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ABSTRACT

Introduction: Antipsychotic treatment in early-onset schizophrenia (EOS) lacks a rich evidence base, and efforts to rank different drugs concerning their efficacy have not proven any particular drug superior. In contrast to the literature regarding adult-onset schizophrenia (AOS), comparative effectiveness studies in children and adolescents are limited in number and size, and only a few meta-analyses based on conventional methodologies have been conducted.

Methods and analyses: We will conduct a network meta-analysis of all randomised controlled trials (RCTs) that evaluate antipsychotic therapies for EOS to determine which compounds are efficacious, and to determine the relative efficacy and safety of these treatments when compared in a network meta-analysis.

Unlike a contrast-based (standard) meta-analysis approach, an arm-based network meta-analysis enables statistical inference from combining both direct and indirect comparisons within an *empirical Bayes* framework. We will acquire eligible studies through a systematic search of MEDLINE, the Cochrane Central Registry of Controlled Trials, Clinicaltrials.gov and Centre for Reviews and Dissemination databases. Eligible studies should randomly allocate children and adolescents presenting with schizophrenia or a related non-affective psychotic condition to an intervention group or to a control group. Two reviewers will—independently and in duplicate—screen titles and abstracts, complete full text reviews to determine eligibility, and subsequently perform data abstraction and assess risk of bias of eligible trials. We will conduct meta-analyses to establish the effect of all reported therapies on patient-relevant efficacy and safety outcomes when possible.

Ethics and dissemination: No formal ethical procedures regarding informed consent are required as no primary data collection is undertaken. The review will help facilitate evidence-based management, identify key areas for future research, and provide a framework for conducting large systematic reviews combining direct and indirect comparisons. The study will be disseminated by peer-reviewed publication and conference presentation.

Trial registration number: PROSPERO CRD42013006676.

Strengths and limitations of this study

- Our study's strengths include clinical expertise in child, adolescent and adult psychiatry, including psychopharmacology.
- The content experts in the group have extensive knowledge of the literature and experience with prescribing antipsychotic treatment.
- The methodologists in the group are members of the GRADE Working Group, and have experience with conducting and reporting randomised clinical trials, systematic reviews and meta-analyses.
- A possible and anticipated weakness may be the quantity and quality of the trials we identify.

INTRODUCTION

Description of the condition

Early-onset schizophrenia (EOS) with onset before age 18 is clinically continuous with adult-onset schizophrenia (AOS).[1 2] Accordingly, in children and adolescents schizophrenia is defined by the same diagnostic criteria as in adults. EOS is relatively rare, but the prevalence rises through adolescence. The onset before age 12 comprises less than 1%, and onset from age 12–18 constitutes about 12–33% of all adult cases of schizophrenia.[3 4] A more pronounced deviation of central nervous system and behavioural developmental trajectories found in children who later as youth develop schizophrenia[5] compared to children with onset delayed until adulthood, may be a prognostic factor that to some degree explains the less-favourable outcome and prognosis in EOS.[6]

Even though treatment with antipsychotic drugs is a well-established intervention in EOS, the evidence for their efficacy and tolerability is scarce compared to the adult field.[7 8] From the available evidence, antipsychotic treatment is efficacious in children and adolescents with schizophrenia spectrum

disorders, but complicated by a reduced treatment response and a more severe profile of adverse events (AEs) compared to adults.[7 9] As in adults, treatment resistance in EOS can be treated with clozapine, which appears efficacious and relatively safe in children and adolescents when closely monitored.[10]

Description of the interventions

First-generation antipsychotics (FGAs) are primarily characterised by antidopaminergic properties at dopamine D2 receptors and were first available during the 1950s. The early second-generation antipsychotic (SGA) clozapine was launched in 1971–1975 (withdrawn due to early fatal cases of agranulocytosis and reintroduced in 1989), followed by several new SGAs since the 1990s. SGAs are also characterised by antidopaminergic properties at dopamine D2 receptors, but in addition have potent antiserotonergic actions.[11] Furthermore, some low-potency FGAs and most SGAs have noradrenergic, histaminergic and cholinergic receptor blocking activities.[12 13] One SGA, aripiprazole, has a unique pharmacological profile, as it is a partial agonist at the dopamine D2 receptor.[14]

Evidence of a lower risk of extrapyramidal adverse events (EPS) with SGAs compared to FGAs has led to an increase in the prescription of SGAs in children and adolescents.[15] The lower EPS risk, however, needs to be balanced against a growing evidence for serious risks of metabolic side effects with many SGAs, indicating less-convincing overall superior tolerability compared to FGAs, especially in children and adolescents who seem to be more prone than adults to weight gain, dyslipidaemia and diabetogenic side effects (ie, side effects that in the long term can cause serious health problems for these patients[16]).

