Antipsychotics in early onset schizophrenia: systematic review and meta-analysis

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CRD summary
This review determined the effectiveness of atypical and typical antipsychotic medications for schizophrenia in children and adolescents. The authors concluded that typical medication appeared to be more effective and to cause less weight gain than atypical medication. The authors' conclusions may not be reliable given the variability of the studies and the limitations of the methods used to analyse the data.

Authors' objectives
To determine the effectiveness of atypical and typical antipsychotic medications for schizophrenia in children and adolescents.

Searching
The authors searched PsycINFO and MEDLINE from inception to July 2003; the search terms were reported. Additional references were identified from the reference lists of relevant reviews.

Study selection
Study designs of evaluations included in the review
Prospective studies were eligible for inclusion. The study designs reported in the review included randomised controlled trials (RCTs), open trials and case series.

Specific interventions included in the review
Studies of antipsychotic treatments (both typical and atypical) were eligible for inclusion. The atypical antipsychotic treatments reported in the review included clozapine, risperidone and olanzapine; the typical antipsychotic treatments included thiothixene, trifluoperazine, fluphenazine, haloperidol and loxapine. The duration of treatment ranged from a mean of 11.3 days to 6 months. Dose regimens varied but were reported in the study tables. Control treatments, where these existed, were other antipsychotic treatments or placebo.

Participants included in the review
Studies of children and adolescents aged 5 to 18 years and diagnosed with schizophrenia using ICD 10 or DSM criteria were eligible for inclusion. The participants in the included studies were treated in in-patient or out-patient settings.

Outcomes assessed in the review
The outcomes included in the review had to assess the treatment response using any rating instrument. The rating instruments reported in the review included the Clinical Global Impressions Rating Scale (CGI), the Brief Psychiatric Rating Scale (BPRS), the Brief Psychiatric Rating Scale for Children, Global Clinical Judgments, Global Improvement and Psychotic Improvement. The side-effects of treatment (weight gain, extrapyramidal symptoms and sedation) were also reported.

How were decisions on the relevance of primary studies made?
A single reviewer examined all of the identified abstracts.

Assessment of study quality
Study validity was assessed using the Jadad scale (randomisation, blinding, and withdrawals or drop-outs). Scores ranged from 0 for a poor-quality study to a maximum of 5 for a high-quality study.

Two reviewers independently rated the quality of each included study and awarded a quality score. An agreement level of 80% between the two reviewers was reported. Any disagreements were resolved by consensus.
Data extraction
The authors did not state how many reviewers extracted the data, or how any disagreements were resolved. For each antipsychotic treatment arm in each study, response rates and standard errors were reported. When CGI-I scores were reported, the participants were considered responders if their scores were three or less ('improved', 'much improved' or 'completely recovered'). Alternatively, the authors used response rates as described in the studies. If response rates were not given they were estimated from other study outcomes where possible. For studies reporting the BPRS as a continuous measure, the mean and standard deviation were extracted for each treatment arm.

Methods of synthesis
How were the studies combined?
Mean response rates were calculated separately for atypical and typical antipsychotic treatments, and the difference between treatments was evaluated using Cohen's standardised difference between means. The weighted average of means on the BPRS for atypical studies was compared with the weighted means on the BPRS for typical studies. The pooled standard deviation for 3 studies was used as a divisor in the effect size. Rates of adverse events were compared using the Yates-corrected chi-squared test.

How were differences between studies investigated?
The reviewers used a chi-squared test to assess the level of homogeneity. In addition, a logistic linear model was used to assess the effect of the type of antipsychotic with and without the effect of quality score. Other differences between the studies were described in the tables and text.

Results of the review
Fifteen studies (294 administered antipsychotic treatments) were included in the analyses: 7 RCTs, 1 uncontrolled trial, 6 open trials and 1 case series. Typical antipsychotic medication was administered to 209 children in 13 study arms; atypical antipsychotic medication was administered to 85 children in 8 arms; placebo was administered to 36 children in 2 arms.

The quality scores varied between 0 and 5 points. Overall, the average quality of the studies of atypical medication was better than that of studies of conventional medication.

Outcome measures.
Significant heterogeneity was found among atypical (P<0.10) and typical (P<0.001) antipsychotics, with more study-to-study variation found within the studies of typical than atypical studies, although this difference was not statistically significant. The average response rate among 8 studies employing atypical antipsychotics was 55.7% (range: 13 to 75), compared with 72.3% (range: 35 to 93) among 13 studies employing typical antipsychotics. The difference was statistically different, but not significant, at the trend level (z=1.65, P<0.10). The effect size for continuous measure BPRS was 0.36 in favour of typical antipsychotics. When study quality was included in the model, the effect of medication type remained unchanged.

Adverse effects.
The average weight gain in patients treated with typical antipsychotics was 1.4 kg, compared with 4.5 kg for those treated with atypical antipsychotics. Sedation was more common among those on atypical antipsychotics (53% versus 38.3%). The rate of extrapyramidal side-effects was similar among the two groups (57.4% and 56.5%).

Authors' conclusions
Antipsychotic medications seem effective for schizophrenia treatment in children and adolescents. Typical antipsychotics appeared more effective and caused less weight gain than atypical antipsychotics. However, more rigorous clinical trials are necessary.
CRD commentary
This review was based on clear inclusion criteria. However, no apparent attempts were made to locate unpublished data, so there is a risk of publication bias. One reviewer selected studies for inclusion and this might have introduced selection bias. It was also unclear how the data were extracted, so reporting errors and biases may be present. The quality of the studies was assessed but was poor in many cases, owing to the inclusion of non-randomised studies. Differences in the study designs, study populations and drug regimens caused a number of problems and significant heterogeneity was identified within the analyses. This suggested that it was inappropriate to pool the data and that summary measures were not an adequate reflection of the data. Some attempt was made to investigate potential causes of heterogeneity, but the authors noted that a number of important variables could not be evaluated because of poor reporting in the original trials. Given this lack of information and the variability between the studies, it is likely that a number of potential confounding factors have not been assessed.

The conclusion regarding the relative effect of different antipsychotic treatments was based on a simple comparison of mean values across intervention arms from a large number of quite different studies. Differences between the studies and the possible effect of confounders make this an unsuitable method for synthesising the data in this instance. Overall, the conclusions of the review should be considered with caution, given the variability amongst the studies and the limitations of the analyses. However, the authors’ recommendations for further, more rigorous trials appears justified.

Implications of the review for practice and research
Practice: The authors stated that typical antipsychotic agents should not be discarded as they appeared to be more effective than atypical agents. Side-effects, weight gain in particular, are common and should be addressed pro-actively.
Research: The authors stated that there is an immediate need to design and conduct studies of antipsychotic medications in children and adolescents with schizophrenia employing rigorous scientific methodologies.

Bibliographic details

PubMedID
16470340

DOI
10.1007/s00787-005-0515-2

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Age of Onset; Antipsychotic Agents /therapeutic use; Brief Psychiatric Rating Scale; Child; Child, Preschool; Humans; Schizophrenia /diagnosis /drug therapy /epidemiology; Severity of Illness Index; Treatment Outcome

AccessionNumber
12006001478

Date bibliographic record published
31/12/2006

Date abstract record published
31/12/2006
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.