Combination therapy with non-clozapine atypical antipsychotic medication: a review of current evidence

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CRD summary
The authors concluded that combination therapy with non-clozapine atypical antipsychotics was worth considering in cases of treatment-resistant schizophrenia where clozapine was deemed inappropriate. However, they recommended caution because of a lack of data on safety. Limitations in the evidence base and review methods suggest that the findings should be treated with caution.

Authors' objectives
To assess the effectiveness and risks of therapy with combinations of atypical antipsychotic drugs other than clozapine in people with schizophrenia.

Searching
The authors searched English language literature using MEDLINE in August 2003, with an update in February 2006. Search terms were reported. Drug manufacturers were contacted to identify unpublished evidence. Reference lists of retrieved articles were also screened.

Study selection
Studies of any design that reported on use of two non-clozapine antipsychotic drugs in adults with schizophrenia were eligible for the review. Studies reporting outcomes related to clinical effectiveness or safety were included.

The review assessed quetiapine augmentation, and seven different combinations and doses of two of the following drugs: amisulpride, aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone. Most of the included studies did not use rating scales to assess outcomes.

Most participants had a diagnosis of schizophrenia, but some had schizo-affective disorder. Indications for combination treatment were treatment-resistant schizophrenia or reduction of adverse effects. Duration of monitoring, where reported, ranged from a few days to over a year.

The authors did not state how studies were selected for the review.

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

Data extraction
The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
A brief narrative was provided under headings relating to clinical effectiveness, worsening of psychotic symptoms, safety, and adverse effects. Differences between studies were discussed in the text and presented in tables. The synthesis was limited by the fact that many drug combinations were only examined in one study.

Results of the review
Four ‘open’ studies, five case series and 12 case reports (62 participants treated with non-clozapine combinations) were included.

Amisulpride/olanzapine (one open retrospective study, n=5 participants; one case series, n=7 participants; and one case report, n=1 participant), olanzapine/risperidone (one open retrospective study, n=5 participants; one case series, data from n=1 participant; and one case report, n=1 participant) and quetiapine/risperidone (three case reports, n=3...
participants) were all associated with improvements from baseline in one or more outcomes in small uncontrolled studies. Data on safety and adverse events were very limited.

**Authors’ conclusions**
Combination therapy with non-clozapine atypical antipsychotics was worth considering in cases of treatment-resistant schizophrenia where clozapine was deemed inappropriate, but caution was recommended due to the lack of data on safety.

**CRD commentary**
The review had clear but broad inclusion criteria. Although the inclusion criteria specified participants with schizophrenia, people with other related disorders were included, potentially limiting the applicability of the findings. The authors searched a limited range of sources and limited the search by language, which meant that some relevant studies could have been missed. Attempts were made to locate unpublished studies but the risk of publication bias was not assessed. Methods used for study selection and data extraction were not reported, so the risk of reviewer errors or bias was uncertain.

Study validity was not assessed, but the included studies provided only weak evidence on effectiveness and especially safety. Some relevant details of included studies were presented. A narrative synthesis was appropriate, although the small number of studies included for any particular combination was a limiting factor.

The authors’ conclusions should be treated with caution in view of the limited evidence base and possible limitations in the review methodology.

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

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

**Research:** The authors stated that there is a need for further well-designed studies of combination therapy, although they also noted that there would be considerable costs and practical difficulties involved in conducting randomised trials.

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