A comparison of olanzapine versus risperidone for the treatment of schizophrenia: a meta-analysis of randomised clinical trials

CRD summary
This review concluded that olanzapine was superior to risperidone for a number of efficacy and safety variables, and these advantages may convey clinical relevance to certain aspects of schizophrenia. A lack of a systematic quality assessment and no details of the review methodology suggest that this conclusion should be treated with caution.

Authors’ objectives
To compare the efficacy and safety of olanzapine with risperidone in the treatment of schizophrenia.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched up to June 2002, along with the bibliography of a relevant Cochrane review.

Study selection
Study designs of evaluations included in the review
Double-blind randomised trials were eligible for inclusion.

Specific interventions included in the review
Studies comparing olanzapine and risperidone directly, or comparing either drug with haloperidol, were eligible for inclusion. Studies where medication had been switched, or was given after previous therapy failure, were excluded. Studies where one treatment arm received benztropine and the other a placebo were also excluded.

Participants included in the review
Studies of people with schizophrenia were eligible for inclusion. No further information about the participants was provided. However, the authors stated that details of the included studies are available on request.

Outcomes assessed in the review
There were no specific inclusion criteria relating to the outcomes. The outcomes chosen for analysis were the number of patients achieving a clinical response, the number requiring anticholinergic medication, and the number (and reason) for discontinuation. The response to several measurement tools was also assessed. Such tools included the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression severity score and the Quality of Life Scale (QLS).

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

Assessment of study quality
The review was restricted to double-blind randomised trials, but there was no systematic assessment of the quality of the included studies. The authors did not state how quality was assessed, or how many reviewers performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the change from baseline in the different measurement and quality of life scales, the
number of patients requiring use of anticholinergics, the number of clinical responders and the number of drop-outs.

**Methods of synthesis**

How were the studies combined?

Olanzapine and risperidone were compared directly and indirectly using haloperidol as the common comparator. Olanzapine and risperidone were evaluated for short-term (12 weeks or less) and long-term (over 12 weeks) efficacy. Pooled odds ratios (ORs) or risk differences with 95% confidence intervals (CIs) were calculated for dichotomous data, and weighted mean differences (WMDs) and 95% CIs for continuous data. A fixed-effect model was used where there was no heterogeneity between the studies, and a random-effects model when heterogeneity was observed. Indirect comparisons of olanzapine and risperidone were made by calculating the OR or WMD in comparison with haloperidol, and comparing them using meta-regression or the normal approximation of each pair of CI. All dichotomous efficacy data were analysed on an intention-to-treat basis, and continuous efficacy data using the last-observation-carried-forward method. Safety and tolerability data came only from treated patients. Quality of life was only assessed using data from the direct comparison trials.

How were differences between studies investigated?

Heterogeneity was evaluated using the chi-squared statistic. Sensitivity analyses were conducted using results for only clinically relevant doses of each antipsychotic: 10 to 15 mg/day for olanzapine, 4 to 6 mg/day for risperidone and 5 to 15 mg/day for haloperidol.

**Results of the review**

Twenty-four randomised controlled trials (RCTs; n=6,321) were included in the review. Four reported direct comparisons between olanzapine and risperidone (n=853), seven compared olanzapine with haloperidol (n=2,915) and fifteen compared risperidone with haloperidol (n=2,618). One trial had three arms, evaluating olanzapine, risperidone and haloperidol. The duration of the studies ranged from 4 weeks to 12 months.

Short-term outcomes.

Direct comparisons showed a statistically significant (P<0.05) reduction in anticholinergic use with olanzapine compared with risperidone (OR 0.65, 95% CI 0.47, 0.90; 3 RCTs). This was supported by the indirect comparisons for all doses (OR 0.97, 95% CI 0.45, 1.50; 13 RCTs) and for clinically relevant doses (OR 0.88, 95% CI 0.41, 1.34; 5 RCTs).

There were no statistically significant differences in efficacy outcomes, drop-outs (due to adverse events, lack of efficacy or for any reason) or quality of life between olanzapine and risperidone when either direct or indirect comparisons were made.

Long-term outcomes.

Direct comparisons showed olanzapine to be superior to risperidone. Statistically significant differences (P<0.05) were observed in the following:

- 40% or more improvement in PANSS score (OR 1.63, 95% CI: 1.05, 2.53; 2 RCTs),
- 50% or more improvement in PANSS score (OR 19.1, 95% CI: 1.09, 3.37; 2 RCTs),
- total change in PANSS score (WMD -5.35, 95% CI: -10.15, -0.55; 2 RCTs),
- PANSS score negative change (WMD -1.39, 95% CI: -2.66, -0.13; 3 RCTs),
- PANSS GPS score (WMD -2.88, 95% CI: -5.20, -0.57; 3 RCTs),
- BPRS total change (WMD -3.23, 95% CI: -6.00, -0.46; 2 RCTs), QLS total change (WMD 5.23, 95% CI: 1.32, 9.15; 2 RCTs), QLS interpersonal relations change (WMD 2.53, 95% CI: 0.83, 4.23; 2 RCTs),
anticholinergic use (OR 0.45, 95% CI: 0.29, 0.70; 3 RCTs), and
drop-outs for any reason (OR 0.60, 95% CI 0.42, 0.88; 3 RCTs).

Only anticholinergic use was improved with olanzapine when indirect comparisons were made (3 RCTs for olanzapine
and 2 RCTs for risperidone; OR 0.88, 95% CI: 0.41, 1.34).

Authors' conclusions
Olanzapine exhibited a favourable clinical profile, with a significant benefit found for a number of efficacy and safety
variables in comparison with risperidone. The clinical efficacy and safety advantages of olanzapine may convey clinical
relevance to certain aspects of schizophrenia.

CRD commentary
The review question was clear in terms of the intervention, participants and study design. However, no criteria relating
to the outcomes were given. Relevant sources were searched, but the search was not extensive and there was no
indication as to whether language restrictions were imposed. Publication and language bias cannot, therefore, be ruled
out and the authors did not investigate the potential for publication bias in the review. There was no information on the
methods used to select studies, extract data or assess validity, so the possibility that error and bias was introduced during
the review process cannot be ruled out.

The authors stated the heterogeneity was assessed statistically, but these results were not reported. In addition, it was
unclear which meta-analyses were conducted using a fixed-effect method and which a random-effects method. In
addition, the studies seemed to be clinically heterogeneous and the pooling of such results may be misleading. The
conservative conclusions drawn by the authors may thus be considered appropriate. However, given the limitations of
the review, including a lack of a systematic quality assessment of the included studies and no details of the review
methodology, they should be treated with caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that a future meta-analysis could examine the speed of onset of antipsychotic action. In
addition, future trials could study the effects of antipsychotics on additional parameters, such as cognition, and other
adverse events. Analyses comparing other atypical antipsychotics on therapeutic and safety outcomes are also required.

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Bibliographic details
olanzapine versus risperidone for the treatment of schizophrenia: a meta-analysis of randomised clinical trials.

Other publications of related interest
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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.