Efficacy of modern antipsychotics in placebo-controlled trials in bipolar depression: a meta-analysis

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CRD summary
This review assessed second-generation antipsychotics for the treatment of bipolar depression and concluded that some modern antipsychotics (quetiapine and olanzapine) demonstrated efficacy in bipolar depressive patients from week one onward. A lack of details on study quality and several concerns in the review methods mean that the authors’ conclusions may not be reliable.

Authors' objectives
To assess the efficacy of atypical second-generation antipsychotics in the treatment of bipolar depression.

Searching
PubMed was searched from 1994 to 2007. Search terms were reported. Conference proceedings from American College of Neuropsychiatry, American Psychiatric Association and International Conference on Bipolar Disorder were searched from 2003 to 2007. ClinicalTrials.gov was searched. The study authors and representatives of pharmaceutical companies were contacted for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared an atypical antipsychotic (aripiprazole, asenapine, clozapine, paliperidone, quetiapine, risperidone, ziprasidone, olanzapine or amisulpride) with a placebo in adult bipolar I and/or II depressive patients were eligible for inclusion. Both monotherapy and studies in which the drug was combined with an antidepressant were eligible. The primary outcome was change in Montgomery-Asberg Depression Rating Scale (MADRS) at week eight. Secondary outcomes were rates of response (defined as the proportion of patients who achieved ≥50% improvement) and remission (defined as the proportion of patients who achieved MARDS ≤12 at an endpoint).

All included studies involved antipsychotic monotherapy; one study also used a combination therapy with an antidepressant (olanzapine-fluoxetine combination). The included studies evaluated quetiapine (dose range 300mg/day to 600mg/day), aripiprazole (dose range 5mg/day to 30mg/day) and olanzapine (dose range 5mg/day to 20mg/day). The intervention duration of all studies was eight weeks.

The authors did not state how many reviewers assessed studies for inclusion.

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

Data extraction
For continuous outcomes, means and standard deviations were extracted to enable calculation of mean differences (MDs) and 95% confidence interval (CIs). Where standard deviation of the mean was not available, standard deviation of the median was used. For dichotomous outcomes, event rates were extracted to enable calculation of odds ratios (ORs) and 95% CIs.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
The studies were combined in meta-analyses using a random-effects model. Only the monotherapy arm from the olanzapine trial was used in meta-analyses. Pooled odds ratios or weighted mean differences (WMDs), with 95% CIs, were calculated. The authors did not state which statistic was used to assess statistical heterogeneity. Sensitivity analyses
were performed by exclusion of aripiprazole studies, which failed to show positive results for the primary outcome. Separate analyses were performed for the primary outcome by week (weeks one to seven).

Results of the review
Five RCTs that detailed eight treatment comparisons were included in the review (n=2,506).

Compared with placebo, atypical antipsychotics (quetiapine, olanzapine and aripiprazole) were associated with a significant reduction in MARDRS scores at week eight (WMD -3.91, 95% CI -5.55 to -2.26; five RCTs, seven treatment comparisons). Separate analyses by week showed similar results for this outcome.

There were significant differences in response rate (OR 0.66, 95% CI 0.49 to 0.89; five RCTs) and remission rate (OR 0.67, 97% CI 0.45 to 0.98; five RCTs) between the treatment and placebo groups.

Significant heterogeneity was observed in the outcome of MARDRS score (p=0.013), response rate (p=0.018) and remission rate (p=0.001). Sensitivity analyses that excluded aripiprazole studies showed that the degree of heterogeneity was reduced for all these outcomes. Sensitivity analyses did not significantly alter the results.

Authors’ conclusions
Some modern antipsychotics (quetiapine and olanzapine) demonstrated efficacy in bipolar depressive patients from week one onward.

CRD commentary
The review’s inclusion criteria were clear. The authors searched only one database, so relevant studies may have been missed. Efforts were made to find published and unpublished studies, which minimised the possibility of publication bias. The authors did not state whether language restrictions were applied in the search, which made it difficult to assess the risk of language bias. It was unclear whether sufficient attempts were taken to minimise errors and bias in the review process. No formal validity assessment was performed. Very few details were provided for included studies and so the generalisability of findings was unclear. Statistical heterogeneity was assessed, but it was unclear which statistic was used. Appropriate methods were used to pool results. Relevant subgroup analyses were conducted. The authors did not report full details on the calculation of odds ratios, which made it difficult to interpret the direction of the treatment effect in terms of the response and remission outcomes.

A lack of details on study quality and several concerns in the review methods mean that the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that some atypical antipsychotics (quetiapine and olanzapine) may be considered as a first-line management option in acute bipolar I and/or II depression, even for poor responder subgroups (such as rapid cyclers) and those with psychotic conditions.

Research: The authors stated that further placebo-controlled studies were required to evaluate the antidepressant effect of atypical antipsychotic as monotherapy. Further adjunctive studies with mood stabilisers were required to compare the benefit-risk ratio.

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Other publications of related interest

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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.