In spite of rapidly growing antipsychotic prescription rates for young patients in many countries,[17–19] most antipsychotic medications have not been specifically approved to treat EOS, mainly because such medications have not been thoroughly tested in the young. In Europe, until recently just one compound—aripiprazole—was approved for the use in adolescent schizophrenia, and only in June 2014 another antipsychotic, paliperidone, was approved for the same indication (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000746/WC500034925.pdf). However, both drugs are approved by the European Medicines Agency (EMA) for the treatment of EOS only from ages 15–17, while in the US, five SGAs (ie, aripiprazole, olanzapine, paliperidone, risperidone and quetiapine) are approved by the Food and Drug Administration (FDA) for the treatment of EOS patients aged 13 through 17. Finally, seven FGAs (chlorpromazine, loxapine, perphenazine, thiothixene, thioridazine, trifluoperazine and haloperidol) are FDA approved for paediatric patients of different ages below age 12 and for ages 12 and above, but none of these approvals would withstand modern criteria of positive, well-powered and well-conducted randomised, placebo-controlled trials. Consequently, antipsychotics are often used off-label in children and adolescents.[19 20] Off-label use (ie, medication used to treat a condition or age group not specifically listed in its prescribing label) is a common and legal practice.

This systematic review and meta-analysis will focus on antipsychotics that have been investigated in randomised clinical trials (RCTs) for the treatment of EOS spectrum disorders.

Why it is important to do this review

Recent efforts to evaluate and compare the efficacy and AEs of different antipsychotic drugs for the treatment of EOS have been performed in five meta-analyses with conventional methodologies.[21–24] Of 9 active comparator RCTs and 13 placebo-controlled RCTs, the National Institute for Health and Care Excellence (NICE) Guidelines 2013 rated the general evidence for antipsychotic treatment of psychosis and schizophrenia in young people low to very low and found only minimal differences in efficacy among the compounds (not including clozapine), but relatively large differences in AEs profiles.[21] In a Cochrane review, Kennedy *et al*[22] meta-analysed six active comparator RCTs in children with onset of schizophrenia from age 0 through 12 years, revealing only scant evidence regarding the effects of antipsychotic medication. However, some benefits were identified with the SGA clozapine compared with the FGA haloperidol for treatment-resistant schizophrenia. Yet, these benefits were offset by an increased risk of serious adverse effects. Another Cochrane review of the use of SGAs for psychosis in adolescents aged 13–16 years (N=13 RCTs, n=1112 participants) concluded that SGAs are not superior to FGAs, but SGAs may be more acceptable to young people because fewer symptomatic AEs are seen in the short term.[25] In a meta-analysis of three RCTs, Ardizzone *et al*[23] could not demonstrate any superiority among the SGAs risperidone, olanzapine and aripiprazole concerning efficacy or all-cause discontinuation. However, aripiprazole had the lowest incidence of neuromotor AEs and weight gain. In another meta-analysis of five RCTS covering patients aged 5 through 18 years with EOS, the response rate for FGA treatment was reported to be significantly higher and the risk of weight gain significantly lower compared to SGA treatment.[24] Of note, this work included older studies with patients diagnosed with childhood schizophrenia in which populations of schizophrenia and autism spectrum disorders were mixed together.

Meta-analysis is the statistical technique used to synthesise evidence from experiments addressing the same research question (ie, PICO framework: patient/population, intervention, comparison, outcomes). It is often used to combine data from clinical trials regarding the relative benefit or harm of two interventions in order (I vs C), for example, to infer about whether drug I and C are equally effective. The main drawback of the current state of the art is that meta-analysis focuses on

comparing only two alternatives. However, decision-makers and clinicians need to know the relative ranking of a set of alternative options and not only whether option I is better than C. The statistical methodology applied to synthesise information over a complex network of comparisons involving all alternative treatment options for the same condition is called 'Network Meta-Analysis'.

