazole arm) 2) Comorbidities – ADHD (44% of olanzapine arm vs 41% of aripiprazole arm), OCD (5% of olanzapine arm vs 5% of aripiprazole arm), SUD (22% of olanzapine arm vs 9% of aripiprazole arm) 3) Co-medications – psychostimulants (16% of olanzapine arm vs 21% of aripiprazole arm), antidepressants (17% of olanzapine arm vs 26% arm), mood stabiliser (43% of olanzapine arm vs 21% of aripiprazole arm) - downgraded 1 level*

[4] *Single study analysis*

[5] *Serious imprecision as the 95% CIs are wide and crosses over the default appreciable benefit (0.75) - downgraded 1 level*

[6] *Dyskinesia defined as treatment emergent dyskinesia in patients without dyskinesia in a prior rating, or as an increase of ≥2 on the abnormal involuntary movement scale in patients with dyskinesia at baseline*
[7] *Very serious imprecision as the 95% Cis are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25) – downgraded 2 levels*
[8] *Akathisia defined as a rating of >1 on the BARNES Akathisia rating scale (BARS)*
[9] *Reported as discontinuation due to extrapyramidal side effect*

Table 5: GRADE profile for Olanzapine versus Aripiprazole - continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Aripiprazole	Mean difference (95%CI)	
Outcome: metabolic side effects										
Weight change at 12 weeks in kg										
1 (Correll 2009)	Prospective cohrt	Serious[1]	Serious[2]	N/A[3]	No serious	None	41	45	MD (95%CI): 4.10 (2.77 to 5.43)	VERY LOW
BMI change at 12 weeks										
1 (Correll 2009)	Prospective cohrt	Serious[1]	Serious[2]	N/A[3]	No serious	None	41	45	MD (95%CI): 1.34 (0.84 to 1.84)	VERY LOW
Fasting glucose change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospective cohrt	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	41	45	MD (95%CI): 2.60 (-1.46 to 6.66)	VERY LOW
Fasting total cholesterol change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospective cohrt	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	41	45	MD (95%CI): 11.83 (0.61 to 23.05)	VERY LOW
Fasting LDL cholesterol change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospective cohrt	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	41	45	MD (95%CI): 4.16 (-5.60 to 13.92)	VERY LOW
Fasting HDL cholesterol change at 12 weeks in mg/dl										
1	Prospe	Serious[1]	Serious[2]	N/A[3]	Serious[5]	None	41	45	MD (95%CI): -1.56 (-	VERY

Quality assessment							No of patients		Effect estimate	Quality
(Correll 2009)	ctive cohrt								5.09 to 1.97)	LOW
Fasting triglycerides change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospe ctive cohrt	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	41	45	MD (95%CI): 26.74 (4.79 to 48.69)	VERY LOW

1 [1]*Serious risk of bias 1) blinding not described*
2 [2]*Serious indirectness 1) heterogeneous sample of diagnoses 2) cocomintant medictions permitted but numbers not reported*
3 [3]*Single study analysis*
4 [4]*Serious imprecision as confidence interval cross the default appreciable harm (+0.5 standard deviations)*
5 [5]*Serious imprecision as confidence interval crosses the default appreciable benefit*

6 **Table 6: GRADE profile for Olanzapine versus Quetiapine - dichotmous outcomes**

Quality assessment							No of patients		Effect estimate		Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Olanzapine**	**Quetiapine**	**Relative (95% CI)**	**Absolute**	
Outcome: neurological side effects											
Drug induced parkinsonism at 12 weeks[1]											
1 (Carbon 2015)	Prospe ctive cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	4/51 (8%)	1/50 (2%)	RR: 3.92 (0.45 to 33.88)	-	VERY LOW
Dyskinesia at 12 weeks[6]											
1 (Carbon 2015)	Prospe ctive cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	3/51 (6%)	2/50 (4%)	RR: 1.47 (0.26 to 8.43)	-	VERY LOW
Akathisia at 12 weeks[7]											
1 (Carbon 2015)	Prospe ctive cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	2/51 (4%)	0/50 (0%)	RR: 4.90 (0.24 to 99.66)	-	VERY LOW
Outcome: metabolic side effects											
Hyperglycemia ≥100 to 125mg/dl at 3 months											
1 (Arango 2014)	Prospe ctive cohort	Serious[8]	Serious[9]	N/A[4]	Very serious[5]	None	6/35 (17%)	2/32 (6%)	RR: 2.74 (0.60 to 12.63)	-	VERY LOW

Quality assessment							No of patients		Effect estimate		Quality
Diabetes ≥126mg/dl at 3 months											
1 (Arango 2014)	Prospective cohort	Serious[8]	Serious[9]	N/A[4]	Not estimable[10]	None	0/35 (0%)	0/32 (0%)	Not Estimable[10]	-	VERY LOW
Hypercholesterolemia (≥170mg/dl) at 3 months											
1 (Arango 2014)	Prospective cohort	Serious[8]	Serious[9]	N/A[4]	Serious[11]	None	18/35 (51%)	12/32 (38%)	RR: 1.37 (0.79 to 2.38)	-	VERY LOW
Hypertriglyceridemia (≥110mg/dl) at 3 months											
1 (Arango 2014)	Prospective cohort	Serious[8]	Serious[9]	N/A[4]	Very serious[5]	None	12/35 (34%)	7/32 (22%)	RR: 1.57 (0.70 to 3.49)	-	VERY LOW
≥7% weight increase											
1 (Arango 2014)	Prospective cohort	Serious[8]	Serious[9]	N/A[4]	Serious[11]	None	28/35 (80%)	22/32 (69%)	RR: 1.16 (0.87 to 1.55)	-	VERY LOW
Outcome: cardiac side effects											
Systolic blood pressure >90th percentile											
1 (Arango 2014)	Prospective cohort	Serious[8]	Serious[9]	N/A[4]	Very serious[5]	None	4/35 (11%)	3/32 (9%)	RR: 1.22 (0.30 to 5.03)	-	VERY LOW
Outcome: leaving the study early for any reason[12,13, 14]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	1/58 (2%)	0/66 (0%)	RR: 3.41 (0.14 to 82.04)	-	VERY LOW
1 (Noguera 2013)	Prospective cohort	Serious[15]	Serious[16]	NA[4]	Very serious[5]	None	8/18 (44%)	4/16 (25%)	RR: 1.78 (0.66 to 4.80)	-	VERY LOW

[1] *Drug induced parkinsonism defined as patients fulfilling 1 or more of the following criteria: mean Simpson Angus Scale (SAS) score >0.33 in patients with baseline mean SAS ≤0.33; start of anticholinergic medication; or marked increase of total SAS ratings of ≥2 in patients with baseline positive rating for EPS.*

[2] *Serious risk of bias: described as not blinded – downgraded 1 level*

[3] *Serious risk of bias: 1) heterogeneous sample of diagnoses –28% of olanzapine arm and 26% of aripiprazole arm had schizophrenia spectrum disorders,(rest of the population were a mix of mood spectrum disorders (50% in olanzapine arm vs 41% in aripiprazole arm) and aggression spectrum disorder (22% in olanzapine arm vs 33% in aripiprazole arm) 2) Comorbidities – ADHD (44% of olanzapine arm vs 41% of aripiprazole arm), OCD (5% of olanzapine arm vs 5% of aripiprazole arm), SUD (22% of*

olanzapine arm vs 9% of aripiprazole arm) 3) Co-medications – psychostimulants (16% of olanzapine arm vs 21% of aripiprazole arm), antidepressants (17% of olanzapine arm vs 26% arm), mood stabiliser (43% of olanzapine arm vs 21% of aripiprazole arm) - downgraded 1 level

[4] *Single study analysis*

[5] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25) - downgraded 2 levels*

[6] *Dyskinesia defined as treatment emergent dyskinesia in patients without dyskinesia in a prior rating, or as an increase of ≥2 on the abnormal involuntary movement scale in patients with dyskinesia at baseline*

[7] *Akathisia defined as a rating of >1 on the BARNES Akathisia rating scale (BARS)*

[8] *Serious risk of bias as allocation to treatment groups not described in detail, blinding not described.*

[9] *Serious indirectness 1) Heterogeneous sample of diagnoses – schizophrenia spectrum (35% vs 31%), mood spectrum disorders (40% vs 22%), behavioural disorders (12% vs 27%), other diagnoses (14% vs 19%) 2) comedications – antidepressants (32% vs 9%), benzodiazapines (41% vs 25%), mood stabilisers (16% vs 12%) 3) substance use – tobacco (37% vs 36%), alcohol (28% vs 29%), cannabis (30% vs 32%)*

