Clozapine v. conventional antipsychotic drugs for treatment-resistant schizophrenia: a re-examination

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CRD summary
This poorly reported review compared clozapine with conventional anti-psychotics for treatment-resistant schizophrenia. The author concluded that clozapine was not shown to be consistently and definitively better than conventional anti-psychotics. The review has several methodological weaknesses and its unclear whether the quality of the included studies and the synthesis of them, can be relied upon.

Authors' objectives
To compare clozapine with conventional antipsychotics for treatment-resistant schizophrenia, and to investigate potential sources of differences in effect between studies.

Searching
Trials were identified from a previous Cochrane review (see Other Publications of Related Interest). MEDLINE and EMBASE were searched from 1998 to April 2003 for trials published after the Cochrane review.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not specified in terms of study design. However, it appears that the included studies were randomised controlled trials (RCTs). The duration of the included studies ranged from 6 weeks to 2 years.

Specific interventions included in the review
Studies comparing clozapine with conventional antipsychotics were eligible for inclusion. The included studies compared clozapine (176 to 600 mg/day) with the following antipsychotics: chlorpromazine (600 to 1,200 mg/day), haloperidol (16 to 28 mg/day), or usual care with 1,386 chlorpromazine equivalents.

Participants included in the review
Studies of patients with treatment-resistant schizophrenia were included in the review. The included studies used different definitions of treatment resistance. All but one study included patients who had failed to respond to at least two conventional antipsychotic drugs. Some studies defined failure to respond as serious difficulty in functioning, symptoms moderate or above on the Brief Psychiatric Rating Scale (BPRS), or as both of these conditions; other studies did not define this term. At baseline, the patients’ BPRS scores ranged from 38 to 84. The studies included children and adults (including patients aged older than 55 years). Most studies were of patients who had been hospitalised for between 9 months and 18 years. Two studies were of out-patients.

Outcomes assessed in the review
The inclusion criteria were not specified in terms of outcomes. The main outcome in the review was the symptom score at the end of the study, or the change in symptoms. All of the included studies assessed symptoms using either the BPRS or the Positive and Negative Syndrome Scale (PANSS). The review also assessed rates of hospitalisation and discharge, and withdrawal rates.

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

Assessment of study quality
The author did not state that they assessed validity.
Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Data extracted included the post-treatment BPRS or PANSS symptom score reduction in the clozapine and control group in each study, and the proportion of patients improved in each group. Data were also extracted on the mean symptom score post-treatment, or the mean change in symptoms from baseline, and its standard deviation, in each group. The data were extracted on an intention-to-treat basis where possible.

Methods of synthesis
How were the studies combined?
The difference in post-treatment symptom scores between clozapine and control in each trial were converted into a percentage of the post-treatment score in the control group, and a narrative synthesis was undertaken. A meta-analysis was used to combine the mean differences to obtain a pooled weighted standardised mean difference (SMD) in treatment effect.

How were differences between studies investigated?
In the meta-analysis, statistical heterogeneity was tested using the Q statistic and heterogeneity among the studies was illustrated using a forest plot. Differences between the studies were discussed in the text of the review with reference to definition of treatment resistance and baseline severity of the patients’ condition. A sensitivity analysis was used to re-calculate the SMD for post-treatment scores for one study after excluding patients in the control group who received clozapine during the study, and using non intention-to-treat data in another study. A univariate analysis was used to explore the relationship between the results and the following potential sources of heterogeneity: study duration; sample size; year of publication; severity of the patients' condition at baseline in terms of BPRS; financial support from the pharmaceutical industry; high-dose treatment used before study entry; and the ratio of dosage of clozapine to the chlorpromazine equivalent of the control drug. The univariate analysis was repeated using non intention-to-treat data for two studies. There were too few studies to perform a multivariate analysis.

Results of the review
Nine trials (1,199 patients) were included.

The results varied considerably between studies for the main outcome reported as a percentage of the post-treatment score in the control group (the results varied from less than 4% to 44.4%). The withdrawal rates varied from 9.5 to 43% with clozapine and from 8 to 72% with the control drug.

Re-hospitalisation or discharge (2 studies): one study showed no difference in discharge rates, while the other showed no difference in the proportion of patients who were readmitted.

Meta-analysis: overall, clozapine reduced symptoms compared with the control but significant heterogeneity was detected. The effect size (SMD) using a random-effects model was 0.44 (95% confidence interval: 0.15, 0.73). Heterogeneity remained after grouping studies as long or short term.

The univariate meta-regression using intention-to-treat data showed that studies of shorter duration (P<0.001), studies with patients with a higher baseline BPRS (P=0.02), and studies funded by a pharmaceutical company (P=0.003) found a greater benefit for clozapine.

An analysis excluding withdrawals and treatment crossovers from two trials gave similar results and showed that an earlier year of publication (P<0.001) might also favour clozapine.

Authors' conclusions
Clozapine was not shown to be consistently and definitively better than conventional antipsychotics. The author also concluded that study duration, funding from a pharmaceutical company, and more severe symptoms at baseline may explain the heterogeneity among studies, and that meta-analysis may not be an appropriate method of combining studies.
comparing clozapine with conventional antipsychotics.

**CRD commentary**
The review question was clear in terms of the participants and intervention but none of the inclusion criteria were explicitly defined. Limiting the search to two databases and studies identified by a previous systematic review may have resulted in the omission of other relevant studies. It was unclear whether any language limitations had been applied. No attempt to locate unpublished studies was reported, raising the possibility of publication bias. The methods used to select the studies and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged. The validity assessment was limited to withdrawals and crossovers. Some relevant information on the included studies was tabulated, but it was not entirely clear that all the included trials were RCTs. The author's conclusions about the benefits of clozapine in comparison with conventional drugs is open to question, because the methods used in the review were not adequate to address that question.

**Implications of the review for practice and research**
The author did not state any implications for practice or further research.

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