Network meta-analyses allow a unified, coherent analysis of all RCTs that compare antipsychotic treatments in children with schizophrenia spectrum disorders, while fully respecting randomisation within the included trials. This methodology is especially relevant, as the aforementioned meta-analyses were inconclusive or even somewhat contradictory and because head-to-head trials of different antipsychotic treatments are either scarce or comprise a small number of patients. In this situation, a multiple treatment or network meta-analysis can to some extent overcome the limitations of small samples with limited power to examine comparative efficacy and safety across commonly used antipsychotics. Moreover, such a meta-analysis will allow efficacy and safety/tolerability ranking of medications by taking advantage of the measured differences versus common comparators, even if the medications are not or only insufficiently compared head to head.[26 27] Although network meta-analyses are based on the assumption that trial designs and populations are comparable across time, sensitivity and subgroup analyses can help to test these assumptions and minimise potential cohort effects.[28]

OBJECTIVES

To comprehensively explore the efficacy and tolerability of all antipsychotic therapies tested in RCTs for children and adolescents with schizophrenia-spectrum disorders using a network meta-analysis that takes into account both direct and indirect comparisons.

METHODS

This protocol prespecifies the objectives and methods of the systematic review.

The protocol specifies outcomes of major interest, and explain how we will extract and use the information about those outcomes quantitatively. We anticipate that the final meta-analysis developed according to this protocol will appear transparent, and restrict the likelihood of reviewers biased interpretation.

Protocol and registration

We will follow a standard protocol for all review steps. Our protocol is registered on PROSPERO (CRD42013006676); our manuscript will conform to the 'Preferred Reporting Items for Systematic reviews and Meta-Analyses' (PRISMA) guidelines for reporting systematic reviews and meta-analyses.[29]

Eligibility criteria

1. Studies must be RCTs that examine the administration of an antipsychotic treatment compared with placebo or another antipsychotic drug for children and adolescents aged 0 through 19 with schizophrenia spectrum disorders (not including affective psychoses, see no 3 below). Per definition, EOS refers to patients with onset of illness before age 18 years. However, it is well known that several clinical studies of EOS include patients aged 0 through 19, because the cohorts are investigated within the first couple of years after onset, that is, many patients have onset at age 17 but are not treated until they are 18 or 19 years old—the average duration of untreated psychosis is 2 years.[30 31]
2. Any antipsychotic drugs used in the RCTs in this meta-analysis must have been identified from WHO ATX code index, ATC N05A.[32] Trial records will not restrict studies from any geographic area, except for exclusion of trials conducted in China due to concerns about the validity of such randomised trial data.[33] Such concerns include lack of ability to verify true randomisation due to ways the studies are reported or conducted, following convenience samples during hospitalisation without follow-up beyond discharge and frequent lack of any dropouts. Owing to such concerns, for example, the recent, most comprehensive network meta-analysis of acute RCTs of antipsychotics in adults with schizophrenia published in *Lancet*[8] excluded a priori all Chinese RCTs. In order to allow better comparability between out meta-analysis of the same trials in youth, we will follow the same methodology and exclude RCTs originating from China.
3. For a study to be eligible, explicit reference to the diagnostic criteria defining schizophrenia spectrum disorders is needed. All patients should fulfil diagnostic criteria for schizophrenia spectrum disorders according to validated diagnostic manuals/classifications: either presently Diagnostic and Statistical Manual 5 (DSM-5)[34] (schizophrenia (295.90), schizophreniform disorder (295.40), schizoaffective disorder (295.70), delusional disorders (297.1), other schizophrenia spectrum and other psychotic disorder (298.8), unspecified schizophrenia spectrum and other psychotic disorder (298.9) or International Classification of Diseases 10 (ICD-10)[35] (schizophrenia (F20), persistent delusional disorders (F22), acute and transient psychotic disorders (F23), induced delusional disorder (F24), schizoaffective disorders (F25), other non-organic psychotic disorders (F28), Unspecified non-organic psychosis (F29)) or subsidiary correlating diagnoses according to earlier DSM/ICD revisions or other validated diagnostic classifications.

