Use of atypical neuroleptics in child and adolescent psychiatry

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Authors' objectives
To present the most recent information concerning the use of atypical neuroleptics in children and adolescents.

Searching
An English language MEDLINE search (1974 to 1998) was conducted (keywords: clozapine, risperidone, olanzapine, sulpride, tiapride, amisulpride, remoxipride, clothiapine, children and adolescents). In addition, a handsearch was carried out of all issues of the Journal of Child and Adolescent Psychopharmacology (Excerpta Medica), and published bibliographies were cross-referenced.

Study selection
Study designs of evaluations included in the review
No a priori study designs were mentioned. Study designs included are: double-blind placebo-controlled clinical trials, open-label clinical trials, retrospective studies, and case series. Only studies in which the number of participating children and adolescents was specified separately from adults were included.

Specific interventions included in the review
Atypical neuroleptics for children and adolescents:

- **Clozapine** (dose ranged from 50-900 mg/d, treatment duration ranged from 3 weeks to 75 months).
- **Amilsulpride** (dose 50 mg/d, treatment duration ranged from 6 to 15 weeks).
- **Tiapride** (dose ranged from 150-500 mg/d, treatment duration ranged from 3 to 20 weeks).
- **Risperidone** (dose ranged from 0.5-10 mg/d, treatment duration ranged from 3 to 20 weeks).
- **Olanzapine** (dose ranged from 5-20 mg/d, treatment duration ranged from 5 to 9 weeks).
- **Sulpiride** (dose ranged from 50-1200 mg/d, treatment duration ranged from 4 weeks to 48 months).
- **Remoxipride** (dose ranged from 50-250 mg/d, treatment duration 8 weeks).
- **Clothiapine** (dose ranged from 10-20 mg/d, treatment duration 4 months).

Participants included in the review
Children and adolescents with schizophrenia, mood disorders, pervasive developmental disorders (PDD), (acute) psychosis, prolactinoma, (tardive) dyskinesia, developmental delay, obsessive-compulsive disorder (OCD), (mild) mental retardation (MR), (chronic motor) tics, attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), conduct disorder (CD), idiopathic segmental dystonia, prominent negative symptoms, oppositional defiant disorder (ODD), school phobia, anxiety, Tourette's disorder (TD), cerebromotor disorders, stuttering, self-mutilation, or schizotypal. Mean age ranged from 4 to 24 years.

Outcomes assessed in the review
Outcome measures included:

- **Brief Psychiatric Rating Scale (BPRS).**
- **Clinical Global Impression Scale (CGI).**
Bunney-Hamburg Scale (BHS).
Scale for the Assessment of Positive Symptoms (SAPS).
Scale for the Assessment of Negative Symptoms (SANS).
Simpson-Angus Scale for Extrapyramidal Side Effects (SAS).
Abnormal Involuntary Movement Scale (AIMS).
Children's Global Assessment Scale (CGAS).
Positive and Negative Syndrome Scale (PANS).
Wechsler Intelligence Scale for Children-Revised (WISC-R).
Allen Cognitive Level Test (ACLT).
Tardive Dyskinetic Rating Scale (TDRS).
Yale Global Tic Severity Scale (YGTSS).
Children's version of the Yale-Brown Obsessive Compulsive Scale (CY-BOCS).
NIMH Obsessive Compulsive Scale (OCS).
Children's Psychiatric Rating Scale (CPRS).
Conners Rating Scale, Childhood Autism Rating Scale (CARS).
Vineland Adaptive Behaviour Scale.
Children's Depression Inventory (CDI).
Aberrant Behaviour Checklist (ABC).
Beck Depression Inventory (BDI).
Terman-Merril test, Montgomery-Asberg Depression Rating Scale (MADRS).
Behavioural Summarized Evaluation (BSE).
Parent Teacher Questionnaire (PTQ).
Dosage and Record Treatment Emergent Symptoms scale (DOTES).
Tourette's Syndrome Global Scale (TSGS).
Tourette Syndrome Symptom List (TSSL).
Observed Tic Count (OTC) and Visual Analogue Scale (VAS).

In 27 studies there was no outcome measure available.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted on drug, study design, diagnosis and comorbidity, mean age, treatment duration, mean doses, outcome measures and results.