[10] *Not estimable as number of events is 0*

[11] *Serious imprecision as 95%CIs wide and cross the default appreciable harm (+1.25)*

[12] *Carbon 2015: Reported as discontinuation due to extrapyramidal side effect*

[13] *Noguera 2013: Reasons included adverse reaction (n=2 vs 1); insufficient response (n=5 vs 1); lost to follow up (n=1 vs 1); not available (n=0 vs 1)*

[14] *Arango 2014: Reasons included lost to follow up (n=2 vs 7), symptom remission (n=5 vs 2), change of treatment (n=1 vs 4), intolerance (n=1 vs 0), nonadherence (n=0vs1), drug withdrawal (n=0 vs 1)*

[15] *Serious risk of bias – blinding not described, subjects allowed to change treatment during the course of the study, unclear whether doses stated are medians or means as text says medians but table states means.*

[16] *Serious indirectness 1) Heterogeneous sample of diagnoses at baseline (schizophrenia n=8); schizoaffective disorder (n=5), schizophreniform disorder (n=30), psychotic disorder not otherwise specified (n=42); major depressive disorder with psychotic symptoms (n=12) and bipolar disorder (n=13)*

Table 7: GRADE profile for Olanzapine versus Quetiapine - continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Quetiapine	Mean difference (95%CI)	
Outcome: metabolic side effects										
Weight change in kg at 12 weeks										
1 (Correll 2009)	Prospective cohort	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	45	36	MD (95%CI): 2.48 (0.90 to 4.06)	VERY LOW
Weight gain in kg at 6 months										
1 (Castrofornilles 2008)	Prospective cohort	Serious[4]	Serious[5]	N/A[3]	Serious[4]	None	14	15	MD (95%CI): 5.70 (1.46 to 9.94)	VERY LOW
BMI change at 12 weeks										
1	Prospe	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	45	36	MD (95%CI): 0.89	VERY

Quality assessment							No of patients		Effect estimate	Quality
(Correll 2009)	ctive cohort								(0.33 to 1.45)	LOW
BMI change at 6 months (units not reported)										
1 (Castrof ornilles 2008)	Prospe ctive cohort	Serious[5]	Serious[6]	N/A[3]	Serious[4]	None	14	15	MD (95%CI): 2.50 (0.32 to 4.68)	VERY LOW
BMI change at 6 months in kg/m^2										
1 (Noguer a 2013)	Prospe ctive cohort	Serious[7]	Serious[8]	N/A[3]	Serious[4]	None	16	20	MD (95%CI): 1.80 (0.49 to 3.11)	VERY LOW
BMI change at 3 months in kg/m^2										
1 (Arango 2014)	Prospe ctive cohort	Serious[9]	Serious[10]	N/A[3]	Serious[4]	None	35	32	MD (95%CI): 1.15 (0.22 to 2.08)	VERY LOW
Fasting glucose change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospe ctive cohort	Serious[1]	Serious[2]	N/A[3]	No serious	None	45	36	MD (95%CI): 0.50 (-3.47 to 4.47)	VERY LOW
Glucose change at 3 months in mg/dl										
1 (Arango 2014)	Prospe ctive cohort	Serious[9]	Serious[10]	N/A[3]	Serious[4]	None	35	32	MD (95%CI): 7.83 (0.40 to 15.26)	VERY LOW
Fasting total cholesterol change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospe ctive cohort	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	45	36	MD (95%CI): 6.53 (-5.35 to 18.41)	VERY LOW
Total cholesterol change at 3 months in mg/dl										
1 (Arango 2014)	Prospe ctive cohort	Serious[9]	Serious[10]	N/A[3]	Serious[4]	None	35	32	MD (95%CI): 2.41 (-11.01 to 15.83)	VERY LOW
Fasting LDL cholesterol change at 12 weeks in mg/dl										
1	Prospe	Serious[1]	Serious[2]	N/A[3]	Serious[4]	None	45	36	MD (95%CI): 7.66 (-	VERY

Quality assessment							No of patients		Effect estimate	Quality
(Correll 2009)	ctive cohort								2.50 to 17.82)	LOW
Fasting HDL cholesterol change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospe ctive cohort	Serious[1]	Serious[2]	N/A[3]	None	None	45	36	MD (95%CI): 0.20 (-4.05 to 4.45)	VERY LOW
Fasting triglycerides change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospe ctive cohort	Serious[1]	Serious[2]	N/A[3]	Serious[11]	None	45	36	MD (95%CI): -12.62 (-42.13 to 16.89)	VERY LOW
Triglycerides change at 3 months in mg/dl										
1 (Arango 2014)	Prospe ctive cohort	Serious[9]	Serious[10]	N/A[3]	Serious[4]	None	35	32	MD (95%CI): 20.85 (3.89 to 37.81)	VERY LOW
Outcome: neurological side effects										
Change as measured on UKU										
1 (Castrof ornilles 2008)	Prospe ctive cohort	Serious[4]	Serious[5]	N/A[3]	Serious[11]	None	14	15	MD (95%CI): -0.2 (-0.79 to 0.39)	VERY LOW
1 (Noguer a 2013)	Prospe ctive cohort	Serious [13]	Serious[14]	N/A[3]	Serious[11]	None	16	20	MD (95%CI): -0.2 (-0.7 to 0.3)	VERY LOW
Outcome: cardiac side effects										
Diastolic blood pressure change at 3 months in mmHg										
1 (Arango 2014)	Prospe ctive cohort	Serious[9]	Serious[10]	N/A[3]	Serious[4]	None	35	32	MD (95%CI): 1.06 (-4.72 to 6.84)	VERY LOW
Systolic blood pressure change at 3 months in mmHg										
1 (Arango 2014)	Prospe ctive cohort	Serious[9]	Serious[10]	N/A[3]	Serious[4]	None	35	32	MD (95%CI): 4.07 (-4.31 to 12.45)	VERY LOW

1 [1] *Serious risk of bias as blinding not described*

[2] *Serious indirectness as 1) heterogenous sample of diagnoses 2) comedications permitted but numbers not reported*
[3] *Single study analysis*
[4] *Serious imprecision as confidence interval crosses the default appreciable harm (+0.5 standard deviations)*
[5] *Allocation to treatment groups not described in detail – 51% were already receiving treatment, unclear whether these subjects carried on with same treatment or not. Study also not blinded.*
[6] *Serious indirectness: 1) heterogeneous sample of diagnoses (schizophrenia type disorder – 39%; psychotic disorder NOS 38%; depressive disorder 12%; bipolar/manic episode with psychotic symptoms 11%) – breakdown by study arms not reported*
[7] *Serious risk of bias as allocation to treatment groups not described in detail, blinding not described.*
[8] *Serious indirectness 1) Heterogeneous sample of diagnoses – schizophrenia spectrum (35% vs 31%), mood spectrum disorders (40% vs 22%), behavioural disorders (12% vs 27%), other diagnoses (14% vs 19%) 2) comedications – antidepressants (32% vs 9%), benzodiazapines (41% vs 25%), mood stabilisers (16% vs 12%) 3) substance use – tobacco (37% vs 36%), alcohol (28% vs 29%), cannabis (30% vs 32%)*
[9] *Serious risk of bias as allocation to treatment groups and blinding not described. Percentages and numbers reported in study do not match in all cases as denominators are not clearly reported – these have therefore been re-calculated by analyst based on N reported in figure 1 of study at different time points.*
[10] *Serious indirectness as heterogeneous sample of diagnoses, comedications permitted and substance use.*
[11] *Serious imprecision as 95%CI crosses the default appreciable benefit (-0.5)*
[12] *Serious risk of bias as blinding not described, subjects allowed to change treatment during the course of the study, unclear whether doses stated are medians or means as text says medians but table states means.*
[13] *Serious indirectness 1) Heterogeneous sample of diagnoses at baseline (schizophrenia n=8); schizoaffective disorder (n=5), schizophreniform disorder (n=30), psychotic disorder not otherwise specified (n=42); major depressive disorder with psychotic symptoms (n=12) and bipolar disorder (n=13)*