We allow for trials including schizophrenia spectrum disorders according to diagnostic manual versions from DSM-3[36] and ICD-9[37] or later because only after 1980 these major diagnostic classification systems endorsed the practice of using the same criteria to diagnose schizophrenia in children and adults. Prior to that time,

Table 1 Seven major and 15 minor outcomes

Major outcomes—efficacy	Minor outcomes—efficacy
Mean change in overall symptom scores: ▶ PANSS total score or ▶ BPRS total score Mean change in positive symptoms scores: ▶ PANSS positive score or ▶ BPRS positive score or ▶ SAPS score	Response rates (study defined – if choices between several definitions, prefer 30% reduction or higher) Mean change in negative symptoms: ▶ PANSS negative score or ▶ SANS score Global impression: ▶ CGI-I scores ▶ Mean change in CGI-S score Mean change in global/social function: ▶ CGAS score or ▶ GAF score ▶ CAFAS score Mean change in depressive symptoms: ▶ PANSS depression subscale or ▶ BPRS depression subscale or ▶ HAM-D score or ▶ MDI score or ▶ CDCS or CDRS scores Frequency of discontinuation due to lack of efficacy
Major outcomes—adverse events	**Minor outcomes—adverse events**
Frequency of all-cause discontinuation Mean weight change Frequency of EPS/use of antiparkinson medication Frequency of akathisia Mean change in triglycerides	Mean change in prolactin concentration Mean change in QTc interval Mean change in total cholesterol Frequency of sedation Frequency of insomnia Frequency of weight gain ≥7% Frequency of SAEs Frequency of discontinuation due to side effects Frequency of AEs

Categorical and continuous measures of benefit and harm in prioritised order.
AEs, Adverse Events; BPRS, Brief Psychiatric Rating Scale; CAFAS, The Child and Adolescent Functional Assessment Scale; CDSS, Calgary Depression Scale for Schizophrenia; CDRS, Child Depression Rating Scale; CGAS, Children's Global Assessment Scale; CGI, Clinical Global Impressions Scale (-I=Improvement; -S=severity); EPS, extrapyramidal symptoms; GAF, Global Assessment of Functioning Scale; HAM-D, Hamilton Rating Scale for Depression; MDI, Major Depression Inventory; PANSS, Positive and Negative Syndrome Scale; SAEs, serious adverse events; SANS, The Scale for the Assessment of Negative Symptoms; SAPS, The Scale for the Assessment of Positive Symptoms.

the construct of childhood-onset schizophrenia was used to denote a relatively heterogeneous group of children with adult-type schizophrenia, infantile autism and other psychotic conditions. Hence, studies including patients with diagnoses that are not equivalent to the criteria listed above, primarily relating to the historical concept of 'Childhood Schizophrenia,' are excluded.

Information sources and search

We will search the following bibliographic databases: the Cochrane Central Register of Controlled Trials (the Cochrane Library, latest issue), MEDLINE via Pubmed (1950), and Clinicaltrials.gov (full electronic search strategies; online supplementary appendix 1). Relevant reviews will be identified (including search in the Centre for Reviews and Dissemination (CRD) databases) and bibliographies will be scrutinise for further relevant trials.

Study selection

Two independent reviewers from the author group will perform all steps in the selection procedure in duplicate. The titles and abstracts of identified articles will be evaluated, and an article will be rejected only if (1) it is an article that does not report an RCT of antipsychotic treatment in children and/or adolescents with schizophrenia spectrum disorders, (2) antipsychotic drugs used in the trial were not identified from WHO ATX code index, ATC N05A or (3) the trial was conducted in China. If a reviewer is uncertain about the appropriateness of an article, the full text article will be retrieved. Following this initial screening, reviewers will based on full text reviews select studies to be included according to the eligibility criteria. We will resolve any disagreements about study inclusion by consensus and consult a third and fourth author if required.

Data collection process and data items

Two reviewers will independently extract all data. We will collect data on the general characteristics of the RCT: date of publication, journal, funding source (public, private, or unreported) and sample size. We will note the interventions being compared, including the

dosages and regimens (flexible or fixed dose) that apply. Further, we will record whether the RCT was a single-centre or a multicentre trial (defined as ≥2 different centres) and the number of centres involved. We will record whether RCTs were open-label, single-blinded or double-blinded. First/corresponding authors from trial reports and/or antipsychotic drug manufacturers will be contacted for missing data.

