Risperidone augmentation of clozapine: a critical review

CRD summary
The authors concluded that existing evidence encourages the use of risperidone as augmentation of clozapine (CLZ) in at least a group of CLZ-resistant patients. Given the absence of a formal validity assessment and methodological limitations in the review process and analysis, the authors’ conclusions should be treated with caution.

Authors' objectives
To review the literature on the efficacy and safety of risperidone (RIS) as an adjunctive agent in clozapine (CLZ)-resistant patients with schizophrenia or schizoaffective disorder.

Searching
MEDLINE was searched from January 1988 to June 2005; the search terms were reported. The references of identified papers and reviews were checked.

Study selection
Studies of RIS used as an adjunctive agent to CLZ in people who have CLZ-resistant schizophrenia or schizoaffective disorder were eligible for inclusion. Studies were excluded if patients had not previously received CLZ as monotherapy. Where reported in the included studies, the CLZ dosage in combined therapy ranged from 150 to 900 mg/day and the RIS dosage from 1 to 10 mg/day. The participants in the included studies had a mean age of 38.4 years, and the majority had a diagnosis of schizophrenia. The included studies were of both in-patient and out-patient populations. Inclusion criteria for the outcomes were not defined. The included studies used the Brief Psychiatric Rating Scale, the Positive and Negative Syndrome Scale, the Clinical Global Impression - Improvement Scale and subjective clinical impression as outcome measures. A variety of standardised scales were used to assess side-effects. Inclusion criteria for the study design were not defined. The included studies were randomised controlled trials (RCTs), open trials and case studies. The duration of the included studies ranged from 1 to 28 weeks (mean 7.9).

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. However, they drew attention to some methodological limitations in their discussion.

Data extraction
The authors did not state how the data were extracted for review, or how many reviewers performed the data extraction. The authors also appear to have extracted the number of patients responding to treatment for each study.

Methods of synthesis
The numbers of patients responding to treatment were pooled to calculate a percentage response to treatment. The studies were combined in a narrative and data were presented in tabular format. The results were discussed separately according to the different study designs. Differences between the studies were evident from the text and tables.

Results of the review
Thirteen studies (n=120) were included in the review: 2 RCTs (n=70), 3 open trials (n=37) and 8 case studies (n=13).

The results were based on the 86 patients receiving the intervention. The control groups were not included in the discussion of the results.

Results on the efficacy of CLZ and RIS combined therapy were mixed. Overall, RIS augmentation of CIS was effective in 43% of patients, as measured by the improvement in psychopathology. One RCT found CLZ and RIS combination therapy to be more effective than placebo; the other RCT had negative findings. Two open trials reported a reduction of...
20% or more on measures of psychopathology (5 to 10 points; no p-values reported). A reduction in psychopathology of 20% or more was observed in 25% of patients treated with CLZ and RIS in the RCTs and in 45.9% of patients in the open trials. CLZ and RIS combined therapy was effective in 84.6% of patients in the case studies.

Several side-effects of RIS augmentation of CLZ were reported: the most frequently reported were extrapyramidal symptoms or akathisia (9.3% of patients), sedation (7% of patients) and hypersalivation (5.8% of patients). One RCT found a significant reduction in extrapyramidal side-effects with RIS augmentation compared with CLZ combined with placebo (no p value reported). The other RCT generally found no significant differences between the RIS and placebo groups on measures of side-effects, apart from an increase in sedation in the RIS group (no p-values reported).

Authors' conclusions
Existing evidence encourages the use of RIS augmentation of CLZ in a group of CLZ-resistant schizophrenic or schizoaffective patients. However, the strength of the evidence is limited by methodological shortcomings in the included studies.

CRD commentary
The review question was clear in terms of the intervention and patients. Inclusion criteria for the outcomes and study design were not defined, resulting in a variety of included study designs and the inclusion of some studies that did not use outcome measures. Only one database was searched and it is unclear whether appropriate steps were taken to minimise language or publication bias; important data may therefore have been omitted. There was insufficient information about the study selection and data extraction processes to rule out the possibility of error and bias. A validity assessment does not appear to have been carried out. Several methodological limitations were evident in the studies used. These limitations and the predominance of case studies limit the validity and reliability of the results. The narrative analysis was appropriate given the clinical heterogeneity of the included studies. Furthermore, the pooling of data from RCTs to achieve a total percentage response rate was an inappropriate method of synthesis. Given the absence of a formal validity assessment and methodological limitations in the review process and analysis, the authors' conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that RIS augmentation of CLZ is encouraged in a group of CLZ-resistant patients.

Research: The authors stated that further carefully conducted controlled trials are needed.

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