To combine or not to combine: a literature review of antidepressant combination therapy
Dodd S, Horgan D, Malhi G S, Berk M

CRD summary
This review aimed to assess the efficacy and utility of combinations of antidepressants for treatment-resistant depression. The authors concluded that this is a useful treatment option, especially if the antidepressants combined have different mechanisms of action, though further research is required. The authors’ conclusions may not be reliable as there were several methodological weaknesses in the conduct of the review.

Authors’ objectives
To review the evidence demonstrating the efficacy and utility of combinations of antidepressants for the treatment of treatment-resistant depression (TRD).

Searching
EMBASE, PsycLIT and MEDLINE were searched up to January 2005; the search terms were reported. The reference lists of articles, books and review papers were also checked, and major pharmaceutical companies were contacted.

Study selection

Specific interventions included in the review
Studies of combinations of antidepressants were eligible for inclusion. The included studies used various antidepressant combinations and comparators. The double-blind randomised controlled trials (RCTs) were of fluoxetine plus desipramine or mianserin, phenelzine plus amitriptyline, mirtazapine plus other antidepressant, or sertraline plus mianserin. The comparators were an antidepressant alone, a combination, or electroconvulsive therapy (ECT). Where reported, the duration of treatment was 4 to 8 weeks.

Participants included in the review
Studies of people with depression were eligible for inclusion. Where reported, the majority of the included studies were of patients described as having TRD though some patients were not treatment resistant.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not specified. The outcomes reported included response rates, remission rates, the Hamilton rating scale for depression (HAMD) and the Montgomery-Asberg depression rating scale (MADRS). Adverse events were also reported.

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
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.
Methods of synthesis
How were the studies combined?
A summary of individual studies, grouped by study design, was provided.

How were differences between studies investigated?
Differences between the studies were reported in the text and, for some studies, in a table.

Results of the review
Twenty-four studies were included: 8 double-blind RCTs (n=2,273) and 16 open-label studies. The authors also referred to a number of case series and case reports, but few details were provided.

The results of the 8 double-blind RCTs were varied. In five of the studies there was evidence of improvement with combination therapy compared with controls; in the other studies there was no significant benefit with combination therapy, or combination therapy was inferior to the comparator. A range of adverse events were reported for the individual studies but these were not synthesised. From the information presented in the review, it is not possible to provide an overall summary of the findings of the open-label studies. Although case series and case reports were eligible for inclusion, the findings of these studies were not reported. Adverse events were reported for individual studies though the overall impact of combined therapy was not explored.

Authors’ conclusions
Antidepressant combination therapies can be a useful treatment option in TRD, especially if the antidepressants combined have different mechanisms of action. However, further research is required to determine the relative efficacy, particularly in the long term.

CRD commentary
The review question was somewhat unclear. Although the population of interest was people with TRD, the inclusion criteria were wider than this and patients whose depression was not treatment resistant were included. Also, although all study designs were eligible, case series and case reports were not systematically included. A number of relevant databases were searched and unpublished studies were sought. The review methodology was not well described, and it was unclear whether appropriate procedures were used to reduce error and bias in the study selection and data extraction processes. The studies were not quality assessed and study findings were not systematically considered in the context of methodological quality. The narrative synthesis was appropriate, although the authors did not go beyond reporting the results of individual studies and there was limited exploration of the contradictory findings. Given the methodological weaknesses of this review, the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that the risks and benefits of any combination treatment need to be considered.

Research: The authors stated that large, high-quality RCTs comparing combination therapy with placebo are required.

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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.