Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials

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CRD summary
This review concluded that atypical antipsychotics were effective augmentation agents in major depressive disorder, but were associated with an increased risk of discontinuation due to adverse events. Given some shortcomings in the review process, small sample sizes of a number of trials and the uncertain quality of the included trials, the authors' conclusions should be interpreted with caution.

Authors' objectives
To determine the efficacy and tolerability of adjunctive atypical antipsychotic agents in major depressive disorder.

Searching
MEDLINE and the Cochrane Central Register of Clinical Trials (CENTRAL) were searched to January 2009. Search terms were reported. Additional studies were sought through the abstracts of major psychiatric meetings since 2000 and online trial registries. Manufacturers of atypical antipsychotic agents without online registries were contacted for published and unpublished reports.

Study selection
Double-blind randomised controlled trials (RCTs) that compared adjunctive atypical antipsychotic agents with placebo in patients with non-psychotic unipolar major depressive disorder were eligible for inclusion. Patients had to have non-psychotic major depressive disorder that was resistant to prior antidepressant treatment determined by either history or a prospective trial. Outcomes included response (defined as an improvement of at least 50% from baseline to endpoint on either the Hamilton Depression Rating Scale or Montgomery-Asberg Depression Rating Scale), remission and rates of discontinuation.

In the included trials, atypical antipsychotic agents comprised olanzapine, risperidone, quetiapine, and aripiprazole. Antidepressants included fluoxetine, various agents and serotonin re-uptake inhibitors-serotonin noradrenaline re-uptake inhibitors. Duration of the included trials ranged from four to 12 weeks; nearly all were between six and eight weeks.

The authors did not state how the papers were selected for review, or how many reviewers performed the selection.

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

Data extraction
Data for outcomes were extracted to calculate odds ratios (OR). Where necessary, sponsors or investigators were contacted for further information or missing data.

Data were extracted by one author and checked by the second.

Methods of synthesis
Pooled odds ratios and their 95% confidence intervals (CIs), were calculated using a fixed-effect model. Heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. Significant heterogeneity was defined as $I^2 \geq 50\%$. Sensitivity analysis for some analyses was based on differences between the agents, duration of the adjunctive trial and definition of treatment resistance based on whether it was historical or prospective. Publication bias was assessed using a funnel plot.

Results of the review
Sixteen RCTs were included (n=3,480 patients, range 15 to 487). The presence of publication bias was suggested by the funnel plot.

Compared with placebo, adjunctive atypical antipsychotics were significantly more effective for response (OR 1.69, 95% CI 1.46 to 1.95; 16 RCTs) and remission (OR 2.00, 95% CI 1.69 to 2.37; 16 RCTs), but had significantly greater discontinuation rates (OR 3.91, 95% CI 2.68 to 5.72; 15 RCTs). There was no significant heterogeneity for these comparisons.

Odds ratios did not differ among the atypical agents and were not affected by trial duration or method of establishing treatment resistance.

**Authors’ conclusions**

Atypical antipsychotics were effective augmentation agents in major depressive disorder, but were associated with an increased risk of discontinuation due to adverse events.

**CRD commentary**

The review question and inclusion criteria were clear. A limited literature search was undertaken to identify potential studies, but it was unclear whether specific language limitations were included; some attempts were made to locate unpublished material, so publication and language bias could not be ruled out. An assessment of publication bias was undertaken, with some suggestion of publication bias. The extraction of data for the review was undertaken by one author and checked by the other, but it was unclear whether this extended to the study selection. It was unclear whether methods were used to minimise error and bias for all parts of the review process. No assessment of study validity was reported, which made it difficult to assess the reliability of the included data. A third of trials contained less than 60 participants and few trial details were provided. Appropriate methods were employed for the meta-analysis, with suitable methods undertaken to assess statistical heterogeneity, which was found to be absent. Given the shortcomings for parts of the review process, small sample sizes of a number of trials and the uncertain quality of the included trials, the authors’ conclusions should be interpreted with caution.

Both authors received multiple grants for providing consultancy services for pharmaceutical manufacturers.

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

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

**Research:** The authors stated that trials of longer duration are required to assess long-term efficacy and safety data of adjunctive atypical antipsychotic agents.

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