Methods of synthesis
How were the studies combined?
Study results were not pooled. A summary by drug of the clinical reports is presented in a table, and the published experience with each drug is described narratively.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Sixty-three studies were included: 5 double-blind placebo-controlled clinical trials (total 105 patients) 1 with clozapine, 2 with amisulpride, and 2 with tiapride; 24 open-label clinical trials (total 387 patients) with clozapine (10 studies), risperidone (studies), olanzapine (1 study), sulpiride (4 studies), tiapiride (1 study), and remoxipride (1 study); one retrospective study (8 patients) with olanzapine; and 33 case series (115 patients) on the use of clozapine (14 studies), risperidone (13 studies), sulpiride (3 studies), tiapiride (1 study), clothiapine (1 study), and olanzapine (1 study).

Clozapine (n=25 studies): Results from one double-blind controlled study, one open clinical trial and all 14 case studies suggest that clozapine is generally effective in children and adolescents with schizophrenia. Clozapine is generally safe and well tolerated.

Risperidone (n=20 studies): Risperidone appeared to be effective in reducing tic frequency and intensity in tic disorders. Risperidone also looks promising for children and adolescents with Tourette's disorder, schizophrenia, pervasive developmental disorders, ADHD, mood disorder, conduct disorder, obsessive-compulsive disorder, mental retardation, and idiopathic segmental dystonia. Adverse effects of risperidone include weight gain, fatigue/sedation, motor side effects, photophobia, light-headedness, depression, and galactorrhea.

Olanzapine (n=3 studies): One study found olanzapine at least as effective as Clozapine, while another study suggested that clozapine is superior to olanzapine for the treatment of neuroleptic-nonresponsive childhood-onset schizophrenia. Olanzapine is moderately well tolerated; the most common treatment-induced adverse effects were increased appetite, constipation, nausea/vomiting, headache, somnolence, insomnia, difficulty concentrating, sustained tachycardia, transient elevation of liver transaminase levels, and increased agitation.

Sulpiride (n=7 studies): Currently, the major indication for sulpiride treatment is schizophrenia. Its role in the treatment of ADHD, school phobia, and mood and anxiety disorders remains doubtful. Sulpiride was generally well tolerated.

Tiapiride (n=4 studies): Tiapiride was found to improve severe stuttering in an open study and reduced tic severity in a placebo controlled trial. There were no adverse effects on neuropsychologically measurable cognitive parameters.

Amisulpride (n=2 studies): Amisulpride significantly improved negative symptoms in 8 of the 27 schizophrenic patients in one double-blind placebo study, and improved predominantly negative symptomatology in a randomised, double-blind trial. It was generally well tolerated, and side effects were mild.

Remoxipride (n=1 study): One open label trial of remoxipride showed improved illness ratings and decreased tic ratings in 6 and 7 out of 7 patients, respectively. Adverse effects were transient and mild. Remoxipride was withdrawn from the market in 1994 because it induces aplastic anaemia.
Clothiapine (n=1 case report): Although clothiapine was found to be effective in one 8-year-old schizophrenic child, de novo compulsive symptoms emerged shortly after initiation of treatment.

Authors' conclusions
The most convincing evidence of the efficacy of atypical neuroleptics in children and adolescents concerns clozapine in the treatment of schizophrenia. Data on other atypical neuroleptics in other disorders are still sparse.

CRD commentary
The synthesis of results is presented in a narrative way which seems clear and appropriate. The authors do not provide sufficient details of inclusion and exclusion criteria and the review suffers from a lack of other methodological details. Only one electronic database was searched (MEDLINE), and the review was limited to English-language reports; relevant publications may have been missed and publication bias may be present. There is no information on the quality of studies included, nor on the way decisions were taken on the relevance of primary studies and on the way data was extracted from primary studies. There was no discussion of heterogeneity between studies. Considering the above factors and the authors own statement that the evidence was limited the findings from this review should be interpreted with caution.

Implications of the review for practice and research
Practice: Some of the atypical neuroleptics may become the first-line treatment for childhood schizophrenia and pervasive development disorders.

Research: Data on other neuroleptics (other than clozapine) are still sparse and further research is needed.

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