As major outcomes (table 1) we will assess (1) the mean overall change in symptoms, according to the following hierarchy: change in Positive and Negative Syndrome Scale (PANSS)[38] total score from baseline, if not available, then the change in the Brief Psychiatric Rating Scale (BPRS)[39] total score, and then values of these scales at study end point, all based on the intention-to-treat (ITT) population whenever available; (2) the mean change in positive symptoms, according to the hierarchy PANSS positive score or BPRS positive score or The Scale for the Assessment of Positive Symptoms (SAPS)[40] score; (3) frequency of all-cause discontinuation; (4) mean weight change; (5) frequency of EPS according to the hierarchy number of EPS AEs or number of patients treated with antiparkinsonian drugs; (6) frequency of akathisia; and (7) mean change in blood level of triglycerides. As minor outcomes (table 1), we will assess (1) whether a treatment response rate of at least 30% reduction from baseline in total PANSS or BPRS scores, or a score of 'much improved' or 'very much improved' on the Clinical Global Impressions Scale (CGI) improvement (CGI-I) score[41] was achieved (these will be the prespecified cut-off thresholds for response,[42] but when the above thresholds are not available, we will apply the authors' definitions of response); (2) mean change in negative symptoms according to the hierarchy PANSS negative score or SANS score,[43] (3) global impression according to the hierarchy CGI-I or change in CGI-S (severity) mean score at end point; (4) mean change in global/social function according to the hierarchy Children's Global Assessment Scale (CGAS) score[44] or Global Assessment of Functioning Scale (GAF) score[45] or The Child and Adolescent Functional Assessment Scale (CAFAS) score[46]; (5) mean change in depressive symptoms according to the hierarchy PANSS depression subscale or BPRS depression subscale or Hamilton Rating Scale for Depression (HAM-D) score[47] or Major Depression Inventory (MDI) score[48] or Calgary Depression Scale for Schizophrenia score (CDSS)[49] or Child Depression Rating Scale (CDRS)[50]; (6) frequency of discontinuation due to lack of efficacy; (7) mean change in blood prolactin concentration; (8) mean change in QTc interval; (9) mean change in blood total cholesterol; (10) frequency of sedation; (11) frequency of insomnia; (12) frequency of weight gain ≥7%; (13) frequency of serious adverse events (SAEs), (14) frequency of discontinuation due to side effects and (15) frequency of AEs.

From the above outcomes, it can be seen that all-cause discontinuation and discontinuation due to treatment inefficacy are included as more global effectiveness and efficacy measures, while discontinuations due to AEs is included as a proxy for patient-relevant adverse effects, anticipating that they will reflect the ultimate decision of the participant and/or physician to discontinue treatment.[51] SAEs will be extracted from the trial reports—presumably according to the definition by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, as SAEs are considered critical for decision-making.[51]

Risk of bias in individual studies

The risk of bias within each RCT will be assessed using the domains of the risk of bias tool, as recommended by the Cochrane Collaboration.[52] The following issues will be investigated: Methods for sequence generation and maintaining allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each domain is rated as low, high or unclear risk of bias; each RCT will subsequently be assigned an overall risk of bias in terms of low risk (low for all key domains), high risk (high for ≥1 key domains), and unclear risk (unclear for ≥1 key domains[53]).

Meta-analyses

Owing to systematic differences in patient populations and response patterns to antipsychotic treatment, meta-analyses will be conducted separately for RCTs in treatment-resistant patients and for RCTs of non-treatment-resistant patients. For continuous outcomes, we will analyse the results as the standardised mean difference (SMD). The SMD is used as a summary effect size, anticipating the studies all assess the same outcome, (ie, construct), but measure it in a variety of ways.[54] We will use the number of patients who responded, the number of patients who dropped out due to AEs, the number of patients who dropped out due to any causes, the number of patients who had a SAE, the number of patients who had an AE and the number of patients who are categorised according to the selected AE types above. For the dichotomous data, we will calculate ORs with 95% (95% CIs) for each study.

The contrast-based meta-analysis of data will be performed by applying random-effect models by default in order to accommodate the anticipated heterogeneity among study results. All data will be entered into Review Manager V.5.2 software, provided by the Cochrane Collaboration (http://ims.cochrane.org/revman). We will apply the DerSimonian and Laird random-effects model throughout.[55] In addition to reviewing forest plots, we will statistically analyse heterogeneity of the data using the Cochran's Q test[56] and evaluate via the I^2 index for inconsistency, which can be interpreted as the percentage of total variation across several studies.[57] An I^2 value greater than 50% may indicate substantial heterogeneity. We will use the χ^2 test for heterogeneity when appropriate for the direct analyses.

