Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia
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CRD summary
The authors concluded that antipsychotic medications significantly reduce the symptoms of early-onset schizophrenia spectrum disorder in children and adolescents, but extrapyramidal symptoms, sedation, prolactin elevation and weight gain are common. Although these conclusions appear justified by the data presented, it is difficult to assess their reliability given the rather limited search and poor reporting of the review.

Authors' objectives
To evaluate the use of antipsychotics for children and adolescents with early-onset schizophrenia spectrum (EOSS) disorder.

Searching
MEDLINE was searched from 1980 to 2007. Relevant reference lists and conference proceedings were handsearched, and investigators and drug manufacturers were asked whether they knew of any additional studies.

Study selection
Double-blinded randomised controlled trials (RCTs) of over four weeks' duration and with 15 or more participants were eligible for inclusion. Eligible participants were children and adolescents with EOSS disorder (defined as onset of psychotic symptoms before the age of 18). The mean age of the participants in most of the included studies was 14 to 16 years (range across all studies: approximately 8.9 to 16.2). The review included one study in which 40% of the participants had psychotic disorders other than EOSS disorder. Studies of antipsychotics were eligible for inclusion.

The interventions in the review included first- and second-generation antipsychotics (FGAs and SGAs, respectively). The FGAs (mean daily dose) were haloperidol (1.8 to 16.0 mg), loxapine (87.5 mg), thiothixene (16.2 mg) and thioridazine (178 mg). The SGAs (mean daily dose) were olanzapine (11.1 to 26.2 mg), risperidone (1 to 6 mg), aripiprazole (10 to 30 mg) and clozapine (176 to 403 mg). The studies compared antipsychotic drugs against each other or placebo. The duration of most interventions was 6 to 8 weeks (range: 4 to 12). One study followed up some participants for 2 years. No inclusion criteria were specified with respect to the outcomes. The outcomes reported in the review included effectiveness, measured using a variety of tools such as the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression - Improvement Scale (CGI-I), the Clinical Global Impression - Severity of Illness Scale (CGI-S), the Brief Psychiatric Rating Scale for Children (BRPS-C), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), and the Positive and Negative Syndrome Scale (PANSS). Other outcomes reported in the review were treatment response rates and adverse effects.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The data were reported descriptively in a table and in the text. In some cases proportions or percentages were reported for binary data and numerical scores for continuous data, and in some cases p-values were also reported.

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The findings were combined in a narrative, grouped by the type of intervention and comparator. In addition to the included studies, other related literature was discussed in the 'Results' section.
Results of the review

Ten RCTs (n=816) were included: one crossover (n=16) and nine parallel-group (n=800) design.

FGAs (3 RCTs).

Two studies compared FGAs with placebo: a 6-week crossover RCT (n=16) found that haloperidol significantly reduced CGI-I scores, while another RCT (n=75), of 4 weeks' duration found that both haloperidol and loxapine significantly improved BPRS scores, with no significant difference between the active treatment groups. Treatment effects in both these studies were described in the review as modest. A third RCT (n=21), of 6 weeks' duration, compared thioridazine with thiothixene and found that BPRS scores improved significantly from baseline in both groups. In these studies, extrapyramidal symptoms (EPS) such as muscle rigidity affected 70% of the participants taking haloperidol or loxapine and 50% of those taking thiothixene. In addition, there was marked and often intolerable sedation in the active treatment groups.

SGAs (7 RCTs).