Table 8: GRADE profile for Olanzapine versus Risperidone - continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Risperidone	Mean difference (95%CI)	
Outcome: metabolic side effects										
Weight gain in kg at 12 weeks										
1 (Crocq 2007)	Prospective cohort	Serious[1]	No serious	N/A[2]	Serious[7]	None	16	26	MD (95%CI): 2 (0.76 to 3.24)	VERY LOW
Weight change in kg at 12 weeks										
1 (Correll 2009)	Prospectice cohort	Serious[3]	Serious[4]	N/A[2]	No serious	None	45	135	MD (95%CI): 3.20 (1.96 to 4.44)	VERY LOW
Weight gain in kg at 6 months										
1 (Castrof ornilles	Prospective cohort	Serious[5]	Serious[6]	N/A[2]	Serious[7]	None	14	31	MD (95%CI): 5.60 (1.99 to 9.21)	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
2008)										
BMI change in kg/m^{2}at 12 weeks										
1 (Crocq 2007)	Prospective cohort	Serious[1]	No serious	N/A[2]	Serious[7]	None	16	26	MD (95%CI): 0.70 (0.22 to 1.18)	VERY LOW
BMI change at 12 weeks										
1 (Correll 2009)	Prospctice cohort	Serious[3]	Serious[4]	N/A[2]	No serious	None	45	135	MD (95%CI): 1.09 (0.65 to 1.53)	VERY LOW
BMI change at 6 months (units not reported)										
1 (Castrof ornilles 2008)	Prospective cohort	Serious[5]	Serious[6]	N/A[2]	Serious[7]	None	14	31	MD (95%CI): 2.00 (0.42 to 3.58)	VERY LOW
BMI change at 6 months in kg/m^2										
1 (Noguera 2013)	Prospective cohort	Serious[8]	Serious[9]	N/A[2]	No serious	None	16	36	MD (95%CI): 2.5 (1.3 to 3.7)	VERY LOW
BMI change at 3 months in kg/m^2										
1 (Arango 2014)	Prospective cohort	Serious[10]	Serious[11]	N/A[2]	Serious[7]	None	35	118	MD (95%CI): 1.16 (0.45 to 1.87)	VERY LOW
Fasting glucose change at 3 months in mg/dl										
1 (Arango 2014)	Prospective cohort	Serious[10]	Serious[11]	N/A[2]	No serious	None	35	118	MD (95%CI): -1.46 (-7.17 to 4.25)	VERY LOW
Fasting glucose change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospctice cohort	Serious[3]	Serious[4]	N/A[2]	Very serious[12]	None	45	135	MD (95%CI): 2.00 (-1.09 to 5.09)	VERY LOW
Fasting total cholesterol change at 12 weeks I mg/dl										
1	Prospe	Serious[3]	Serious[4]	N/A[2]	Very	None	45	135	MD (95%CI): 12.12	VERY

Quality assessment							No of patients		Effect estimate	Quality
(Correll 2009)	ctice cohort				serious[12]				(2.36 to 21.88)	LOW
Fasting total cholesterol change at 3 months in mg/dl										
1 (Arango 2014)	Prospective cohort	Serious[10]	Serious[11]	N/A[2]	Very serious[12]	None	35	118	MD (95%CI): 3.74 (-6.58 to 14.06)	VERY LOW
Fasting LDL cholesterol change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospective cohort	Serious[3]	Serious[4]	N/A[2]	Serious[7]	None	45	135	MD (95%CI): 11.33 (2.80 to 19.86)	VERY LOW
Fasting HDL cholesterol change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospective cohort	Serious[3]	Serious[4]	N/A[2]	Serious[13]	None	45	135	MD (95%CI): -1.60 (-4.52 to 1.32)	VERY LOW
Fasting triglycerides change at 12 weeks in mg/dl										
1 (Correll 2009)	Prospective cohort	Serious[3]	Serious[4]	N/A[2]	Serious[7]	None	45	135	MD (95%CI): 14.60 (-2.27 to 31.47)	VERY LOW
Fasting triglycerides change at 3 months in mg/dl										
1 (Arango 2014)	Prospective cohort	Serious[10]	Serious[11]	N/A[2]	Serious[7]	None	35	118	MD (95%CI): 15.99 (0.11 to 31.87)	VERY LOW
Outcome: neurological side effects										
Change as measured on UKU										
1 (Castrofornilles 2008)	Prospective cohort	Serious[5]	Serious[6]	N/A[2]	Serious[13]	None	14	31	MD (95%CI): -1.00 (-1.91 to -0.09)	VERY LOW
1 (Noguera 2013)	Prospective cohort	Serious[8]	Serious[9]	N/A[2]	Serious[13]	None	16	36	MD (95%CI): -0.9 (-1.69 to -0.11)	VERY LOW
Outcome: cardiac side effects										

Quality assessment							No of patients		Effect estimate	Quality
Diastolic blood pressure change at 3 months in mmHg										
1 (Arango 2014)	Prospective cohort	Serious [10]	Serious[11]	N/A[2]	Serious[13]	None	35	118	MD (95%CI): -5.7 (-10.07 to -1.33)	VERY LOW
Systolic blood pressure change at 3 months in mmHg										
1 (Arango 2014)	Prospective cohort	Serious [10]	Serious[11]	N/A[2]	Serious[13]	None	35	118	MD (95%CI): -2.09 (-8.42 to 4.24)	VERY LOW

[1] *Serious risk of bias as allocation to treatment groups not described, open label, inclusion and exclusion criteria not reported, concomitant medications used not reported.*
[2] *Single study analysis*
[3] *Serious risk of bias as blinding not described*
[4] *Serious indirectness as 1) heterogenous sample of diagnoses 2) comedications permitted but numbers not reported*
[5] *Allocation to treatment groups not described in detail – 51% were already receiving treatment, unclear whether these subjects carried on with same treatment or not. Study also not blinded.*
[6] *Serious indirectness: 1) heterogeneous sample of diagnoses (schizophrenia type disorder – 39%; psychotic disorder NOS 38%; depressive disorder 12%; bipolar/manic episode with psychotic symptoms 11%) – breakdown by study arms not reported*
[7] *Serious imprecision as 95%CIs wide and crosses the default appreciable harm (+0.5 standard deviations)*
[8] *Serious risk of bias – blinding not described, subjects allowed to change treatment during the course of the study, unclear whether doses stated are medians or means as text says medians but table states means.*
[9] *Serious indirectness 1) Heterogeneous sample of diagnoses at baseline (schizophrenia n=8); schizoaffective disorder (n=5), schizophreniform disorder (n=30), psychotic disorder not otherwise specified (n=42); major depressive disorder with psychotic symptoms (n=12) and bipolar disorder (n=13)*
[10] *Serious risk of bias as allocation to treatment groups not described in detail, blinding not described.*
[11] *Serious indirectness 1) Heterogeneous sample of diagnoses – schizophrenia spectrum (35% vs 31%), mood spectrum disorders (40% vs 22%), behavioural disorders (12% vs 27%), other diagnoses (14% vs 19%) 2) comedications – antidepressants (32% vs 9%), benzodiazapines (41% vs 25%), mood stabilisers (16% vs 12%) 3) substance use – tobacco (37% vs 36%), alcohol (28% vs 29%), cannabis (30% vs 32%)*
[12] *Very serious imprecision as 95%CIs wide and crosses both the default appreciable benefit and harm (-0.5 and +0.5 standard deviations)*
[13] *Serious imprecision as 95% CIs wide and crosses the defaultappreciable benefit (-0.5)*

Table 9: GRADE profile for Olanzapine versus Risperidone - dichotmous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Risperidone	Relative (95% CI)	Absolute	
Outcome: neurological side effects											
Drug induced parkinsonism at 12 weeks[1]											

