Acute Antipsychotic Treatment of Children and Adolescents With Schizophrenia-Spectrum Disorders: A Systematic Review and Network Meta-Analysis

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Objective: To determine the comparative efficacy and safety of antipsychotics for youth with early-onset schizophrenia using network meta-analytic methods combining direct and indirect trial data.

Method: The authors systematically searched MEDLINE, the Cochrane Library, and clinicaltrials.gov and selected randomized controlled trials allocating youth with schizophrenia spectrum disorders to a (non-clozapine) antipsychotic versus placebo or another antipsychotic. Major efficacy outcomes were Positive and Negative Syndrome Scale (PANSS) total and positive symptoms. Major safety outcomes were weight, plasma triglyceride levels, extrapyramidal symptoms, akathisia, and all-cause discontinuation. Sixteen additional outcomes were analyzed. A random-effects arm-based network meta-analysis was applied, and consistency was assessed by pairwise meta-analysis. Confidence in PANSS total estimates was assessed by applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results: Twelve 6- to 12-week trials (N = 2,158; 8–19 years old; 61% boys) involving 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) were analyzed. PANSS total symptom change was comparable among antipsychotics (low- to moderate-quality evidence), except ziprasidone (very low- to low-quality evidence), and all antipsychotics were superior to placebo (low- to high-quality evidence), except ziprasidone and asenapine (low- to moderate-quality evidence). PANSS positive changes and additional efficacy outcomes were comparable among antipsychotics. Weight gain was primarily associated with olanzapine; extrapyramidal symptoms and akathisia were associated with molindone; and prolactin increased with risperidone, paliperidone, and olanzapine. Serious adverse events, discontinuation of treatment, sedation, insomnia, or change in triglycerides did not differ among antipsychotics.

Conclusion: This network meta-analysis showed comparable efficacy among antipsychotics for early-onset schizophrenia, except that efficacy appeared inferior for ziprasidone and unclear for asenapine. Adverse reaction profiles varied substantially among the investigated antipsychotics and were largely consistent with prior findings in adults.

Protocol registration information—Antipsychotic Treatment for Children With Schizophrenia Spectrum Disorders: Network Meta-Analysis of Randomised Trials; https://www.crd.york.ac.uk/PROSPERO/; CRD42013006676.

Key words: antipsychotics, schizophrenia, network meta-analysis

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Comparative effectiveness trials of antipsychotics for early-onset schizophrenia (EOS; onset ≤18 years of age) are limited by number and size compared with those of adult-onset schizophrenia (AOS).[1,2] EOS incidence increases through adolescence[3,4] and is clinically continuous with AOS,[5,6] but represents a more severe phenotype[7] and prognosis.[8] Different antipsychotics have been evaluated for EOS in randomized controlled trials (RCTs) and in standard pairwise meta-analyses (PMAs),[9-13] showing little overall evidence for antipsychotics for EOS, minimal efficacy differences among antipsychotics (except clozapine for treatment-resistant EOS), and significant differences in adverse event (AE) profiles. Furthermore, long treatment durations, decreased response, and more severe AEs compared with AOS[1,14] present significant challenges for antipsychotic treatment of EOS. Therefore, methods to maximize the information from existing data are needed.

Network meta-analysis (NMA) techniques can overcome the limitations of small samples by examining

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comparative efficacy and safety across interventions. NMA takes advantage of the measured differences versus common comparators, even if the treatments are not or only insufficiently compared head to head.[15,16] When head-to-head trials are lacking, NMA uses direct and indirect trial evidence to estimate their effects.

Using an NMA approach, we assessed the relative effectiveness and tolerability of all antipsychotic RCTs for children and adolescents with schizophrenia spectrum disorders.

METHOD

Protocol and Registration

Before initializing this study, we published a thorough protocol[17] (PROSPERO: CRD42013006676). This report conforms to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[18] and the PRISMA extension statement incorporating NMAs.[19]

Eligibility Criteria

RCTs that examined an antipsychotic compared with placebo or another antipsychotic for youth 0 to 19 years old with schizophrenia spectrum disorders (excluding affective psychoses) were considered. Any antipsychotic identified from the World Health Organization Anatomical Therapeutic Chemical classification system (code N05A, antipsychotics) was considered.[20] Patients fulfilling diagnostic criteria for schizophrenia spectrum disorders according to the *DSM-5*[21] or *International Classification of Diseases, Tenth Revision*[22] or corresponding diagnoses in revisions from the *DSM-III*[23] and *International Classification of Diseases, Ninth Revision*[24] or later (details in protocol) were considered.[17]

Trials conducted in China were excluded because of validity concerns.[25]

Search Strategy

We searched the Cochrane Library (latest issue), MEDLINE by PubMed (1950), and clinicaltrials.gov (full electronic search strategies in published protocol).[17] Relevant reviews were identified, and bibliographies were scrutinized for further relevant trials. We (C.U.C.) contacted the relevant pharmaceutical companies asking for unpublished data from published studies.

