Risperidone versus haloperidol - I: meta-analysis of efficacy and safety

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Authors' objectives
To compare risperidone and haloperidol for the treatment of schizophrenia in terms of clinical response, prescription of anticholinergic agents and treatment drop-outs.

Searching
MEDLINE and EMBASE were searched and enquiries were made to the manufacturer of risperidone.

Study selection
Study designs of evaluations included in the review
Randomised double blind studies of at least 4 weeks duration that compared risperidone and haloperidol were included. Reasons were given for exclusion of identified studies. When more than one report used data from the same trial, the published version or the latest available report was selected.

Specific interventions included in the review
Risperidone in the recommended dosage of 4 to 8 mg/d or in a flexible dose regime (dose titrated to clinical response) was compared with haloperidol (actual dose ranged from 2.9 to 20 mg/d. Actual dosages of risperidone ranged from 2.5 to 12.0 mg/d. Minimum duration of therapy was 4 weeks, with actual duration ranging from 4 to 12 weeks.

Participants included in the review
Patients with a DSM-III-R (American Psychiatric Association) or ICD-9 diagnosis of schizophrenia were included. Actual subjects had chronic schizophrenia as defined above with a minimum Positive and Negative Syndrome Scale score of 60 (or a Brief Psychiatric Rating Scale score of 30) at baseline and fulfilled criteria for schizophrenia established by the World Health Organization international classification of diseases. Mean age across studies ranged form 36.4 to 43 years and percentage male ranged from 67% to 96%. Patients included inpatients and those who were hospitalized for only the first three weeks of treatment. A study of patients with schizoaffective disorder was excluded.

Outcomes assessed in the review
The following outcomes were assessed: clinical improvement measured by the percentage of patients with 20% or greater reduction in the score on the Positive and Negative Syndrome Scale (PANSS) or the Brief Psychiatric Rating Scale (BSRS); proportion of patients requiring anticholinergic medication for drug-induced extrapyramidal symptoms (EPS); and the proportion of drop-outs.

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
No formal assessment of validity was undertaken.

Data extraction
The following data appear to have been extracted: dosage of medication; duration of trial; number improved; selection criteria; and patient characteristics. Data were analysed according to strict interpretation of the intention-to-treat criteria (or last observation carried forward). Point estimates for the difference in rates between treatment groups and 95% confidence limits were calculated. The authors do not state how many of the reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
Data were pooled using the random-effects model of DerSimonian and Laird to give treatment difference and 95% CI for the three outcome measures (see Other Publications of Related Interest no.1). Trials using flexible dosing were included although the mean dose given exceeded 8mg (upper limit for included trials with fixed dose).

How were differences between studies investigated?
A chi-squared test was used to detect statistical heterogeneity and sources of clinical heterogeneity were discussed. Sensitivity analyses were undertaken by repeating the analyses using only data from trials employing a 10 mg dose of haloperidol and by including 3 trials initially excluded from the meta-analyses (inclusion of patients with schizoaffective disorder and use of different rating scale, patients received 5 or 10 mg risperidone but results were not reported separately and did not report data for anticholinergic use, and the inclusion of patients with mixed diagnosis).

Results of the review
Six trials were included (1047 patients).

Inspection of individual trials suggested the following potential heterogeneity differences: use of differing patient inclusion criteria; inclusion of one trial with mean dose exceeding the reviews inclusion criteria; use of different rating scales; differing baseline rates of anticholinergic medications; differing mean number of previous hospitalizations; and differing percentages of males.

Clinical efficacy: the clinical response rate was significantly higher in patients receiving risperidone. Mean difference 13.9% (95% CI: 5.6%, 22.3%; P < 0.05). No evidence of statistical heterogeneity was found.

Rate of anticholinergic medication: the rate of anticholinergic medication prescription was significantly lower in patients receiving risperidone. Mean difference 17.7% (95% CI: 9.4%, 25.9%; P < 0.05). No evidence of statistical heterogeneity was found.

Drop-out rate: the drop-out rate was significantly lower in patients receiving risperidone. Mean difference 12.7% (95% CI: 4.3%, 21.2%; P < 0.05). No evidence of statistical heterogeneity was found.

Sensitivity analyses:
Limiting analyses to trials using a 10 mg haloperidol dose: results were similar although point estimates for the difference were reduced. Mean difference in clinical response = 8.1% (95% CI: 1.3%, 14.8%). Mean difference in anticholinergic use = 12.2% (95% CI: 6.0%, 18.3%). Mean difference in drop-outs = 7.9% (95% CI: 1.8%, 14.0).

Including 3 trials excluded from the initial analyses: the authors report that results still favoured risperidone, though some fail to reach statistical significance. Mean difference in clinical efficacy = 8.3% (95% CI: -0.7%, 17.2%). Mean difference in anticholinergic medication = 16.6% (95% CI: 10.0%, 23.6%). Mean difference in drop-outs = 7.8% (95% CI: 0.9%, 14.8%).

Cost information
The authors state that data from the meta-analysis were used in a subsequent economic analysis of the comparative effectiveness of risperidone and haloperidol (see Other Publications of Related Interest no.2).

Authors’ conclusions
Compared to haloperidol, risperidone was associated with a significantly higher clinical response rate, significantly less prescription of anticholinergic medication, and significantly lower treatment drop-out rates. These results demonstrate the greater treatment efficacy associated with risperidone compared with haloperidol and suggest a lower incidence of extrapyramidal symptoms and improved treatment compliance.
This review was clearly presented. The aims and inclusion criteria were stated. Attempts were made to locate unpublished material. Some relevant details of the primary studies were clearly presented in tabular format. Analyses were conducted on an intention-to-treat basis with a stated method of handling missing data. Statistical heterogeneity was assessed and illustrated graphically and sources of clinical heterogeneity discussed. Sensitivity analyses were undertaken. Results were clearly presented. The discussion included consideration of the following: relevance of a 20% reduction in PANSS score; use of prescription of anticholinergic medications as a surrogate measure of EPS; use of drop-outs to assess compliance; and dosage of haloperidol selected for comparison.

No details were given of terms or dates used or language restrictions applied to the literature search. PsycLIT was not searched. Methods used to select primary studies and extract data were not described. Validity was not formally assessed. Only one of the trials exceeded 8 weeks in duration, thus evidence on long term effects was lacking.

The evidence supported the authors' conclusions, though including results from a formal assessment of validity would have increased the strength of the evidence presented. The findings were based predominately on trials lasting 8 weeks or less.

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

**Practice:** The authors do not report any clinical implications of the review.

**Research:** The authors do not report any research implications of the review.

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