The clinical value of risperidone and olanzapine: a meta-analysis of efficacy and safety

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Authors' objectives
To synthesise the clinical trial data currently available on two novel antipsychotics, risperidone and olanzapine, and to compare them with conventional products in terms of efficacy and safety.

Searching
MEDLINE, EMBASE, and PsycLIT were searched for articles published between January 1991 and June 1998. The search terms included both brand and generic names of all known antipsychotic medications used for the treatment of human schizophrenia.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials, which involved either a risperidone or an olanzapine arm, were included in the review. The included studies reported the mean values, along with the variance, of the baseline and outcome data for a minimum of ten patients.

Studies were excluded if they: failed to report variance data; were single-arm or open-label trials; used inappropriate or incompatible outcome measures; were combined reports of individual trials; or were multiple publications of the same data.

Specific interventions included in the review
Clinical trials comparing risperidone or olanzapine with conventional neuroleptics (haloperidol, perphenazine and methotrimeprazine) were included in the review.

For included trials, study arms were extracted for doses recommended within the existing product labelling: 4 to 8 mg/day inclusive for risperidone and 5 to 20 mg/day inclusive for olanzapine. Trials in which there was no fixed dose were also included if the average dose of risperidone was 4 to 8 mg/day.

Participants included in the review
The authors did not specify any inclusion criteria with respect to the characteristics of the study participants.

Baseline demographic and clinical characteristics were combined for all included studies. There were no significant differences between risperidone, olanzapine and conventional neuroleptic treatment groups for the following variables: age, gender, duration of treatment, duration of illness, schizophrenia subtype (disorganised or paranoid), baseline Positive and Negative Symptom Scale (PANSS) score.

Outcomes assessed in the review
Efficacy was assessed using PANSS (see Other Publications of Related Interest no.1), and by the number of withdrawals due to lack of efficacy. The requirement for medication for anti-extra-pyramidal symptoms (EPS) was used to assess safety.

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 quality was undertaken.
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 the following: baseline demographic and clinical characteristics of the study participants; the type and dosage of antipsychotic treatment used; the mean duration of treatment; the conventional neuroleptic used in the control group; outcomes, i.e. PANSS score, withdrawals due to lack of efficacy, and requirement for anti-EPS medication.

Methods of synthesis
How were the studies combined?
A random-effects model was used to combine the results across trials, and a meta-regression was used to compare product categories. The weights for each trial were calculated from the random-effects weights, as defined by DerSimonian and Laird (see Other Publications of Related Interest no.2). Meta-regression analysis was also used to identify potential, independent statistical predictors of outcome.

How were differences between studies investigated?
Between trial variance for each outcome measure was assessed using the P-value from Cochran's test of homogeneity (see Other Publications of Related Interest no.2).

Results of the review
A total of 15 studies were included in the analysis. There were 11 trials involving 1,208 patients on risperidone, and 5 trials involving 2,018 patients on olanzapine. The total number of included participants, as well as the numbers of patients on conventional neuroleptics, was unclear as not all of the included trials reported the latter.

The use of risperidone and olanzapine reduced the total PANSS score by a mean of -23.7 and -21.5, respectively; a smaller reduction (- 15.4) in the PANSS score was observed in patients receiving conventional neuroleptics. Compared with conventional neuroleptics, the change in PANSS score reduction for risperidone was -8.3 (95% confidence interval, CI: -13.8, -2.7), which was statistically significant; the change for olanzapine was not significant (-6.1, 95% CI: -12.8, +0.6).

Risperidone was associated with fewer withdrawals due to the inefficacy of treatment (9%) than either the conventional neuroleptics (27%) or olanzapine (24%). The odds of withdrawal due to lack of efficacy were significantly lower for risperidone than for conventional neuroleptics (odds ratio, OR=0.28, 95% CI: 0.14, 0.56), whereas those for olanzapine were not significantly different from those for conventional neuroleptics (OR=0.85,95% CI: 0.36, 2.04).

There were significantly fewer patients requiring anti-EPS medication in the risperidone group (20%) than in the group receiving conventional neuroleptics (38%). The OR for requirement of anti-EPS medication for risperidone versus conventional neuroleptics was 0.42 (95% CI: 0.19, 0.96). There were no comparable data available for olanzapine for this parameter, due to the smaller number of trials available and the absence of identifiable data in some cases.

The influence of statistically-independent predictors of outcome was analysed by a meta-regression. The age of the patient and the duration of treatment appeared to be significant factors for all outcome measures. Gender and prior duration of disease were only influential in the case of withdrawal due to lack of efficacy.

Authors' conclusions
Patients receiving novel antipsychotics are likely to gain improved control of symptoms of schizophrenia, and are less likely to require medication to counteract EPS than patients receiving conventional neuroleptics.

CRD commentary
The review question was clearly set out and was well-defined in terms of treatment, study design, and outcome
measures. The authors did not specify any inclusion criteria relating to the participants' characteristics, although a summary of baseline demographic and clinical data was included in the report.

The literature search was restricted to three databases and the search terms used were not described in detail. Given the limited nature of the search, as described, and the lack of any follow-up searching of references from retrieved articles or additional handsearching, complete retrieval of all available articles seems unlikely. In addition, no attempt was made to identify any unpublished data. In the absence of any reported assessment of publication bias, the possible impact of such bias on the findings of this review should be considered.

The authors did not report any formal assessment of the methodological quality of the included studies. The possible impact of biases, introduced by methodological flaws in the primary studies, should therefore be considered when interpreting the findings of this review. This problem is to some extent mitigated by the restriction of the review to randomised controlled trials, and the specific exclusion of single-arm and open-label trials.

It was difficult to assess the external validity of the review since there were limited details provided on the design of the individual studies, and the baseline participant characteristics were summarised for all of the studies.

The results of the studies included in the review were appropriately combined, and the meta-analysis was rigorously conducted. The authors' conclusions, though following broadly from the reported results, could have been more conservative given that the improved outcomes reported for novel antipsychotics over conventional neuroleptics were only statistically significant for risperidone, and not for olanzapine.

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

Practice: The authors state that in terms of clinical practice, the findings of this comparative efficacy and safety meta-analysis indicate that these novel antipsychotics, particularly risperidone, are superior to conventional neuroleptics. Patients treated with these novel antipsychotics are likely to achieve better control of symptoms, and are less likely to require medication to control EPS. The efficacy data presented here, taken together with the superior cost-effectiveness of risperidone over olanzapine (see Other Publications of Related Interest nos.3-5), suggest that risperidone should be considered as a first-line agent for treatment of patients with schizophrenia.

Research: The authors did not state any implications for further research.

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**Bibliographic details**

**Other publications of related interest**

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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.