Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis

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CRD summary
This review evaluated the efficacy and overall tolerability of standard antidepressants augmented with atypical antipsychotic agents for treatment-resistant major depressive disorder. There were several methodological limitations to the review, which suggested that the augmentation of standard antidepressants with atypical antipsychotics may be effective in these patients.

Authors' objectives
To examine the efficacy and overall tolerability of standard antidepressants augmented with atypical antipsychotic agents for treatment-resistant major depressive disorder (TRDD).

Searching
MEDLINE (via PubMed), EMBASE and the Cochrane Library were searched. The search terms were reported, but the search dates were not. There were no restrictions on language or publication year. Abstracts of major psychiatric meetings held since 2000 were screened and authors or study sponsors were contacted for details. The authors also searched several clinical trial registries for completed unpublished trials. Companies without clinical trial registries were contacted directly.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that were double-blinded were eligible for inclusion.

Specific interventions included in the review
Studies assessing adjunctive treatment of standard antidepressants with an atypical antipsychotic were eligible for inclusion. Eligible studies used a placebo comparator. Studies that did not investigate the acute phase of treatment were excluded. The included studies evaluated olanzapine with fluoxetine, risperidone with various antidepressants, and quetiapine with a selective serotonin re-uptake inhibitor or serotonin-norepinephrine re-uptake inhibitor. The duration of treatment ranged from 4 to 12 weeks.

Participants included in the review
Studies of participants with TRDD were eligible for inclusion. Reports that focused exclusively on the treatment of patients with bipolar disorder, dysthymic disorder, psychotic major depressive disorder, minor depressive disorder or seasonal affective disorder, or depressed patients with a specific medical condition or active alcohol or substance abuse disorders were excluded. All participants in the included studies were out-patients. No details of the study populations were provided.

Outcomes assessed in the review
Studies that used either the Hamilton Rating Scale for Depression (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS) as their primary outcome measure were eligible for inclusion. Six of the included studies used the HAM-D and six used the MADRS. The primary outcome was remission rates, which were estimated using the HAM-D and MADRS scores. The definition of remission differed between the included studies. Secondary outcomes included a comparison of the rates of response, overall discontinuation, discontinuation due to inefficacy and discontinuation due to adverse events.

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 beyond the inclusion criterion that trials be double-blinded.

**Data extraction**
The authors stated that the data were extracted using a pre-coded form, but did not state how many reviewers performed the data extraction. Data were extracted on the primary outcome measure used (HAM-D or MADRS), along with response rates and remission rates for the primary outcome measure, and secondary outcomes such as overall discontinuation rates and discontinuation rates due to adverse events and inefficacy. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

**Methods of synthesis**

How were the studies combined?
RRs of remission rates and secondary outcomes were pooled in a random-effects meta-analysis.

How were differences between studies investigated?
Statistical heterogeneity was investigated using a chi-squared test.

**Results of the review**

Ten placebo-controlled RCTs (n=1,500) were included in the review.

There was no evidence of statistical heterogeneity between trials.

Augmentation of standard antidepressants was associated with a statistically significant increase in remission (RR 1.75, 95% CI: 1.36, 1.63, p<0.0001) and response rates (RR 1.35, 95% CI: 1.13, 1.63, p<0.001).

Treatment with placebo, compared with intervention, was associated with a statistically significant lower rate of discontinuation due to adverse events (RR 3.38, 95% CI: 1.98, 5.76, p<0.0001). There was no difference between groups in terms of the overall discontinuation rate (RR 1.18, 95% CI: 0.93, 1.49, p=0.929) and rate of discontinuation due to inefficacy (RR 0.66, 95% CI: 0.39, 1.13, p=0.133).

**Authors' conclusions**

There was evidence that the augmentation of standard antidepressants with atypical antipsychotics may be effective in patients with TRDD. This was specific to patients that had not experienced sufficient improvement following an adequate trial of antidepressants.

**CRD commentary**
The research question was well defined and the inclusion criteria were clear with regard to the intervention, participants, outcomes and study design. The authors searched three relevant databases. Unpublished literature was sought and there were no language restrictions, thereby minimising the risk of publication and language bias. The authors did not specify how decisions about inclusion were made, how the data were extracted, or whether a validity assessment was performed, so it is not known whether any steps were taken to minimise bias and error in the review process. Statistical heterogeneity was investigated, although the authors commented that the included studies may have been clinically heterogeneous, therefore the pooling of these studies might not have been appropriate. The authors acknowledged that the findings of this study may not be generalisable to certain population groups or beyond the acute phase of treatment (4 to 12 weeks). The authors’ conclusions are supported by the evidence presented and are sufficiently cautious considering the limitations of the review.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

**Funding**
National Institute of Mental Health, grant numbers K23 MH069629 and K24 MH01741.

**Bibliographic details**

PubMedID
17592905

Indexing Status
Subject indexing assigned by NLM

MeSH
Antidepressive Agents /adverse effects /therapeutic use; Antipsychotic Agents /adverse effects /therapeutic use; Depressive Disorder, Major /drug therapy; Drug Therapy, Combination; Humans; Randomized Controlled Trials as Topic; Remission Induction

AccessionNumber
12007002509

Date bibliographic record published
10/03/2008

Date abstract record published
09/08/2008

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.