Three 6-week studies compared SGAs with placebo. One RCT (n=107) found that flexible dose olanzapine improved BPRS-C and CGI-S scores significantly more than placebo (p=0.003 and p=0.004, respectively). There was no significant difference between the active treatment group and the placebo group in treatment response rates (37.5% versus 25.7%). The active treatment group experienced somnolence, liver enzyme abnormalities, prolactin elevation and significant weight gain compared with the placebo group (4.3 ± 3.3 kg versus 0.1 ± 2.8 kg, p<0.001). A second RCT (n=160) found that both low- and high-dose risperidone (1 to 3 mg and 4 to 6 mg, respectively) were associated with significantly greater improvement in PANSS total score than placebo (-21.3 ± 19.6, -21.2 ± 18.3 and -8.9 ± 16.1). Side-effects included somnolence, agitation and headache in the lower-dose treatment group and EPS, dizziness and hypertonia in the higher-dose treatment group. A third RCT (n=302) found that both low- and high-dose aripiprazole (10 and 30 mg, respectively) were associated with significantly greater improvement in PANSS total score than placebo (p=0.04 and p=0.006, respectively). Side-effects in the treatment groups included EPS, tremor and somnolence. The incidence of marked weight gain (i.e. >7%) was modest in all arms in this study, and no adverse effects related to prolactin, glucose/lipid metabolism were reported.

Four studies compared SGAs with active comparators. One 8-week RCT (n=50) comparing risperidone, olanzapine and haloperidol in participants with psychosis (of whom 60% had EOSS disorder) found no statistically significant difference in effectiveness between the interventions, though the time to treatment discontinuation was significantly longer in the olanzapine group in this study (p<0.05). There was marked weight gain, especially in the SGA groups, and EPS were frequently reported in all treatment groups. Three other studies compared clozapine with other antipsychotics. One 6-week RCT (n=21) found that clozapine had a more beneficial effect than haloperidol on symptom scores, but one third of the clozapine group discontinued treatment because of neutropenia or seizures. Two RCTs, of 8 and 12 weeks' duration (n=25 and n=75, respectively), compared clozapine with olanzapine at standard (327 mg) and higher (403 mg) doses (respectively) in young people who had failed to benefit from two trials of SGAs. Both these studies found that clozapine was more effective than olanzapine in improving SANS and/or CGI-I scores. A reduction of 30% or more in the BPRS was found in 66% of participants receiving clozapine and 33% of those receiving olanzapine in the larger study. Marked weight gain occurred in both groups in these studies, and there was also a high incidence of dyslipidaemia and prediabetes in the larger study, which was associated with both the study drugs. Among a group of 15 patients from the smaller study who were followed up 2 years later, 6 (40%) had dyslipidaemia.

Authors' conclusions

Compared with placebo, antipsychotic medications reduce the severity of psychotic symptoms in children and adolescents with EOSS disorder. Few comparative data were available, but clozapine appears to be superior to haloperidol and olanzapine for treatment-refractory EOSS disorder. Short-term studies suggest that adverse effects such as EPS, sedation, prolactin elevation and weight gain are common.

CRD commentary

The objectives and inclusion criteria of the review were clear, even though the outcomes of interest were not specified. The literature search was limited to one database, thus some studies might have been missed. It was unclear whether steps were taken to reduce the risk of error and bias in the review by having more than one reviewer independently
make decisions about the study selection and data extraction processes, and there was no indication that study validity was assessed; this makes it difficult to interpret the reliability of the findings. Moreover, it was not always clear whether the results were statistically significant and no estimates of variance were provided. Few details were reported about the participants in the primary studies (e.g. gender, duration of illness, clinical severity) and clinical heterogeneity was not discussed. Although the conclusions appear to be supported by the data presented, it is difficult to assess their reliability given the rather limited search, poor reporting of review methods and lack of information about study validity.

**Implications of the review for practice and research**

**Practice:** The authors stated that antipsychotic drugs are effective for reducing the symptoms of EOSS in young people, but adverse effects such as EPS, sedation, prolactin elevation and weight gain appear common. Therapeutic strategies should be instigated early in the course of treatment to reduce the risk of weight gain and diabetes.

**Research:** The authors stated that studies on the treatment of EOSS disorder should focus on long-term functional outcomes and should compare SGAs head-to-head. Research is also needed into the mechanisms by which antipsychotic drugs work in children and adolescents, and the means to address adverse effects such as weight gain. Studies should be multisite (in order to improve recruitment), should include a psychosocial intervention, and should consider including young people who are already taking a stable dose of mood-stabilising drugs (e.g. for at least 30 days).

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