Quality assessment							No of patients		Effect estimate		Quality
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	4/51 (8%)	7/101 (7%)	RR: 1.13 (0.35 to 3.69)	-	VERY LOW
Dyskinesia at 12 weeks[6]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	3/51 (6%)	1/101 (1%)	RR: 5.94 (0.63 to 55.7)	-	VERY LOW
Akathisia at 12 weeks[7]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	2/51 (4%)	2/101 (2%)	RR: 1.98 (0.29 to 13.66)	-	VERY LOW
Outcome: leaving the study early for any reason[8, 9, 10,11]											
1 (Carbon 2015)	Prospective cohort	Serious[2]	Serious[3]	NA[4]	Very serious[5]	None	1/58 (2%)	6/137 (4%)	RR: 0.39 (0.05 to 3.20)	-	VERY LOW
1 (Castrofornilles 2008)	Prospective cohort	Serious[12]	Serious[13]	N/A[4]	Very serious[5]	None	1/14 (3%)	5/31 (16%)	RR: 0.44 (0.06 to 3.45)	-	VERY LOW
1 (Noguera 2013)	Prospective cohort	Serious[14]	Serious[15]	N/A[4]	Very serious[5]	None	8/18 (44%)	22/51 (43%)	RR: 1.03 (0.56 to 1.89)	-	VERY LOW
1 (Arango 2014)	Prospective cohort	Serious[16]	Serious[17]	N/A[4]	Very serious[5]	None	9/44 (20%)	39/157 (25%)	RR: 0.82 (0.43 to 1.57)	-	VERY LOW
Outcome: metabolic side effects											
Hyperglycemia (≥100 to 125mg/dl) at 3 months											
1 (Arango 2014)	Prospective cohort	Serious[16]	Serious[17]	N/A[4]	Serious[18]	None	6/35 (17%)	10/118 (8%)	RR: 2.02 (0.79 to 5.17)	-	VERY LOW
Diabetes (≥126mg/dl) at 3 months											
1	Prospective	Serious	Serious[17]	N/A[4]	Very serious[5]	None	0/35	2/118	RR: 0.66 (0.03 to	-	VERY

Quality assessment							No of patients		Effect estimate		Quality
(Arango 2014)	cohort	[16]					(0%)	(2%)	13.46)		LOW
Hypocholesteraemia (≥170mg/dl) at 3 months											
1 (Arango 2014)	Prospective cohort	Serious [16]	Serious[17]	N/A[4]	Serious[18]	None	18/35 (51%)	45/118 (38%)	RR: 1.35 (0.91 to 2.00)	-	VERY LOW
Hypertriglyceridemia (≥110mg/dl) at 3 months											
1 (Arango 2014)	Prospective cohort	Serious [16]	Serious[17]	N/A[4]	Serious[18]	None	12/35 (34%)	18/118 (15%)	RR: 2.25 (1.20 to 4.20)	-	VERY LOW
≥7% weight increase in kg at 3 months											
1 (Arango 2014)	Prospective cohort	Serious [16]	Serious[17]	N/A[4]	Serious[18]	None	28/35 (80%)	74/118 (63%)	RR: 1.28 (1.03 to 1.58)	-	VERY LOW
Outcome: cardiac side effects											
Systolic blood pressure >90th percentile at 3 months											
1 (Arango 2014)	Prospective cohort	Serious [16]	Serious[17]	N/A[4]	Very serious[5]	None	4/35 (11%)	28/118 (24%)	RR: 0.48 (0.18 to 1.28)	-	VERY LOW

[1] *Drug induced parkinsonism defined as patients fulfilling 1 or more of the following criteria: mean Simpson Angus Scale (SAS) score >0.33 in patients with baseline mean SAS ≤0.33; start of anticholinergic medication; or marked increase of total SAS ratings of ≥2 in patients with baseline positive rating for EPS.*

[2] *Serious risk of bias: described as not blinded – downgraded 1 level*

[3] *Serious risk of bias: 1) heterogeneous sample of diagnoses –28% of olanzapine arm and 26% of aripiprazole arm had schizophrenia spectrum disorders,(rest of the population were a mix of mood spectrum disorders (50% in olanzapine arm vs 41% in aripiprazole arm) and aggression spectrum disorder (22% in olanzapine arm vs 33% in aripiprazole arm) 2) Comorbidities – ADHD (44% of olanzapine arm vs 41% of aripiprazole arm), OCD (5% of olanzapine arm vs 5% of aripiprazole arm), SUD (22% of olanzapine arm vs 9% of aripiprazole arm) 3) Co-medications – psychostimulants (16% of olanzapine arm vs 21% of aripiprazole arm), antidepressants (17% of olanzapine arm vs 26% arm), mood stabiliser (43% of olanzapine arm vs 21% of aripiprazole arm) - downgraded 1 level*

[4] *Single study analysis*

[5] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25) - downgraded 2 levels*

[6] *Dyskinesia defined as treatment emergent dyskinesia in patients without dyskinesia in a prior rating, or as an increase of ≥2 on the abnormal involuntary movement scale in patients with dyskinesia at baseline*

[7] *Akathisia defined as a rating of >1 on the BARNES Akathisia rating scale (BARS)*

[8] *Carbon 2015 - reported as discontinuation due to extrapyramidal side effect*

[9] *Castrofornilles 2008 – discontinued due to side effects, details not reported*

[10] *Noguera 2013 – reasons included adverse reaction (n=2 vs 5); insufficient response (n=5 vs 11), lost to follow up (n=1 vs 4); other (n=0 vs 1); not available (n=0 vs 1).*

[11] *Arango 2014 – reasons included lost to follow up (n=2 vs 17), symptom remission (n=5 vs 2), change of treatment (n=1 vs 8), intolerance (n=1 vs 0), drug withdrawal (n=0 vs 4), nonadherence (n=0 vs 2), lack of efficacy (n=0 vs 1), other reasons (n=0 vs 5) . Dropouts 3 to 6 months were similar reasons (not due to adverse effects).*

[12] *Allocation to treatment groups not described in detail – 51% were already receiving treatment, unclear whether these subjects carried on with same treatment or not. Study also not blinded.*
[13] *Serious indirectness: 1) heterogeneous sample of diagnoses (schizophrenia type disorder – 39%; psychotic disorder NOS 38%; depressive disorder 12%; bipolar/manic episode with psychotic symptoms 11%) – breakdown by study arms not reported*
[14] *Serious risk of bias – blinding not described, subjects allowed to change treatment during the course of the study, unclear whether doses stated are medians or means as text says medians but table states means.*
[15] *Serious indirectness 1) Heterogeneous sample of diagnoses at baseline (schizophrenia n=8); schizoaffective disorder (n=5), schizophreniform disorder (n=30), psychotic disorder not otherwise specified (n=42); major depressive disorder with psychotic symptoms (n=12) and bipolar disorder (n=13)*
[16] *Serious risk of bias as allocation to treatment groups not described in detail, blinding not described.*
[17] *Serious indirectness 1) Heterogeneous sample of diagnoses – schizophrenia spectrum (35% vs 31%), mood spectrum disorders (40% vs 22%), behavioural disorders (12% vs 27%), other diagnoses (14% vs 19%) 2) comedications – antidepressants (32% vs 9%), benzodiazapines (41% vs 25%), mood stabilisers (16% vs 12%) 3) substance use – tobacco (37% vs 36%), alcohol (28% vs 29%), cannabis (30% vs 32%)*
[18] *Serious imprecision as 95% CIs wide and cross the default appreciable harm (1.25)*

H.2[7] GRADE profiles for evidence from RCT studies - direct studies i.e. age ≤18 years

[18] **Table 10: GRADE profile for Olanzapine versus Risperidone - continuous outcomes**

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Risperidone	Mean difference (95%CI)	
Outcome: Metabolic side effects										
Weight in kg at week 8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95%CI): 7.7 (-8.9 to 24.3)	VERY LOW
Weight gain in kg at week 12										
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Serious[9]	None	N=12	N=13	MD (95%CI): 1.33 (-1.30 to 3.96)	VERY LOW
Weight change in kg at week 8										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Serious[9]	None	N=35	N=41	MD (95%CI): 2.50 (0.79 to 4.21)	LOW
BMI in kg/m^2 at week 8 (endpoint)										

Quality assessment							No of patients		Effect estimate	Quality
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Serious[9]	None	N=16	N=19	MD (95%CI): 1.4 (-2.87 to 5.67)	VERY LOW
BMI change in kg/m^2 at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Serious[9]	None	N=35	N=41	MD (95%CI): 0.90 (0.29 to 1.51)	VERY LOW
Random glucose in mg/dl at week8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Serious[9]	None	N=16	N=19	MD (95% CI): 18.2 (6.84 to 29.56)	VERY LOW
Fasting glucose change in mg/dl										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Very serious[4]	None	N=12	N=22	MD (95%CI): -0.60 (-9.99 to 8.79)	VERY LOW
Fasting total cholesterol change in mg/dl at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	No serious	None	N=12	N=22	MD (95%CI): 30.1 (12.57 to 47.63)	LOW
Fasting HDL cholesterol change in mg/dl at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Very serious[4]	None	N=12	N=21	MD (95%CI): 5.1 (-1.08 to 11.28)	VERY LOW
Random HDL in mg/dl at week 8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95% CI): -5.2 (-14.68 to 4.28)	VERY LOW
Random LDL in mg/dl at week 8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95% CI): -12.6 (-30.66 to 5.46)	VERY LOW
Fasting LDL cholesterol change in mg/dl at 8 weeks										

