A systematic review of augmentation strategies for patients with major depressive disorder
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CRD summary
The review concluded that relatively consistent evidence of higher responses after augmentation of antidepressants with antipsychotics needed to be balanced against the adverse effects. There was inconsistent evidence for lithium augmentation and a lack of supporting evidence for other augmentation strategies. The review had some methodological problems and caution is warranted when interpreting the authors' conclusions.

Authors' objectives
To determine the most appropriate and effective augmentation strategies for treatment-resistant depression.

Searching
MEDLINE and EMBASE were searched from January 1980 to July 2008 for published articles in English, French, German, Spanish or Italian. Search terms were reported. The American Psychiatric Association and manufacturer's trial registries were searched for unpublished studies from 2000 to 2008. Reference lists of retrieved articles and reviews were searched.

Study selection
Double-blind randomised controlled trials (RCTs) that evaluated augmentation therapy in combination with antidepressants in adults were eligible for inclusion. Augmentation therapy was defined as medication that was not approved as monotherapy for depression and was added to an antidepressant after an unsuccessful course of therapy. Trials had to include at least 10 participants in the augmentation arm. Studies had to be head-to-head trials. The relevant outcomes were Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HAM-D), response, remission and withdrawals due to adverse events.

The included RCTs examined various antidepressants in combination with lithium, buspirone, stimulant drugs, atypical antipsychotics, antidepressants, thyroid hormone and other augmentation strategies in patients with treatment-resistant depression. Doses and dosing regimens varied. Study duration ranged from one week to 12 weeks.

The authors did not state how many reviewers were involved in study selection.

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

Data extraction
Data were extracted on HAM-D, MADRS, remission, response and withdrawals due to adverse events.

Data were extracted by one reviewer and checked by a second reviewer.

Methods of synthesis
Trials were narratively synthesised and grouped according to intervention.

Results of the review
Thirty-two trials were included (number of participants not reported for all studies). Trial sample size, where stated, ranged from 21 to 500 participants.

Atypical antipsychotics had statistically significantly higher response rates compared with antidepressants alone and also had more withdrawals due to adverse events. Lithium and thyroid augmentation generally showed positive results compared with placebo, but there were inconsistencies across trials. Trials of atomoxetine, inositol, buspirone, yohimbine, testosterone and methylphenidate did not show any statistically significant clinical benefits.
Authors' conclusions
There was relatively consistent evidence of a higher response after augmentation of antidepressants with antipsychotics, but this needed to be balanced against the adverse effects. There was inconsistent evidence for lithium augmentation and a lack of supporting evidence for a number of other augmentation strategies.

CRD commentary
Inclusion criteria for the review were broadly defined. Several relevant data sources were searched for articles in several languages. Publication bias was not assessed but unpublished data was sought. The authors attempted to minimise reviewer error and bias during data extraction; it was unclear whether they did so for study selection. It appeared that no quality assessment was made, which made determining the quality of the included trials difficult. Trials were narratively synthesised, which was appropriate given that they were quite disparate in terms of interventions, comparators and populations. The authors declared conflicts in the form of employment and collaborations with various pharmaceutical companies, chiefly Bristol-Myers Squibb.

Overall, the review had some methodological problems and the quality of the included trials was uncertain, so caution is warranted when interpreting the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors stated that in order to replicate effective workplace nutritional interventions, studies should consider the key success factors and barriers identified in the review.

Research: The authors stated that future research should investigate how long augmentation therapy should last and whether it should be offered as periodic boosters or long-term therapy. There was a need for a consensus on what constituted treatment response and inadequate response. Future research should consider the efficacy of other common strategies in clinical practice, such as switching therapies, dose increases and combination therapies.

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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.