Management of psychiatric disorders in children and adolescents with atypical antipsychotics: a systematic review of published clinical trials

Jensen P S, Buitelaar J, Pandina G J, Binder C, Haas M

CRD summary

This review concluded that there is evidence to support atypical antipsychotics for treating disruptive behavioural disorders and pervasive developmental disorders, but a lack of controlled data for paediatric psychotic disorders and bipolar disorder, and that research into long-term safety is needed. Although this review suffers from some methodological weaknesses, the conclusions appropriately reflect the evidence identified from published clinical trials.

Authors' objectives

To review the evidence for treatment of paediatric psychiatric disorders with atypical antipsychotics.

Searching

MEDLINE and EMBASE were searched from January 1994 to March 2006 for published studies; the search terms were reported. Unpublished studies and conference abstracts were not eligible for inclusion.

Study selection

Study designs of evaluations included in the review

Clinical trials of at least 8 weeks' duration and including 20 or more participants were eligible for inclusion. However, some of the included studies appear to have had smaller sample sizes and a shorter duration than this.

Specific interventions included in the review

Studies of atypical antipsychotics were eligible for inclusion. The drugs used in the included studies were risperidone, olanzapine, ziprasidone, clozapine, risperidone plus divalproex, and quetiapine plus divalproex. Where used, the comparators were placebo, other antipsychotics (typical or atypical), other drugs, or no treatment.

Participants included in the review

Studies of children and adolescents with psychiatric disorders were eligible for inclusion. The included studies focused on disruptive behavioural disorders, pervasive developmental disorders, tics/Tourette's syndrome, schizophrenia, mania/bipolar disorder, and general safety and tolerability (mixed disorders).

Outcomes assessed in the review

No inclusion criteria were specified for the outcomes. The review reported efficacy, safety and tolerability outcomes.

How were decisions on the relevance of primary studies made?

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 report a systematic assessment of study quality, but methodological limitations of the studies were listed and discussed. These included comment on sample size, drop-out rates, inclusion and exclusion criteria, outcome measurement, blinding and other potential sources of bias.

Data extraction

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on efficacy, safety and tolerability were extracted. For placebo-controlled double-blind studies, effect sizes were calculated for efficacy outcomes.

Methods of synthesis

How were the studies combined?

The studies were grouped by indication and combined in a narrative.

How were differences between studies investigated?
Effect size comparisons were made for double-blind placebo-controlled studies. Other study designs were discussed separately.

Results of the review

Forty-one studies, involving 2,539 participants in total, were included. Nineteen studies were described as double-blind (13 of which were placebo-controlled) and the remaining 22 were described as open label, most of which had no control group.

Disruptive behavioural disorders: 12 studies (1,389 participants) were identified. Six double-blind controlled studies found consistently that risperidone was better than placebo at reducing symptoms. Where calculable, the effect size ranged from -0.6 to -1.5 (3 studies). Further studies showed that significant behavioural improvement was seen within 1 to 2 weeks of commencing treatment, and that efficacy was maintained long term. One very small open-label uncontrolled study showed a positive response to olanzapine within 2 weeks.

Pervasive developmental disorders: 10 studies (548 participants) were identified. Five double-blind studies demonstrated greater efficacy in reducing symptoms, or preventing relapse, for risperidone compared with placebo. Where calculable, the effect size ranged from -0.8 to -1.2 (3 studies). Further studies reported longer term efficacy of risperidone, and one study reported benefits of treatment with olanzapine.

Tic disorders: 4 studies (84 participants) were identified. Two double-blind studies found significantly greater improvements in tic severity with risperidone compared with pimozide or placebo. Risperidone was also better at improving obsessive compulsive traits than clonidine (1 double-blind study). One double-blind study demonstrated ziprasidone to be more effective at reducing tic severity than placebo.

Schizophrenia and related disorders: 6 studies (190 participants) were identified. One double-blind study found clozapine to be better at improving symptoms than haloperidol, while another reported similar efficacy of haloperidol, risperidone and olanzapine. Open-label studies reported treatment responses for clozapine, olanzapine and risperidone.

Mania in bipolar disorder: 6 studies (179 participants) were identified. One double-blind study found quetiapine plus divalproex to give superior control of mania in adolescents than divalproex plus placebo, without an increase in major side-effects, although there was a higher drop-out rate amongst those on quetiapine. Further open-label studies have also reported efficacy of olanzapine and risperidone.

Safety and tolerability: 3 studies (149 participants), plus safety data from treatment efficacy studies, were identified. In general, risperidone, clozapine and olanzapine were well-tolerated; the most common side-effects were sedation and weight gain. One open-label study found that most weight gain with risperidone occurred in the first 2 months of treatment. One study suggested that this weight gain is reversible. Extrapyramidal symptoms were not often noted with atypical antipsychotics, nor were cognitive adverse events. Some serious adverse events were reported, particularly haematological adverse events with clozapine.

Authors' conclusions

There is evidence to support the use of atypical antipsychotics for disruptive behavioural disorders and pervasive developmental disorders, but a lack of controlled data for paediatric psychotic disorders and bipolar disorder. Long-term safety data are also lacking and further research is needed.

CRD commentary

The review question was broad but fairly clearly defined. However, some included studies appeared not to meet the specified inclusion criteria for study design. Only two electronic databases were used for the literature search and only published full papers were eligible for inclusion, which might have introduced publication bias. Review methods were not described, so it is unclear whether steps were taken to minimise the introduction of reviewer error and bias in the review process. Although a formal assessment of study quality was not described, aspects of methodological rigour were discussed within the synthesis and considered when drawing conclusions. The studies were appropriately combined given the heterogeneity between them, and the authors' conclusions, in essence a description of the published

literature rather than specific recommendations for practice, follow from the evidence presented. Overall, although this review suffers from some methodological weaknesses, the authors' conclusions appropriately reflect the evidence identified from published clinical trials.

Implications of the review for practice and research

Practice: The authors stated that for children and adolescents with disruptive behavioural disorders and pervasive developmental disorders that have not responded to other treatments, atypical antipsychotics may be effective, but that given a lack of long-term safety data, the side-effects of treatment need to be carefully managed. In particular, clozapine and ziprasidone may be associated with serious adverse events.

Research: The authors stated that future studies should measure long-term cognitive, academic and social development, and the need for long-term maintenance therapy. Controlled studies of atypical antipsychotics for paediatric psychotic disorders and bipolar disorder are particularly lacking. Studies of long-term safety are also required.

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