Quality assessment							No of patients		Effect estimate	Quality
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	No serious	None	N=12	N=20	MD (95%CI): 24.3 (9.93 to 38.67)	LOW
Random triglycerides in mg/dl at week 8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95% CI): 28 (-15.74 to 71.74)	VERY LOW
Fasting triglycerides change in mg/dl at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Very serious[4]	None	N=12	N=21	MD (95%CI): 14.5 (-25.1 to 54.1)	VERY LOW
Outcome: Neurological side effects										
Simpson-angus EPS score at week 8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95%CI): -0.20 (-1.74 to 1.34)	VERY LOW
Simpson-angus rating scale change at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Very serious[4]	None	N=35	N=41	MD (95%CI): -0.20 (-1.19 to 0.79)	VERY LOW
Barnes Rating Scale change for Drug induced Akathisia at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Very serious[4]	None	N=35	N=41	MD (95%CI): -0.20 (-1.21 to 0.81)	VERY LOW
AIMS change at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	Very serious[4]	None	N=35	N=41	MD (95%CI): 0.00 (-0.94 to 0.94)	VERY LOW
Outcome: Hormonal side effects										
Prolactin in ng/Ml at week 8 (endpoint)										
1 (Sikich	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95%CI): -7.2 (-18.12 to 3.72)	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
2004)										
Prolactin change in ug/l at 8 weeks										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	No serious	None	N=35	N=41	MD (95%CI): -21 (-30.39 to -11.61)	LOW
Outcome: Cardiac side effects										
QT_c interval in msecs at week 8 (endpoint)										
1 (Sikich 2004)	RCT	Serious[1]	Serious[2]	N/A[3]	Very serious[4]	None	N=16	N=19	MD (95%CI): 0.00 (-15.92 to 15.92)	VERY LOW
QT_c change in msecs at week 8										
1 (Sikich 2008)	RCT	Serious[7]	Serious[8]	N/A[3]	No serious	None	N=35	N=41	MD (95%CI): 10.7 (0.09 to 21.31)	LOW

[1] *Serious risk of bias, allocation concealment not described, co-morbidities not reported – downgraded 1 level*
[2] *Serious indirectness 1) heterogeneous sample of diagnoses (schizophrenia spectrum 31% in the olanzapine arm vs 68% in the risperidone arm; affective disorders 69% in the olanzapine arm vs 32% in the risperidone arm) 2) Concomitant medications (benztropine, amantadine, propranolol, lorazepam, initial antidepressant, mood stabiliser) – 88% of olanzapine arm vs 89% of risperidone arm*
[3] *Single study analysis*
[4] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (-0.5 and +0.5 standard deviations) - downgraded 2 levels*
[5] *Serious risk of bias – randomisation method and allocation concealment not described, open label study. Inclusion criteria not reported, small sample size.*
[6] *Serious indirectness – use of concomitant medications (100% vs 69%), comorbidities (33% vs 54%)*
[7] *Serious risk of bias as randomisation and allocation concealment not described. 285 subjects not enrolled – reasons not provided.*
[8] *Serious indirectness – use of concomitant medication with anticholinergic agents, propranolol, benzodiazepines, mood stabilisers, antidepressants were guided by algorithms.*
[9] *Serious imprecision as 95% CIs wide and cross over the default appreciable harm (+0.5 standard deviations) – downgraded 1 level*

Table 11: GRADE profile for Olanzapine versus Risperidone - dichotomous outcomes

No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Risperidone	Relative (95% CI)	Absolute	
Outcome: Neurological outcomes											
Akathisia at week 8 (endpoint)[1]											
1	RCT	Serious[2]	Serious[3]	N/A[3]	Very serious[4]	None	2/16	0/19	RR: 5.88	-	VERY

(Sikich 2004)							(14%)	(0%)	(0.30 to 114.28)		LOW
Extrapyramidal side effects as assessed by the Simpson Angus Scale and Barnes Akathisia Rating Scale:											
Gait											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	3/12 (25%)	5/13 (39%)	RR: 0.65 (0.20 to 2.15)	-	VERY LOW
Arm dropping											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	0/12 (0%)	4/13 (31%)	RR: 0.12 (0.01 to 2.01)	-	VERY LOW
Shoulder shaking											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	0/12 (0%)	3/13 (23%)	RR: 0.15 (0.01 to 2.70)	-	VERY LOW
Elbow rigidity											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	1/12 (8%)	4/13 (31%)	RR: 0.27 (0.04 to 2.10)	-	VERY LOW
Wrist rigidity											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	0/12 (0%)	4/13 (31%)	RR: 0.12 (0.01 to 2.01)	-	VERY LOW
Leg pendulousness											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	1/12 (8%)	2/13 (17%)	RR: 0.54 (0.06 to 5.24)	-	VERY LOW
Head dropping											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	1/12 (8%)	2/13 (17%)	RR: 0.54 (0.06 to 5.24)	-	VERY LOW
Glabellar tap											
1	RCT	Serious[5]	Serious[6]	N/A[3]	Serious[7]	None	4/12	9/13	RR: 0.48	-	VERY

(Mozes 2006)							(33%)	(69%)	(0.20 to 1.16)		LOW
Tremor											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	6/12 (50%)	9/13 (69%)	RR: 0.72 (0.37 to 1.41)	-	VERY LOW
Salivation											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	4/12 (33%)	5/13 (39%)	RR: 0.87 (0.30 to 2.49)	-	VERY LOW
Akathisia objective											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	2/12 (17%)	1/13 (8%)	RR: 2.17 (0.22 to 20.94)	-	VERY LOW
Akathisia subjective											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	2/12 (17%)	2/13 (17%)	RR: 1.08 (0.18 to 6.53)	-	VERY LOW
Distress related to restlessness											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	2/12 (17%)	0/13 (0%)	RR: 5.38 (0.28 to 101.96)	-	VERY LOW
Global clinical assessment of akathisia											
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	2/12 (17%)	1/13 (8%)	RR: 2.17 (0.22 to 20.94)	-	VERY LOW
Outcome: leaving the study early for any reason[8,9]											
1 (Sikich 2004)	RCT	Serious[2]	Serious[3]	N/A[3]	No serious	None	2/16 (13%)	9/19 (47%)	RR: 0.26 (0.07 to 1.05)	-	LOW
1 (Mozes 2006)	RCT	Serious[5]	Serious[6]	N/A[3]	Very serious[4]	None	1/12 (8%)	4/13 (31%)	RR: 0.27 (0.04 to 2.10)	-	VERY LOW

1 (Sikich 2008)	RCT	Serious [10]	Serious[11]	N/A[3]	Serious[12]	None	18/35 (51%)	13/42 (32%)	RR: 1.62 (0.93 to 2.82)	-	VERY LOW

1 [1] *Unclear how akathisia was assessed*
2 [2] *Serious risk of bias, allocation concealment not described, co-morbidities not reported – downgraded 1 level*
3 [3] *Serious indirectness 1) heterogeneous sample of diagnoses (schizophrenia spectrum 31% in the olanzapine arm vs 68% in the risperidone arm; affective disorders 69% in the olanzapine arm vs 32% in the risperidone arm) 2) Concomitant medications (benztropine, amantadine, propranolol, lorazepam, initial antidepressant, mood stabiliser) – 88% of olanzapine arm vs 89% of risperidone arm*
6 [4] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25) - downgraded 2 levels*
7 [5] *Serious risk of bias – randomisation method and allocation concealment not described, open label study. Inclusion criteria not reported, small sample size.*
8 [6] *Serious indirectness – use of concomitant medications (100% vs 69%), comorbidities (33% vs 54%)*
9 [7] *Serious imprecision as 95% CIs wide and crosses over the default appreciable benefit (0.75)*
10 [8] *Sikich 2004 - reasons for dropout: insufficient response (n=2 vs 2); EPS (n=0 vs 1); weight gain (n=0 vs 3); other side effects (n=0 vs 1); noncompliance (n=0 vs 2); moved to remote site (n=0 vs 1)*
12 [9] *Mozes 2006 – reasons for dropout: contact lost (1 vs 0); lack of improvement (0 vs 3); severe hyperprolactinemia (0 vs 1)*
13 [10] *Sikich 2008: Serious risk of bias as randomisation and allocation concealment not described. 285 subjects not enrolled – reasons not provided.*
14 [11] *Sikich 2008: Serious indirectness – use of concomitant medication with anticholinergic agents, propranolol, benzodiazepines, mood stabilisers, antidepressants were guided by algorithms.*
15 [12] *Serious imprecision as 95% CIs wide and crosses over the default appreciable benefit (1.25)*
16 [13]
17
18

