Amisulpride, an unusual 'atypical' antipsychotic: a meta-analysis of randomized controlled trials

Leucht S, Pitschel-Walz G, Engel R R, Kissling W

Authors' objectives
The authors' stated objective was to compare the atypical profile of amisulpride with that of 5-HT2/D2 antagonists (clozapine, risperidone, olanzapine and quetiapine). Their realised objective was to compare amisulpride with conventional antipsychotics and placebo.

Searching
MEDLINE from 1966 to April 2000, and Current Contents from 1997 to April 2000, were searched using the search term 'amisulpride'. The reference lists of reviews and included studies were manually searched, and the manufacturer of the drug was contacted directly for relevant literature. It was unclear whether any language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Any randomised controlled trials (RCTs) comparing amisulpride with conventional antipsychotics and/or placebo were eligible for inclusion in the review.

Specific interventions included in the review
Comparisons of amisulpride with conventional antipsychotics and/or placebo were eligible for inclusion. The most common comparators were haloperidol and placebo, although four studies compared amisulpride with flupentixol, perazine and fluphenazine. Only low doses of amisulpride (50 to 300 mg/day) were used in the studies where the comparator was a placebo. A range of different drug dosages were administered, which are specified in the review. Studies that compared amisulpride with atypical antipsychotics, such as risperidone, were excluded.

Participants included in the review
Patients suffering from schizophrenia and schizophrenia-like psychoses were eligible for inclusion in the review. The patients were typically in their mid-30s and the majority were male. They manifested moderate to severe schizophrenic illness and the duration of their illness ranged from 3 to 37 years. The patients were acutely ill in 11 trials, and in 7, the patients had persistent, predominantly negative symptoms.

Outcomes assessed in the review
Improvement in mental state was assessed. This was measured using the mean changes from baseline to end point in the total score on the Brief Psychiatric Rating Scale (BPRS), and in the score on the Scale for the Assessment of Negative Symptoms (SANS). The number of patients requiring at least one dose of anti-Parkinsonian medication was used to assess extrapyramidal side-effects. The drop-out rates (global) for treatment failure and for adverse effects were also analysed.

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 state that they assessed validity.

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 as intent to treat, last-observation-carried forward wherever possible. A study was only included in the meta-analytic calculation of a specific outcome measure if normal distribution could be assumed; this was checked directly with the statisticians employed by the manufacturer of amisulpride. The effect sizes derived from the included studies were presented as Pearson's correlation coefficients (r) (see Other Publications of Related Interest no.1). For studies that compared several doses of amisulpride with a control, the different dose groups of amisulpride were pooled.

Methods of synthesis

How were the studies combined?
The data were pooled in a meta-analysis. For combining the effect sizes of the single studies, the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2) was used. The mean effect sizes obtained by a fixed-effect model were also calculated. Both were presented as the mean effect size r with the 95% confidence intervals (CIs). Positive r-values indicated effects favouring the new antipsychotic. Z-tests were used to assess the statistical significance of the mean effect sizes, using a p-value of less than 0.05 to indicate statistical significance. Patients suffering from predominantly negative symptoms were excluded from the analysis of the BPRS score.

Publication bias was assessed using two methods. The first approach used the 'funnel-plot' method, wherein the effect sizes of single studies are plotted against the study size (number of participants). In the second approach, the number of un-retrieved studies averaging null results that is required to bring the new overall p to the level just significant (p=0.05) was calculated.

How were differences between studies investigated?
A chi-squared test of homogeneity was calculated, and statistically-significant results were taken to indicate the possible presence of heterogeneity. Two sensitivity analyses were conducted: (1) examining the only optimum doses of amisulpride; and (2) excluding studies that did not use last-observation-carried-forward data.

Results of the review

Eighteen RCTs (n=2,214) were included in the review. All the of the studies were double-blind and used a parallel design, with the exception of one which was an open randomised study. The duration of the studies ranged from 3 weeks to 1 year.

In 11 studies of acutely ill patients, amisulpride was significantly superior to conventional antipsychotics, as measured by the change in BPRS score (r=0.11; 95% CI: 0.06, 0.16; z=4.40, p<0.0001).

For patients suffering from persistent, predominantly negative symptoms, the pooled data (4 studies) found that amisulpride was significantly superior to placebo, as measured by the change in SANS score (r=0.19, 95% CI: 0.19, 0.34; z=6.59, p<0.0001). Only 3 small studies compared amisulpride with conventional antipsychotics for patients with predominantly negative symptoms; these found no significant difference between amisulpride and conventional treatment (r=0.08, 95% CI: 0.12, 0.26; z=0.77, p=0.44). No statistical heterogeneity was found. In 5 RCTs of amisulpride versus conventional antipsychotics in patients with acute exacerbations, the pooled effect size of changes in SANS scores favoured amisulpride (r=0.14, 95% CI: 0.08, 0.19; z=4.53, p<0.0001).