Study Selection and Risk of Bias Assessment

Two independent reviewers performed the selection procedure in duplicate. Titles and abstracts of identified articles were screened, and potentially eligible full-text articles were selected (D.G. and A.F.J.), followed by full-text reviews (A.D.S. and A.K.P.). Any disagreements were resolved by consulting a third reviewer (C.U.C.) and by consensus. Because of significant differences among patient populations and antipsychotic response patterns, we excluded RCTs of treatment-resistant patients.[26] Using the Cochrane Risk of Bias tool,[27] 2 reviewers (A.K.P. and S.T.) assessed the risk of bias (ROB).

Data Extraction

Two reviewers (A.K.P. and S.T.) independently and in duplicate extracted publication date; journal; funding source; sample size; and number of sites, blinding status, and interventions (including dosages and regimens [flexible versus fixed dose]). Authors were contacted for missing data.

Major outcomes were mean change from baseline on total and positive symptoms (Positive and Negative Syndrome Scale [PANSS] or Brief Psychiatric Rating Scale),[28,29] body weight, plasma triglyceride levels, frequency of all-cause discontinuation, extrapyramidal symptoms (EPS) and treatment with antiparkinsonian drugs, and akathisia.

Minor outcomes were study-defined response rates, the mean change from baseline in negative symptoms (PANSS or Brief Psychiatric Rating Scale), depressive symptoms (PANSS or Child Depression Rating Scale),[30] global impression of severity and improvement (Clinical Global Impressions Scale [CGI-Severity and Improvement]),[31] global and social function (Children's Global Assessment Scale or Child and Adolescent Functional Assessment Scale),[32,33] frequency of discontinuations due to lack of efficacy or to side effects, sedation, insomnia, weight gain of at least 7%, prolactin change (pooling data in boys and girls if presented separately), AEs, and serious AEs (SAEs; details in published protocol).[17]

Continuous outcomes were reported mostly as mean change, but sometimes as pre-intervention and post-intervention measurements or percentage of change. In the latter cases, transformations were used to convert these into mean changes. When a standard deviation was unavailable, p values or 95% CIs were used to derive approximate standard deviations corresponding to change from baseline.

Data Synthesis and Analysis

For continuous outcomes, we analyzed the results as standardized mean differences (SMDs) with 95% CIs. For dichotomous outcomes, odds ratios with 95% CIs were used.

An arm-based approach was applied to conduct an NMA combining direct and indirect comparisons.[15] The statistical model for the continuous data used a random-effects approach based on the single-effect model[34]; for dichotomous outcomes, we used mixed-effects logistic regression analyses applying a random-effects model within an empirical Bayesian framework.[35] In the NMA, we evaluated heterogeneity (i.e., between-study variance) using T^2. All NMAs (empirical Bayes analyses) were performed using SAS 9.3 (SAS Institute, Cary, NC).

As recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, we also analyzed all major outcomes with conventional PMA of the direct evidence.[36] PMA was performed by applying random-effect models by default[37] to accommodate the anticipated heterogeneity among study results. Data were entered into Review Manager 5.3 software (http://ims.cochrane.org/revman). In addition to scrutinizing forest plots, we analyzed heterogeneity of the data using the Cochran Q test[38] and interpreted these with the I^2 index for inconsistency (i.e., as the percentage of total variation across studies).[39] For details, see Supplement 1, Methods S1 (available online).

To assess the assumption of transitivity (i.e., similarity in study characteristics) for relative treatment effects (enabling us to infer from indirect comparisons and NMA), we performed a series of sensitivity analyses to evaluate whether potential contextual (i.e., effect) modifiers were comparable across studies (e.g., antipsychotic versus placebo). The following covariates were considered potential contextual factors: study duration (6, 8, or 12 weeks), setting (only United States and/or Europe or not only United States and/or Europe), open label (yes or no), median year of study (below or above median across trials [2002–2005; 2006–2012]), baseline PANSS total score (below or above median across trials [88.4–94.5; 94.6–101.2]), and each of the ROB domains (low, unclear, or high risk) using PANSS total score as the dependent variable. In case any covariates could be considered a potential effect modifier, the NMAs were repeated including the specific variable that could violate the assumption on transitivity. We further explored the possible impact of non-blinded trials on the NMA results by excluding such studies in a sensitivity analysis.