19 **Table 12: GRADE profile for Olanzapine versus Clozapine - continuous outcomes**

Quality assessment							No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Other considerations**	**Olanzapine**	**Clozapine**	**Mean difference (95%CI)**	
Outcome: Metabolic side effects										
Weight gain in kg i.e. change at 8 weeks										
1 (Shaw 2006)	RCT	No serious	Serious[1]	N/A[2]	Very serious[3]	None	13	12	MD (95%CI): -0.2 (-4.23 to 3.83)	VERY LOW
BMI change in kg/m2at 8 weeks										
1 (Shaw 2006)	RCT	No serious	Serious[1]	N/A[2]	Very serious[3]	None	13	12	MD (95%CI): -0.2 (-1.86 to 1.46)	VERY LOW
BMI at 12 weeks, endpoint										
1 (Kumra	RCT	Serious[4]	Serious[5]	N/A[2]	Very serious[3]	None	21	17	MD (95%CI): 0.50 (-2.35 to 3.35)	VERY LOW

Quality assessment							No of patients		Effect estimate	Quality
2008)										
Fasting glucose in mg/dl at 12 weeks										
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Serious[6]	None	21	17	MD (95%CI): -10.1 (-18.74 to -1.46)	LOW
Fasting triglycerides at 12 weeks (units not reported)										
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Serious[6]	None	21	17	MD (95%CI): -20.2 (-66.59 to 26.19)	VERY LOW
Fasting cholesterol at 12 weeks (units not reported)										
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Serious[7]	None	21	17	MD (95%CI): 10.4 (-10.79 to 31.59)	VERY LOW
BMI at 12 weeks (units not reported)										
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Very serious[3]	None	21	17	MD (95%CI): 0.50 (-2.35 to 3.35)	VERY LOW

[1] *Serious indirectness, comorbid ADHD, ODD, CD (23% vs 33%), comorbid anxiety disorders (8% vs 50%), concomitant medications including valproate sodium, clomipramine hydrochloride, guanfacine hydrochloride, lorazepam, diphenhydramine hydrochloride (92% vs 58%)*
[2] *Single study analysis*
[3] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (-0.5 and +0.5 standard deviations) - downgraded 2 levels*
[4] *Serious risk of bias as allocation concealment is not described*
[5] *Serious indirectness as concomitant medications received (lithium, depakoate, mood stabilisers, antidepressants, stimulants, naltrexone – numbers by arm not reported)*
[6] *Serious imprecision as confidence interval crosses the default appreciable benefit (-0.5)*
[7] *Serious imprecision as confidence interval crosses the default appreciable harm (+0.5 standard deviations)*

Table 13: GRADE table for Olanzapine versus Clozapine - dichotomous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Clozapine	Relative (95% CI)	Absolute	
Outcome: cardiac side effects											
Hypertension at 8 weeks											

Quality assessment							No of patients		Effect estimate		Quality
1 (Shaw 2006)	RCT	No serious	Serious[1]	N/A[2]	No serious	None	1/11 (9%)	7/11 (64%)	RR: 0.14 (0.02 to 0.98)	-	Moderate
Tachycardia >100bpm supine at 8 weeks											
1 (Shaw 2006)	RCT	No serious	Serious[1]	N/A[2]	No serious	None	2/12 (17%)	7/10 (70%)	RR: 0.24 (0.06 to 0.90)	-	Moderate
Tachycardia >120bmp supine at 8 weeks											
1 (Shaw 2006)	RCT	No serious	Serious[1]	N/A[2]	Serious[3]	None	0/12 (0%)	1/10 (10%)	RR: 0.28 (0.01 to 6.25)	-	Low
Outcome: metabolic side effects											
At healthy weight (BMI percentile≥5 to <85)											
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Very serious[6]	None	4/21 (19%)	1/17 (6%)	RR: 3.24 (0.40 to 26.34)	-	VERY LOW
Overweight (BMI percentiles ≥85 to <95)											
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Serious[7]	None	5/21 (24%)	9/17 (53%)	RR: 0.45 (0.19 to 1.09)	-	VERY LOW
Obese (BMI percentiles ≥95 percentile)											
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Very serious[6]	None	12/21 (57%)	9/17 (43%)	RR: 1.08 (0.60 to 1.93)	-	VERY LOW
Outcome: leaving the study early [8,9]											
1 (Shaw 2006)	RCT	No serious	Serious[1]	N/A[2]	Serious[3]	None	8/10 (80%)	1/10 (10%)	RR: 8 (1.21 to 52.69)	-	LOW
1 (Kumra 2008)	RCT	Serious[4]	Serious[5]	N/A[2]	Very serious[6]	None	7/21 (33%)	4/18 (22%)	RR: 1.50 (0.52 to 4.31)	-	VERY LOW

1 [1] *Serious indirectness, comorbid ADHD, ODD, CD (23% vs 33%), comorbid anxiety disorders (8% vs 50%), concomitant medications including valproate sodium,*
2 *clomipramine hydrochloride, guanfacine hydrochloride, lorazepam, diphenhydramine hydrochloride (92% vs 58%)*

[2] *Single study analysis*
[3] *Serious imprecision as the 95% CIs are wide and crosses the default appreciable harm (1.25) – downgraded 1 level*
[4] *Serious risk of bias as allocation concealment is not described*
[5] *Serious indirectness as concomitant medications received (lithium, depakoate, mood stabilisers, antidepressants, stimulants, naltrexone – numbers by arm not reported)*
[6] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25) - downgraded 2 levels*
[7] *Serious imprecision as the 95% CIs are wide and crosses the default appreciable benefit (0.75) – downgraded 1 level*
[8] *Shaw 2006: 8/10 subjects in the olanzapine arm for who follow up data were obtained at 2 years dropped out and changed to clozapine due to treatment resistance. 1/10 subjects in the clozapine arm discontinued due to extreme weight gain.*
[9] *Kumra 2008: reasons for dropout included nonresponse (6 vs 0), treatment emergent neutropenia (1 vs0), excessive weight gain (0 vs 2); treatment non-response (0 vs 1); withdrawal of consent (0 vs 1)*

Table 14: GRADE profile for Olanzapine versus Quetiapine - dichotomous outcomes

Quality assessment							No of patients		Effect estimate		Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Quetiapine	Relative (95% CI)	Absolute	
Outcome: Metabolic side effects[1]											
Weight gain at end point at 6 months											
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Serious[5]	None	15/26 (58%)	8/24 (33%)	RR: 1.73 (0.90 to 3.33)	-	VERY LOW
Outcome: Neurological side effects[1]											
Concentration difficulties at 6 months											
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Very serious[6]	None	9/26 (35%)	6/24 (25%)	RR: 1.38 (0.58 to 3.31)	-	VERY LOW
Hypokinesia/akinesia at 6 months											
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Very serious[6]	None	4/26 (15%)	2/24 (8%)	RR: 1.85 (0.37 to 9.18)	-	VERY LOW
Tremor at 6 months											
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Serious[5]	None	4/26 (15%)	4/24 (17%)	RR: 0.92 (0.26 to 3.29)	-	VERY LOW
Akathisia at 6 months											

Quality assessment							No of patients		Effect estimate		Quality
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Very serious[6]	None	3/26 (12%)	0/24 (0%)	RR: 6.48 (0.35 to 119.32)	-	VERY LOW
Outcome: Hormonal side effects											
Increased tendency to sweat at 6 months											
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Very serious[6]	None	5/26 (19%)	1/24 (4%)	RR: 4.62 (0.58 to 36.73)	-	VERY LOW
Outcome: Cardiac side effects											
Palpitations/tachycardia at 6 months											
1 (Arango 2009)	RCT	Very serious[2]	Serious[3]	N/A[4]	Very serious[6]	None	1/26 (4%)	1/24 (4%)	RR: 0.92 (0.06 to 13.95)	-	VERY LOW
Outcome: leaving the study early for any reason[7]											
1 (Arango 2009)	RCT	Very serious[2]	Serious	N/A[4]	Very serious[6]	None	10/26 (38.5%)	8/24 (33%)	RR: 1.15 (0.55 to 2.43)	-	VERY LOW

