Clinical trial response and dropout rates with olanzapine versus risperidone
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CRD summary
This review assessed the use of olanzapine and risperidone for schizophrenia. The authors concluded that olanzapine appears to be associated with a lower drop-out rate than risperidone and it may improve long-term maintenance of response, but further data on long-term maintenance are required. The authors' conclusions may not be reliable in view of the potential for various sources of bias.

Authors' objectives
To compare the drop-out and response rates between olanzapine and risperidone.

Searching
MEDLINE (from 1966 to May 2002), IDIS (from 1966 to May 2002) and the DRUGDEX databank (volume 112) were searched; the search terms were stated. Reference lists in identified studies were also reviewed. The search strategy was restricted to English language publications.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) lasting at least 6 weeks were eligible for inclusion. In addition, observational studies with at least 6 weeks' follow-up were eligible for the assessment of maintenance of response.

Specific interventions included in the review
Studies of olanzapine and risperidone were eligible for inclusion. No details of the interventions, such as drug doses, were reported.

Participants included in the review
Studies of patients with schizophrenia were eligible for inclusion, regardless of the type of previous treatment. Studies assessing maintenance of response included patients who had responded to drug treatment. No details of the included participants were provided.

Outcomes assessed in the review
Studies that assessed drop-outs or response were eligible for inclusion. The review also assessed maintenance of response. The authors' definition of response was accepted by the reviewers. The included studies directly comparing the two drugs defined response as a 20% improvement in the Positive and Negative Symptoms Scale (PANSS) total score. Most of the studies used to assess maintenance of response defined relapse as hospitalisation for psychopathology.

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 authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted the data. Any differences were discussed and documented, and authors were contacted for additional information if required. The data extracted included definition of response, study duration, number of patients in each treatment arm, and the number of patients who dropped out and responded for each
treatment arm.

For each RCT comparing olanzapine with risperidone, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for drop-out and response rates. Outcomes data were extracted for each time period reported. For studies used in the assessment of the maintenance of response, data on treatment failure over time were extracted separately for the olanzapine and risperidone treatment arms. Information on the timing of response was obtained, where possible, from the authors. If this were not possible a computer program was used to provide values. The paper stated that detailed information on the included studies was available on a website (URL: www.labsifo.org/supplements/santarlasci.htm), but this could not be accessed (30/06/2005).

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis. Pooled ORs and 95% CIs were calculated for drop-out and response rates using data from RCTs directly comparing olanzapine and risperidone (uncensored analysis). Fixed-effect and random-effects models were used. The number-needed-to-treat (NNT) to avoid one drop-out was calculated. The drop-out rates over time were examined using Kaplan Meier actuarial curves (censored analysis). The relative risk (RR) and 95% CI of drop-out were calculated using the Cox model, and differences between the drugs were tested using the log rank test. For studies used to assess maintenance of response, the data were pooled to generate a separate Kaplan Meier actuarial curve for each drug. There was no statistical comparison of maintenance of response rates between drugs.

How were differences between studies investigated?
Statistical heterogeneity between RCTs for the uncensored analysis was assessed using the chi-squared statistic. Statistical heterogeneity for the censored analysis was assessed using the statistical significance of the variable 'study' when it was entered into the Cox model. Some potential sources of differences between the studies (e.g. treatment regimen and differential reasons for withdrawal) were discussed in the paper.

Results of the review
Four RCTs (838 patients) directly compared the drop-out rates of olanzapine and risperidone, while two RCTs (716 patients) directly compared the response rates of olanzapine and risperidone. Data from five RCTs of olanzapine (928 patients) and three studies of risperidone (290 patients) were included in the assessment of maintenance of response.

Direct comparison of drop-out rates with olanzapine and risperidone.
The risk of drop-out was significantly greater with risperidone than with olanzapine; the OR (fixed-effect model) was 1.50 (95% CI: 1.13, 2.00, P=0.006). No statistically significant heterogeneity was detected (P=0.80). The results were similar when using the log rank test (P=0.006). The NNT to avoid one drop-out with olanzapine compared with risperidone was 11.

The results were also similar when using the censored approach (Cox analysis); the RR was 1.35 (95% CI: 1.08, 1.69, P=0.008). No statistically significant differences between the studies were detected (P for variable study =0.91).

Direct comparison of response rates with olanzapine and risperidone.
The response rates of risperidone and olanzapine were similar; the OR (fixed-effect model) was 1.03 (95% CI: 0.76, 1.39). No statistically significant heterogeneity was detected (P>0.90).

Maintenance of response.
Kaplan Meier curves showed a slightly worse pattern of maintenance of response for risperidone compared with olanzapine (the curves were presented). Studies of risperidone were of a longer duration than studies of olanzapine: 365 to 800 days with risperidone versus 196 to 365 days with olanzapine.
Authors' conclusions
Olanzapine appears to be associated with a lower drop-out rate over time than risperidone and it may improve long-term maintenance of response. However, further data on long-term maintenance are required.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. However, diagnostic criteria for schizophrenia were not stated as part of the inclusion criteria. Three relevant sources were searched and the search terms were given. No attempts were made to minimise language bias. The methods used to select the studies were not described, so it is not known whether any efforts were made to reduce errors and bias. Methods were used to minimise bias in the data extraction process. Validity was not assessed.

It appears appropriate to have combined the data in a meta-analysis, but more complete information on the included studies was required to compare them. Some information was tabulated, while additional information was reported to be available on a specific website. We were unable to access this site and so were unable to examine the differences between studies, particularly with reference to the characteristics of the population and treatment regimens. Statistical heterogeneity was assessed. In their discussion, the authors commented on the potential lack of statistical power in the analysis of response rates as one explanation for the lack of difference between drugs, but this was not highlighted in the 'Results' section. In view of these limitations, the authors' conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that the advantages of olanzapine over risperidone must be balanced against the overall pattern of drug-related adverse effects.

Research: The authors stated that further data are required on the effects of olanzapine and risperidone on long-term maintenance of response.

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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.