The pooled data from 4 RCTs found that the use of amisulpride was not associated with significantly more use of anti-Parkinsonian medication than placebo (r=0.01, 95% CI: -0.08, 0.10; z=0.22, p=0.82). The pooled data from 12 RCTs of amisulpride versus conventional antipsychotics favoured amisulpride (r=0.25, 95% CI: 0.17, 0.32; z=6.53, p<0.0001).

In 11 studies of acutely ill patients, significantly fewer patients treated with amisulpride dropped out than patients treated with conventional drugs (r=0.17, 95% CI: 0.08, 0.26; z=3.68, p=0.0002). This was because of fewer drop-outs due to adverse events (r=0.15, 95% CI: 0.07, 0.25; z=3.02, p=0.003). No difference in drop-outs due to inefficiency in
the treatment was found ($r=0.01$, 95% CI: -0.04, 0.06; $z=0.34$, $p=0.37$). In studies of patients with predominantly persistent negative symptoms, fewer patients treated with amisulpride left earlier than with placebo, whether because of ineffective treatment ($r=0.17$, 95% CI: 0.07, 0.27; $z=3.13$, $p=0.002$), adverse events ($r=0.13$, 95% CI: 0.03, 0.23; $z=2.56$, $p=0.008$), or for any reason ($r=0.20$, 95% CI: 0.12, 0.28; $z=4.58$, $p<0.0001$). There were no significant differences in the drop-out rates between amisulpride and conventional antipsychotics in 3 studies of negative symptom schizophrenia ($r=0.08$, 95% CI: -0.08, 0.023; $z=0.96$, $p=0.34$). The sensitivity analysis of only optimum doses did not lead to important changes. With the exception of drop-outs due to adverse events, all the effect sizes slightly increased in favour of amisulpride.

A funnel plot of the main outcome variable (mean BPRS score) revealed the potential of publication bias. This suggested that some small studies with negative results may not have been published. However, the method of Rosenthal (see Other Publications of Related Interest no.2) suggested that little publication bias was probably present.

Further details of the findings were provided in the review.

**Authors’ conclusions**

The results of the review cast doubt on the notion that combined 5-HT2/D2 receptor antagonism is the reason why the newer antipsychotic medications are effective for negative symptoms and have fewer extrapyramidal side-effects. The main conclusion is that combined 5-HT2/D2 receptor antagonism is not the only mechanism that makes an antipsychotic atypical.

**CRD commentary**

The review question was unclear, with the stated objectives appearing to differ from the actual analysis undertaken and the results reported. It became clearer as the article progressed that part of the authors’ purpose was to update their earlier review on other 5-HT2/D2 receptor antagonists, and to include the findings on the effects of amisulpride with these. The earlier review (see Other Publications of Related Interest no.3) should be consulted for more comprehensive details of the search strategies, etc. The study selection criteria clearly seemed to pertain to studies that compared amisulpride with conventional antipsychotics and/or placebo. However, while the literature search of the included studies and the statistical tests described all related to this aspect, the 'Results' section contained findings for other 5-HT2/D2 receptor antagonists as well as amisulpride. The results of the indirect comparisons of pooled effect sizes across the different systematic reviews were not reported in this abstract.

The literature search was restricted to MEDLINE and Current Contents and a search of the reference lists of reviews and included studies. The authors made some attempt to locate unpublished studies by contacting the manufacturer of amisulpride. It was unclear whether any language restrictions were applied. No details of the methodology of the review process were provided, in particular, whether any validity assessment was carried out and how the data were extracted. The range of statistical tests described seemed appropriate for the analysis undertaken in the review. The 'Discussion' section related more closely to the review question in terms of comparing the profile of amisulpride with the other 5-HT2/D2 receptor antagonists, but overall, the article was confusing to read as it was presented as a combination of two papers with rather different objectives.

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

Practice: The authors did not state any implications for practice.

Reviewer's statement: The findings of the review suggest that amisulpride is more effective than conventional antipsychotic drugs in the treatment of patients with schizophrenia and schizophrenia-like symptoms.

Research: The review’s conclusions suggest that more information is required to understand what other mechanisms, in addition to the combined 5-HT2/D2 receptor antagonism, make an antipsychotic atypical.

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