Unlike a contrast-based (standard) meta-analysis approach, an arm-based approach will be applied to

conduct a network meta-analysis and combine both direct and indirect comparisons.[27] For continuous outcomes, we will summarise data from each arm as the mean change from baseline (ΔSymptoms), assuming a normal likelihood with a corresponding SE in analogy to a paired t test. We will standardise these results by using the pooled SD for the change across arms within each study (=ΔSymptoms/SD). Following this approach, we will be able to estimate a standardised mean change (SMC) for each arm in any given study. When we subsequently subtract any given intervention SMC value—for instance, from the SMC for the combined placebo arms—this estimate is interpretable as the SMD.[58] The statistical model uses a random-effects approach, based on the single-effect model as described by Welton *et al*.[59] In this model, all variances corresponding to the different interventions in each trial are grouped together as a single variance in each trial.

For dichotomous outcomes, we will perform mixed-effects logistic regression analyses (also) using an arm-based, random-effects model within an *empirical Bayesian* framework.[60] The generalised linear mixed model incorporates a vector of random effects and a design matrix for the random effects. Allowance is made for differences in heterogeneity of effects among different drugs by specifying that the linear predictor vary at the level of the study and the drug across study. In the network meta-analyses, we will evaluate heterogeneity (ie, between-study variance) for the analysis using τ^2 (an estimate for Tau-squared), which examines heterogeneity because of *Study* and *Study×Drug* interaction (smaller values indicate a better model per se).

Sensitivity analyses

Sensitivity analyses of the primary efficacy outcome (change in total scores on PANSS or BPRS) will be performed separately for the treatment-resistant meta-analysis and for the non-treatment-resistant meta-analysis. Using stratified analyses, we will explore the quantitative impact of the following characteristics: Setting (International, US, EU and other); Number of centres (single centre, multicentre); Conflicts of interest (Sponsor a pharmaceutical company, Sponsor not a pharmaceutical company); Age groups (Children (0 through 12 years), Adolescents (13 through 19 year)s, Children and Adolescents (0 through 19 years)); All patients antipsychotic naïve (yes, no); All patients first psychotic episode (yes, no); Diagnosis (Schizophrenia or Schizophrenia Spectrum); Dose applied according to clinical practice (low, normal, high); FDA approved (yes, no) and EMA approved (yes, no). For meta-regression analyses, we will explore the relationship between the following covariates: Study duration (in weeks); Percent males; Age (in years); Percent antipsychotic naïve; Percent first episode; Percent all-cause discontinuation; PANSS/BPRS total baseline score; PANSS/BPRS positive symptoms baseline score. Univariable random-effects meta-regression models[61] will be used for tests of interaction between the main treatment effect and these characteristics. Further, for the purpose of sensitivity, we will also perform stratified analyses according to the risk of bias judgements across different studies for each of the critical domains (ie, selection bias, performance bias, detection bias, attrition bias, reporting bias) in order to derive p values for interaction between trial characteristics and treatment effect.

ETHICS AND DISSEMINATION

As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required. Using data from randomised trials, this study will evaluate different antipsychotic therapies for children and adolescents aged 0 through 19 years with schizophrenia spectrum disorders. Our goal is to help clinicians make evidence-based decisions and help guideline developers with an updated evidence synthesis, which will enable a comprehensive interpretation of the data for benefit and harm. Our review will present data for all antipsychotic treatments, provide relative estimates of effectiveness and tolerability and evaluate the quality of the evidence in a thorough and consistent manner using the GRADE approach.[62] The review will help facilitate evidence-based management, identify key areas for future research, and help provide a framework for conducting large systematic reviews combining direct and indirect comparisons.

Potential limitations of the network meta-analysis of trials on antipsychotic treatment for children and adolescents with schizophrenia spectrum disorders should be mentioned. If the review neglect to determine the quality of the overall network meta-analysis so that the reader cannot determine if the evidence provides strong inferences it will be considered a major limitation. In order to address this, the following aspects will be considered: (1) whether the individual studies are at low risk of bias and publication bias is unlikely; (2) results are consistent in individual direct comparisons and individual comparisons with no-treatment controls and are consistent between direct and indirect comparisons; (3) sample size is large and CIs are correspondingly narrow; and (4) evidence includes direct comparisons.

Dr AKP will draft the paper describing the results of the systematic review and meta-analysis, which will be disseminated by peer-review publication and conference presentation.

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Contributors AKP, ST, DG, ADS, AF-J, CUC and RC participated in the conception and design of this protocol, including search strategy development. AKP, ST, DG, AF-J and ADS participated in search strategy development and will, for the network metanalysis, perform the search and selection in collaboration with CUC. ST and AKP will retrieve the data. ST and RC provided statistical advice for the design. All authors drafted and critically reviewed this manuscript and approved the final version.

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