[1] *As measured with the UKU scale*

[2] *Very serious risk of bias 1) allocation concealment not described 2) open label (neither participants/researchers blinded to treatment) 3) poor reporting of data: percentages and denominator for number of events reported in study do not match up, therefore number randomised has been used as the denominator*

[3] *Serious indirectness 1) heterogeneous sample of diagnosis – schizophrenia (35% vs 33%); bipolar disorder (19% vs 33%); psychosis NOS (33% vs 25%), schizoaffective disorder (25% vs 25%), schizophreniform disorder (17% vs 25%); major depressive disorder (25% vs 25%) 2) Concomitant medications including anticholinergics, beta-blockers, benzodiazepines, antidepressants, antiepileptics, lithium, analgesics, iron compounds, cough medications, all patients were also prescribed risperidone flexible dose 3-5 days prior to randomisation.*

[4] *Single study analysis*

[5] *Serious imprecision as the 95% CIs are wide and crosses the default appreciable harm (1.25) – downgraded 1 level*

[6] *Very serious imprecision as the 95% CIs are wide and crosses over both the default appreciable benefit and harm (0.75 and 1.25) - downgraded 2 levels*

[7] *Reasons for drop out included loss to follow up (n=4 vs 3); symptom remission (n=1 vs 0); poor response (n=2 vs 0); poor compliance (n=0 vs 1);change to treatment (n=2 vs 0); adverse events (n=0 vs 0)*

H.3 GRADE profiles for evidence from observational studies - indirect evidence i.e. mean age <25 years

Table 15: GRADE profile for Olanzapine versus Risperidone - continuous outcomes

Quality assessment							No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Olanzapine	Risperidone	Mean difference (95%CI)	
Outcome: Quality of life[1]										
1 (Montes 2003)	Prospective cohort	Serious[1]	Serious[2]	N/A[3]	No serious	None	114	31	MD (95%CI): -0.01 (-0.13 to 0.11)	VERY LOW

[1] *Serious risk of bias as concomitant medications permitted*
[2] *Serious indirectness as study includes subjects up to 40 years of age, mean age of 24 vs 22.6 years in intervention and comparator arm respectively*
[3] *Single study analysis*

1 Appendix I: Economic search strategy

2 Databases that were searched, together with the number of articles retrieved from each
3 database are shown in Table 16. The search strategy is shown in Table 17. A similar
4 strategy was translated for the other databases listed.

5 **Table 16: Economic search summary**

Economics	Version/files	No. retrieved
MEDLINE (Ovid)	Ovid MEDLINE(R) 1946 to October Week 1 2015	71
MEDLINE in Process (Ovid)	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 12, 2015	53
Embase (Ovid)	Embase 1974 to 2015 Week 41	583
NHS Economic Evaluation Database (NHS EED) (legacy database)	NHS Economic Evaluation Database : Issue 2 of 4, April 2015	31
Health Technology Assessment (HTA Database)	Health Technology Assessment Database : Issue 3 of 4, July 2015	5
PubMed	-	59

6 **Table 17: Economic search strategy**

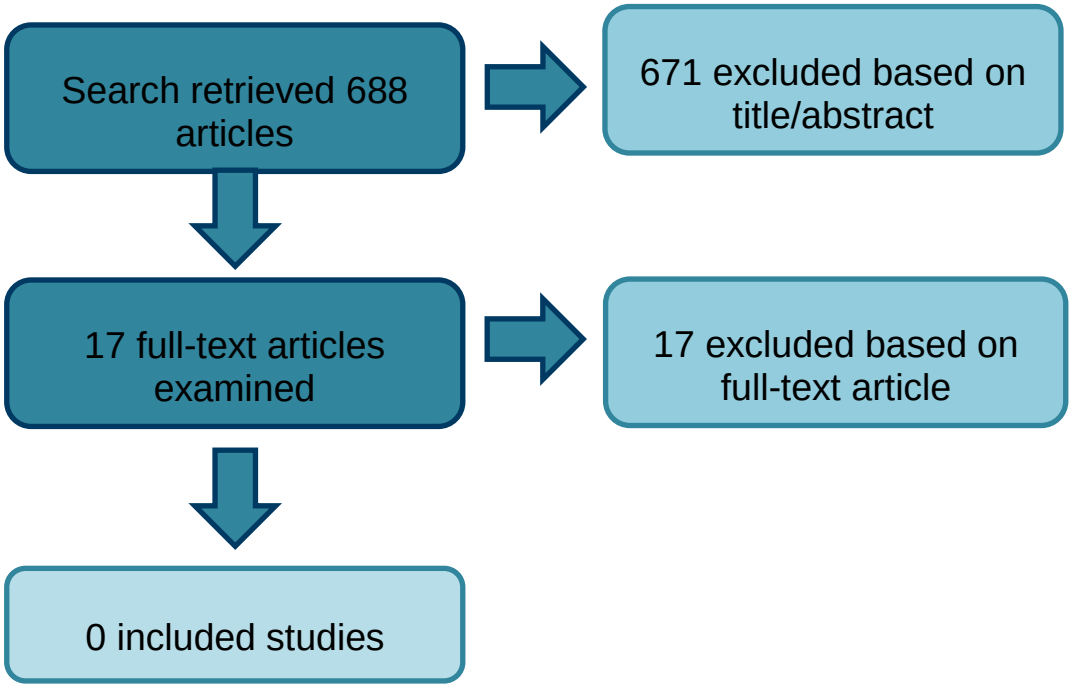
Database: Medline
Strategy used: 1 exp "schizophrenia and disorders with psychotic features"/ (123611) 2 schizophrenia, childhood/ (1490) 3 delusions/ (6779) 4 hallucinations/ (9503) 5 (delusion* or hallucinat* or hebephreni* or oligophreni* or paranoi* or paraphreni* or psychotic* or psychosis or psychoses or schizo*).tw. (148878) 6 or/1-5 (183749) 7 olanzapine*.tw. (6132) 8 (aedon or amulsin or anzatric or anzorin or apsico or apzet or arenbil or arkolamyl or asterilon or atyzyo or axonium or bloonis or caprilon or cinol or clingozan or dopin or elynza or enolex or epilanz or expolid or exzapine or fordep or fredilan or jolyon or joyzol or kynapine or lano or lanopin or lansyn or lanza* or lanzek or lapenza or lapozan or lazap* or lupilan or ly170053 or manza or meltolan or midax or m-olan or neupine or newzypra or niolib or nolian or normiton or nykob or nylsanuc or nyzol or ofans or oferta or olace or oladay or olafer or olafid or olan* or olapax or olapin* or olastazen or olasyn or olaxinn or olazofren or olazax or oleanz or olenxa or oles or olexar or olfrex or olima or olivin or oliza or ollafax or olmyzem or olnegis or olpin* or oltal or olzadin or olzanid or olzap* or olzin or onezyp or onza* or opin or opinox or opirap or oxatech or ozace or ozap* or ozilormar or ozin or parnassan or parnasan or pinolza or psycholanz or psychozap or ranofren or redilanz or relprevv or remittal or rexapin or revertrix or rolanzax or rolyprexa or sanza or sartina or simina or sincris or stygapon or synza or tanssel or tolanz or villamos or xoltiva or zalasta or zalepin or zamil or zanprex or zap or zapilux or zapinex or zappa or zapris or zelta or zeprex or zerpi or zolafren or zolapine or zolaxa or zonapi* or zophix or zopina or zopix or zopridoxin or zoxil or zydis or zylanza or zylap or zypadhera or zypefar or zypine or zyprex* or zyzapin).tw. (8973) 9 (ly adj4 "170053").tw. (2) 10 or/7-9 (8973) 11 6 and 10 (3830) 12 Animals/ not Humans/ (4033465)

