Evidence Base for Using Atypical Antipsychotics for Psychosis in Adolescents

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Atypical antipsychotic medications have been the first line of treatment for adolescents with psychosis in the past couple of decades. Till the late 90s, there were very few randomized controlled trials (RCTs) on the treatment of adolescents with psychosis, although a fifth of schizophrenia starts during adolescence. Most of the treatment guidelines for adolescents with psychosis were derived from data on adults. In the past 10 years, there has been increasing number of studies on adolescents with psychosis. The current paper summarizes the findings of trials on adolescents with psychosis in 4 groups: (a) atypical antipsychotic medications vs placebo, (b) atypical antipsychotic medication vs typical antipsychotic medications, (c) one atypical antipsychotic medication vs another atypical antipsychotic medication, and (d) Low dose vs standard dose of atypical antipsychotic medication. We included 13 RCTs, with a total of 1112 participants. Although our review suggest that atypical antipsychotic medications are as effective as typical antipsychotic medications as regards clinical efficacy, atypical antipsychotic medications have a preferred side effect profile and lesser drop-out rate from trials. Obviously, this is extremely important as treatment adherence is key to successful remission of psychotic symptoms and also in some case prevent relapse of illness. Treatment with olanzapine, risperidone, and clozapine is often associated with weight gain. Aripiprazole is not associated with increased prolactin or with dyslipidemia. Adolescents may respond better to standard-dose as opposed to lower dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective. Future trial should be longer term and have uniform ways of reporting side effects.

Key words: atypical antipsychotic medications/adolescents/psychosis/systematic review/meta-analysis/young people/pharmacology/schizophrenia

Background
Schizophrenia often presents in adolescence, but current treatment guidelines are based largely on studies of adults with psychosis. Over the past decade, the number of studies on treatment of adolescent-onset psychosis has increased. The current systematic review collates and critiques evidence obtained on the use of various atypical antipsychotic medications for adolescents with psychosis. The review has multiple separate comparisons where atypical antipsychotic medications have been used for adolescents with psychosis.

Objectives
To investigate the effects of atypical antipsychotic medications in adolescents with psychosis.

Search Methods
We searched the Cochrane Schizophrenia Group Register, inspected references of all identified studies, and contacted study authors and relevant pharmaceutical companies to ask for more information.

Selection Criteria
We included all relevant randomized controlled trials (RCTs) that compared atypical antipsychotic medication with placebo or another pharmacological intervention or with psychosocial interventions, standard psychiatric treatment, or no intervention in children and young people aged 13–18 years with a diagnosis of schizophrenia, schizoaffective disorder, acute and transient psychoses, or unspecified psychosis.

Data Collection and Analysis
Review authors A.K. and S.S.D. selected the studies, rated the quality of the studies, and performed data extraction.
For dichotomous data, we estimated risk ratios (RRs) with 95% confidence intervals (CIs) using a fixed-effect model. When possible, for binary data presented in the “summary of findings” table, we calculated illustrative comparative risks. We summated continuous data using the mean difference (MD). Risk of bias was assessed for included studies.

Main Results

We included 13 RCTs, with a total of 1112 participants. We found no data on service utilization, economic outcomes, behavior, or cognitive response. Trials were classified into the following groups.

**Atypical Antipsychotics vs Placebo**

Only two studies compared one atypical antipsychotic medication with placebo. In one study, the number of nonresponders treated with olanzapine was not different from the number treated with placebo (1 RCT, \( n = 107 \), RR 0.84, 95% CI 0.65–1.10); however, significantly more (57% vs 32%) people left the study early (1 RCT, \( n = 107 \), RR 0.56, 95% CI 0.36–0.87) from the placebo group compared with the olanzapine group. With regard to adverse effects, young people treated with aripiprazole had significantly lower serum cholesterol compared with those given placebo (1 RCT, \( n = 302 \), RR 3.77, 95% CI 1.88–7.58).

Fig. 1. Comparison of atypical vs typical antipsychotic medications in mean end point mental state score on various scales. B-HPRS, Bunney-Hamburg Psychosis Rating Scale; BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Symptom Scale.
Atypical Antipsychotics vs Typical Antipsychotics

When the findings of all 5 trials comparing atypical antipsychotic medications with a typical antipsychotic medication were collated, no difference in the mean end point Brief Psychiatric Rating Scale (BPRS) score was noted between the 2 arms (5 RCTs, n = 236, MD −1.08, 95% CI −3.08 to 0.93; figure 1). With regard to adverse effects, the mean end point serum prolactin concentration was much higher than the reference range for treatment with risperidone, olanzapine, and molindone in one of the studies. However, fewer adolescents who were receiving atypical antipsychotic medications left the study because of adverse effects (3 RCTs, n = 187, RR 0.65, 95% CI 0.36–1.15) or for any reason (3 RCTs, n = 187, RR 0.62, 95% CI 0.39–0.97).

One Atypical Antipsychotic vs Another Atypical Antipsychotic

The mean end point BPRS score was not significantly different for people who received risperidone compared with those who received olanzapine; however, the above data were highly skewed. Overall, no difference was noted in the number of people leaving the studies early because of any adverse effects between each study arm in the 3 studies comparing olanzapine and risperidone (3 RCTs, n = 130, RR 1.15, 95% CI 0.44–3.04). Specific adverse events were not reported uniformly across the 6 different studies included in this section of the review; therefore, it was difficult to do a head-to-head comparison of adverse events for different atypical antipsychotic medications.

Lower Dose Atypical Antipsychotic vs Standard/Higher Dose Atypical Antipsychotic

Three studies reported comparisons of lower doses of the atypical antipsychotic medication with standard/higher doses of the same medication. One study reported better symptom reduction with a standard dose of risperidone compared with a low dose (1 RCT, n = 257, RR −8.00, 95% CI −13.75 to −2.25). In another study, no difference was reported in the number of participants not achieving remission between the group receiving 10 mg/d and those who received 30 mg/d of aripiprazole (1 RCT, n = 196, RR 0.84, 95% CI 0.48–1.48). Similarly, in the other study, authors reported no statistically significant difference in clinical response between the 2 groups receiving lower dose (80 mg/d) and higher dose (160 mg/d) ziprasidone, as reflected by the mean end point BPRS score (1 RCT, n = 17, MD −4.40, 95% CI −19.20 to 10.40).

Authors’ Conclusions

No convincing evidence suggests that atypical antipsychotic medications are superior to typical medications for the treatment of adolescents with psychosis. However, atypical antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. Little evidence is available to support the superiority of one atypical antipsychotic medication over another, but side effect profiles are different for different medications. Treatment with olanzapine, risperidone, and clozapine is often associated with weight gain. Aripiprazole is not associated with increased prolactin or with dyslipidemia. Adolescents may respond better to standard dose as opposed to lower dose risperidone, but for aripiprazole and ziprasidone, lower doses may be equally effective. Future trials should have uniform ways of reporting (see Cochrane review for full details). The findings are similar to the other reviews on antipsychotic medication use in adults with schizophrenia.

Reference