Case studies of adjunctive agents in clozapine-resistant schizophrenic patients

CRD summary
This review examined case studies of the efficacy and safety of adjunctive agents in clozapine-resistant schizophrenic or schizoaffective patients. The authors concluded that most case studies favoured the use of risperidone as an adjunctive agent, but that evidence was limited. The small included case reports provided insufficient evidence to draw any reliable conclusions.

Authors' objectives
To critically review all published case studies investigating the efficacy and safety of adjunctive agents in clozapine-resistant schizophrenic or schizoaffective patients.

Searching
MEDLINE was searched from January 1980 to February 2004; the search terms were stated. In addition, main review papers and the reference lists of papers identified in the search were screened.

Study selection
Study designs of evaluations included in the review
Case series and case reports were eligible for inclusion in the review.

Specific interventions included in the review
Studies assessing clozapine adjunctive agents were eligible for inclusion. Studies examining electroconvulsive therapy as a clozapine augmentation strategy were not included in the review. The included studies examined the efficacy of sulpride, risperidone, olanzapine, lithium, lamotrigine, fluvoxamine and bromocriptine as adjuncts to clozapine. The dose of clozapine during combined treatment varied from 50 to 900 mg/day and the duration of the combined treatment ranged from 1 week to 15.3 years. Some patients received concomitant medications as well as the study drug of interest. Only 48.5% of patients were reported to have received an adequate duration and dosage of clozapine monotherapy (at least 12 weeks and 300 mg/day).

Participants included in the review
Studies of clozapine-resistant schizophrenic or schizoaffective patients were eligible for inclusion. Twenty-five schizophrenic participants and 8 schizoaffective patients were included in the review. The age of the patients varied from 18 to 60 years across studies. The duration of illness varied from 2.5 to 34 years.

Outcomes assessed in the review
Studies with no efficacy reports were excluded from the review. The outcomes included in the review were clinical outcome, plasma clozapine levels and side-effects. Clinical outcomes was assessed using either the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale, or was judged by subjective clinical impression.

How were decisions on the relevance of primary studies made?
At least three independent reviewers inspected the individual patient data reported in each of the studies before inclusion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Clozapine plasma levels, clinical outcome, outcome measures, results and reported side-effects were extracted from each study. The outcomes were classified as positive or negative, but the statistical significance of all the results was not reported.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
The authors did not investigate differences between the studies. Any differences between the studies can be seen in the tables.

**Results of the review**

Fifteen case studies (n=33) were included in the review.

The outcome was positive in 13 case studies including 31 patients, and negative in the remaining 2 case studies. Risperidone as an adjunct resulted in a positive outcome for 11 out of 13 patients. Sulpride, olanzapine, lithium, lamotrigine, fluvoxamine and bromocriptine were reported as effective in 1 or 2 case studies each.

The combined treatments were generally well tolerated and side-effects did not result in the discontinuation of treatment. The main side-effects reported were: transient lightheadedness, sedation and mild extrapyramidal symptoms for risperidone; hypersalivation for olanzapine; and nausea and dizziness for fluvoxamine. One case study reported exacerbation of obsessive-compulsive symptoms with a clozapine and risperidone combination. One patient developed hyperleukocytosis during treatment with clozapine and lithium.

**Authors' conclusions**

Most case studies favoured the use of risperidone as an adjunctive agent in clozapine-resistant schizophrenia or schizoaffective patients. However, small numbers of patients and other methodological problems mean that the evidence is limited.

**CRD commentary**

Inclusion criteria were specified for the participants, interventions and study design. However, no definition of a clozapine-resistant patient was used to determine which studies should be included. Only one database was searched, thus increasing the possibility that relevant studies might have been missed, and only published studies were included in the review, which increases the risk of publication bias. In addition, the authors did not state whether any language restrictions were applied to the search. Three independent reviewers appear to have selected studies for inclusion, which helps reduce the risk of bias, but it was unclear whether the same methods were applied to the data extraction. The authors did not assess the quality of the included studies, and provided no explanation for only including case studies which tend to be less robust and more prone to error than other study designs.

Adequate study details were presented and the narrative synthesis of studies was appropriate. Given the methodological limitations of the review and the unreliable nature of case studies, the reliability of the evidence presented is poor. The authors' conclusion that the evidence is limited appears appropriate.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that a systematic study of clozapine adjunctive agents should be carried out using carefully conducted controlled trials.
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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.