Database: Medline

13 11 not 12 (3487)
14 limit 13 to english language (3221)
15 limit 14 to ed=20120101-20151031 (607)
16 Economics/ (27199)
17 exp "Costs and Cost Analysis"/ (194377)
18 Economics, Dental/ (1887)
19 exp Economics, Hospital/ (20822)
20 exp Economics, Medical/ (13966)
21 Economics, Nursing/ (3955)
22 Economics, Pharmaceutical/ (2637)
23 Budgets/ (10205)
24 exp Models, Economic/ (11174)
25 Markov Chains/ (10978)
26 Monte Carlo Method/ (22012)
27 Decision Trees/ (9399)
28 econom$.tw. (169950)
29 cba.tw. (8989)
30 cea.tw. (17210)
31 cua.tw. (825)
32 markov$.tw. (12889)
33 (monte adj carlo).tw. (22718)
34 (decision adj3 (tree$ or analys$)).tw. (9170)
35 (cost or costs or costing$ or costly or costed).tw. (333573)
36 (price$ or pricing$).tw. (24919)
37 budget$.tw. (18407)
38 expenditure$.tw. (37694)
39 (value adj3 (money or monetary)).tw. (1441)
40 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (2976)
41 or/16-40 (704982)
42 "Quality of Life"/ (132361)
43 quality of life.tw. (153758)
44 "Value of Life"/ (5517)
45 Quality-Adjusted Life Years/ (8051)
46 quality adjusted life.tw. (6804)
47 (qaly$ or qald$ or qale$ or qtime$).tw. (5557)
48 disability adjusted life.tw. (1415)
49 daly$.tw. (1372)
50 Health Status Indicators/ (21128)
51 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (16740)
52 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1057)
53 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (3006)
54 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (22)
55 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (342)
56 (euroqol or euro qol or eq5d or eq 5d).tw. (4519)
57 (qol or hql or hqol or hrqol).tw. (27689)
58 (hye or hyes).tw. (60)
59 health$ year$ equivalent$.tw. (38)

Database: Medline	
60	utilit$.tw. (123006)
61	(hui or hui1 or hui2 or hui3).tw. (929)
62	disutili$.tw. (242)
63	rosser.tw. (71)
64	quality of wellbeing.tw. (5)
65	quality of well-being.tw. (349)
66	qwb.tw. (179)
67	willingness to pay.tw. (2531)
68	standard gamble$.tw. (696)
69	time trade off.tw. (803)
70	time tradeoff.tw. (220)
71	tto.tw. (644)
72	or/42-71 (350481)
73	41 or 72 (1007707)
74	15 and 73 (71)

Appendix J: Economic review flowchart



1 Appendix K: Excluded economic studies

2 The list of excluded economic studies and the reason for their exclusion is provided in Table
3 18.

4 **Table 18: Excluded economic studies**

Study	Reason for Exclusion
Achilla,E., McCrone,P., The cost effectiveness of long-acting/extended-release antipsychotics for the treatment of schizophrenia: a systematic review of economic evaluations. [Review], Applied Health Economics & Health Policy, 11, 95-106, 2013	Systematic review, individual studies checked and subsequently excluded because they did not meet the inclusion criteria
Ascher-Svanum,H., Furiak,N.M., Lawson,A.H., Klein,T.M., Smolen,L.J., Conley,R.R., Culler,S.D., Cost-effectiveness of several atypical antipsychotics in orally disintegrating tablets compared with standard oral tablets in the treatment of schizophrenia in the United States, Journal of Medical Economics.15 (3) (pp 531-547), 2012.Date of Publication: June 2012., 531-547, 2012	Adult population
Colombo,G.L., Caruggi,M., Di,Matteo S., Rossi,A., An economic evaluation of aripiprazole vs olanzapine adapted to the Italian setting using outcomes of metabolic syndrome and risk for diabetes in patients with schizophrenia.[Erratum appears in Neuropsychiatr Dis Treat. 2008 Dec;4(6):1283], Neuropsychiatric Disease & Treatment, 4, 967-976, 2008	Adult population
Einarson,T.R., Hemels,M.E., Validation of an economic model of paliperidone palmitate for chronic schizophrenia, Journal of Medical Economics, 16, 1267-1274, 2013	Systematic review, individual studies checked and subsequently excluded because they did not meet the inclusion criteria
Furiak,N.M., Ascher-Svanum,H., Klein,R.W., Smolen,L.J., Lawson,A.H., Conley,R.R., Culler,S.D., Cost-effectiveness model comparing olanzapine and other oral atypical antipsychotics in the treatment of schizophrenia in the United States, Cost Effectiveness & Resource Allocation, 7, 4-, 2009	Adult population
Garcia-Ruiz,A.J., Perez-Costillas,L., Montesinos,A.C., Alcalde,J., Oyaguez,I., Casado,M.A., Cost-effectiveness analysis of antipsychotics in reducing schizophrenia relapses, Health Economics Review.2 (1) (pp 1-12), 2012.Date of Publication: 2012., 1-12, 2012	Adult population
Geitona,M., Kousoulakou,H., Ollandezos,M., Athanasakis,K., Papanicolaou,S., Kyriopoulos,I., Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: a cost effectiveness study, Annals of General Psychiatry, 7, 16-, 2008	Adult population
Graham,C.N., Mauskopf,J.A., Lawson,A.H., Ascher-Svanum,H., Bruhn,D., Updating and confirming an industry-sponsored pharmacoeconomic model: Comparing two antipsychotics in the treatment of schizophrenia, Value in Health.15 (1) (pp 55-64), 2012.Date of Publication: January-February 2012., 55-64, 2012	Adult population
Kasteng,F., Eriksson,J., Sennfalt,K., Lindgren,P., Metabolic effects and cost-effectiveness of aripiprazole versus olanzapine in schizophrenia and bipolar disorder, Acta psychiatrica Scandinavica, 124, 214-225, 2011	Adult population

Study	Reason for Exclusion
Kruse,G., Wong,B.J., Duh,M.S., Lefebvre,P., Lafeuille,M.H., Fastenau,J.M., Systematic Literature Review of the Methods Used to Compare Newer Second-Generation Agents for the Management of Schizophrenia: A focus on Health Technology Assessment, PharmacoEconomics, 33, 1049-1067, 2015	Systematic review, individual studies checked and subsequently excluded because they did not meet the inclusion criteria
Lachaine,J., Beauchemin,C., Mathurin,K., Gilbert,D., Beillat,M., Cost-effectiveness of asenapine in the treatment of schizophrenia in Canada, Journal of Medical Economics.17 (4) (pp 296-304), 2014.Date of Publication: 2014., 296-304, 2014	Adult population
Millier,A., Amri,I., Boyer,L., Auquier,P., Toumi,M., Utility decrements associated with side effects in schizophrenia, Journal of Medical Economics.17 (12) (pp 853-861), 2014.Date of Publication: 01 Dec 2014., 853-861, 2014	Not cost-effectiveness analysis
O'Day,K., Rajagopalan,K., Meyer,K., Pikalov,A., Loebel,A., Long-term cost-effectiveness of atypical antipsychotics in the treatment of adults with schizophrenia in the US, ClinicoEconomics and Outcomes Research.5 (1) (pp 459-470), 2013.Date of Publication: 2013., 459-470, 2013	Adult population
Park,T., Kuntz,K.M., Cost-effectiveness of second-generation antipsychotics for the treatment of schizophrenia, Value in Health.17 (4) (pp 310-319), 2014.Date of Publication: June 2014., 310-319, 2014	Adult population
Treur,M., Baca,E., Bobes,J., Canas,F., Salvador,L., Gonzalez,B., Heeg,B., The cost-effectiveness of paliperidone extended release in Spain, Journal of Medical Economics, 15, Suppl-34, 2012	Adult population
Von,Scheele B., Mauskopf,J., Brodtkorb,T.-H., Ainsworth,C., Berardo,C.G., Patel,A., Relationship between modeling technique and reported outcomes: Case studies in models for the treatment of schizophrenia, Expert Review of Pharmacoeconomics and Outcomes Research.14 (2) (pp 235-257), 2014.Date of Publication: April 2014., 235-257, 2014	Systematic review, individual studies checked and subsequently excluded because they did not meet the inclusion criteria
Zeidler,J., Mahlich,J., Greiner,W., Heres,S., Cost effectiveness of paliperidone palmitate for the treatment of schizophrenia in Germany.[Erratum appears in Appl Health Econ Health Policy. 2013 Dec;11(6):689], Applied Health Economics & Health Policy, 11, 509-521, 2013	Systematic review, individual studies checked and subsequently excluded because they did not meet the inclusion criteria

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