Typical and atypical antipsychotics in adolescent schizophrenia: efficacy, tolerability, and differential sensitivity to extrapyramidal symptoms

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Authors' objectives
To evaluate the efficacy and tolerability of antipsychotics for adolescent psychosis.

Searching
MEDLINE was searched for relevant articles and the search was supplemented by selected bibliographies. No details of the search strategy were provided.

Study selection
Study designs of evaluations included in the review
Double-blind and placebo-controlled trials of the efficacy of typical antipsychotics in adolescents with psychotic disorders were included. For atypical antipsychotics, open studies and case reports were acceptable.

Specific interventions included in the review
The following antipsychotic and neuroleptic drugs were included: typical antipsychotics including loxapine, haloperidol, thioridazine, and thiothixene; and atypical antipsychotics including clozapine, risperidone, and olanzapine. Some studies allowed antiparkinsonian medications where necessary.

Participants included in the review
Children and adolescents of both sexes with psychotic disorders including schizophrenia were studied. Schizophrenic patients included those diagnosed according to American Psychiatric Association DSM-III criteria and treatment resistant patients. The participants included hospitalised children.

Outcomes assessed in the review
The following outcomes were assessed: Brief Psychiatric Rating Scale; Nurses Observational Scale for Inpatient Evaluation; Clinical Global Impressions Scale; Children's Psychiatric Rating Scale; Abnormal Involuntary Movements Scale; custom made scales; Children's Global Assessment Scale; Positive and Negative Syndrome Scale; Scale for Assessment of Negative Symptoms; Scale for Assessment of Positive Symptoms; Subjective Emergent Treatment Symptom Scale; Simpson-Angus Neurological Rating Scale; psychometric testing; Bunney Hamburg Rating Scale; and adverse reactions including hepatotoxicity and weight gain.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
No formal assessment of validity was undertaken though some aspects of validity were mentioned.

Data extraction
The following data were extracted: author; sample characteristics and diagnosis; study design and clinical measures; mean final dosage of drugs; results and main side-effects. The methods used to extract data were not reported.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

**How were differences between studies investigated?**
The author does not state how differences between the studies were investigated.

### Results of the review

Three controlled studies (112 patients with schizophrenia) were used to evaluate the efficacy of typical antipsychotics.

One randomised controlled (RCT) double-blind trial (21 patients), 3 open uncontrolled trials (68 patients), and 4 case reports/series were used to evaluate the efficacy of clozapine.

Two open uncontrolled trials (14 patients), 2 retrospective chart reviews (29 patients) and 5 case reports/series were used to evaluate the efficacy of risperidone.

There was one open trial (8 patients) of olanzapine.

The following types of studies in children and adolescents were not identified: controlled or systematic long-term follow-up studies of antipsychotics; well-controlled studies of risperidone; and reports on the use of quetiapine or any of the newer atypical antipsychotics. Results were reported without levels of statistical significance making interpretation difficult.

Typical antipsychotics: the three studies ranged from 4 to 10 weeks in duration and compared different drugs. One 4 week double-blind trial (75 patients) studied loxapine vs haloperidol vs placebo and found that both active drugs were superior to placebo in terms of reduced schizophrenic symptoms but there were few significant differences between the active agents. Somnolence and sedation affecting 21/26 loxapine subjects compared to 13/25 haloperidol subjects.

One single blind 4 to 6 week study (21 adolescents) compared thioridazine and thiothixene and found no significant difference in efficacy or overall occurrence of side-effects between the two drugs. Sedation occurred in 75% of the thioridazine group compared with 54% in the thiothixene group. Extrapyramidal symptoms (EPS) occurred in 54% of the thiothixene group compared to 0% of the thioridazine group. Dose changes to reduce side-effects were reported to be ineffective. One double-blind placebo controlled cross-over trial studied haloperidol in 16 children aged 5 to 12 years and found that 16/16 on haloperidol showed mild/marked improvement compared to 12/16 on placebo. Side-effects were only reported for the first 12 subjects, of whom 8 experienced drowsiness, 1 experienced parkinsonian symptoms and 2 suffered acute dystonic reactions.

Atypical antipsychotics.

Clozapine: 1 RCT of 6 weeks duration compared haloperidol and clozapine and found that clozapine was statistically significantly better than haloperidol on all measure of psychosis. Adverse reactions on clozapine included neutropenia (4/10), seizures (2/10), drowsiness, salivation and weight gain. One of eleven patients on haloperidol developed the neuroleptic malignant syndrome. Other studies were either uncontrolled (3 open trials, including one retrospective study) or case reports (9 patients). Rates of improvement ranged from 11/21 showing 'marked improvement' to 75% showing 'notable symptom improvement'. Side effects included: drowsiness, dizziness, orthostatic hypotension, and hypersalivation, leukopenia (3/36 patients), neutropenia (4/21 on clozapine), EEG changes (44% of 36 patients), seizures (2/21 on clozapine), EPS, and weight gain.

Risperidone: Adverse reaction reported in the case series, chart reviews, and observational studies included extrapyramidal symptoms, dysphoric mood, weight gain, galactorrhea, asymptomatic leukocytopenia, amenorrhoea, and hepatotoxicity. Studies suggested improvement in symptoms.

### Authors' conclusions

Improved tolerability is leading to the increasing use of atypical antipsychotics for adolescent patients, though these new drugs do have specific adverse reactions of their own. There is a need for more controlled studies of atypical antipsychotics in children and adolescents.
CRD commentary
The aims and inclusion criteria were stated. Some relevant details of the included studies were presented in tabular format. The author mentioned the following problems with the primary studies: lack of reporting on how side-effects were rated; no systematic method used to establish the diagnosis; no mention made of concurrent treatment with antiparkinsonian treatment; use of low-dose of active agent; and short follow-up period.

No details of the search strategy were provided. By limiting the literature search to articles identified from one database, other relevant studies may have been omitted. The methods used to extract the data were not described. Validity was not formally assessed, though aspects of validity were mentioned. Given the heterogeneity among trials, a narrative review was appropriate.

Without an assessment of the validity of included trials it was not possible to assess the strength of the evidence for the efficacy of typical antipsychotics or clozapine. No well-conducted studies of the tolerability of other drug agents were included. The author's conclusion that further research is required was supported by the evidence presented.

Implications of the review for practice and research
Practice: The author does not report any clinical implications of the review.

Research: The author considers that there is a need for more controlled studies of atypical antipsychotics in children and adolescents. In particular dose-finding studies are needed to determine the optimal range to produce greatest improvement with the least side effects for each of the new drugs.

Bibliographic details

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