Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis
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CRD summary
This review concluded that second-generation antidepressant monotherapy showed superior efficacy to placebo in bipolar disorder but clinical and statistical heterogeneity was high and an antidepressant class effect of second-generation antipsychotics could not be confirmed. Side effects (somnolence, sedation, akathisia, weight gain and other metabolic problems) may hamper their clinical use. These cautious conclusions are likely to be reliable.

Authors’ objectives
To compare the efficacy of second-generation antipsychotics versus placebo when used in monotherapy for treatment of bipolar depression.

Searching
MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant evidence up to December 2009. Search terms were reported. ClinicalTrials.gov and clinical trials registers of manufacturers of second-generation antipsychotics were searched. References of retrieved papers and relevant trials were examined.

Study selection
Double-blind randomised placebo-controlled trials (RCTs) that evaluated second-generation antipsychotic monotherapy in adult patients with bipolar disorder and a current depressive episode were eligible for inclusion in the review. It appears that two or more reviewers selected trials for inclusion, with decisions reached by consensus.

Trial participants were predominately middle aged, Caucasian, moderately depressed and treated in an outpatient setting. The most commonly evaluated second-generation antipsychotic was quetiapine (300mg/day or 600mg/day), followed by aripiprazole (5mg/day to 30mg/day) and olanzapine (5mg/day to 20mg/day). The primary outcome was mean change in Montgomery-Asberg Depression Rating Scale (MADRS) from baseline to eight weeks' follow-up.

Assessment of study quality
Two authors independently scored trials on the Jadad criteria (maximum score 5) based on the adequacy of randomisation, blinding and accounting for withdrawals.

Data extraction
Two authors independently extracted data on key characteristics and outcomes from the included studies. Weighted mean differences (WMDs) were calculated from means and standard deviations for continuous outcomes. Relative risks (RR) were calculated for dichotomous outcomes. Where there were significant differences between treatments, the number needed to treat (NNT) and number needed to harm (NNH) were calculated.

Methods of synthesis
Pooled weighted mean differences with associated 95% confidence intervals (CIs) were calculated using inverse variance weighting. Pooled relative risks with 95% CIs were calculated using the DerSimonian-Laird random-effects model. Heterogeneity was assessed using the Q statistic.

Results of the review
Seven placebo-controlled RCTs (4,111 patients) were included in the review. Five trials (2,615 patients) evaluated quetiapine, two evaluated aripiprazole (749 patients) and one evaluated olanzapine (747 patients). All met at least three of the Jadad criteria.

A statistically significant reduction in MADRS score at eight weeks was observed for quetiapine 600mg/day (WMD -4.64, 95% CI -5.82 to -3.46; four RCTs), quetiapine 300mg/day (WMD -4.76, 95% CI -5.75 to -3.76; five RCTs) and olanzapine (WMD -3.1, 95% CI -4.57 to -1.63; one RCT). There was no statistical heterogeneity for any of these.
outcomes. The change in MADRS score was not statistically significant for aripiprazole.

Statistically significant increases in somnolence, weight gain, fatigue, sedation, extrapyramidal symptoms and akathisia were observed for all pooled second-generation antipsychotics versus placebo; some of these pooled values incorporated significant statistical heterogeneity. A statistically significant reduction in treatment emergent mania was observed for 600mg quetiapine only.

**Authors’ conclusions**

Second-generation antipsychotics proved to have superior efficacy to placebo but clinical and statistical heterogeneity was high and an antidepressant class effect of second-generation antipsychotics could not be confirmed. Side effects (somnolence, sedation, akathisia, weight gain and other metabolic problems) may hamper their clinical use.

**CRD commentary**

This review addressed a clearly defined research question supported by appropriate inclusion criteria and searches of relevant databases and clinical trials registries. Attempts were made to minimise potential for errors and bias throughout the review process.

The authors’ conclusions acknowledged limitations related to the short length of follow-up (eight weeks) and variability in clinical and treatment characteristics and in definitions of outcome measures. Consequently, these cautious conclusions are likely to be reliable.

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

**Practice:** The authors stated that, despite side effects, second-generation antipsychotics like quetiapine and olanzapine had a place in treatment of patients with bipolar depression, for whom treatment options were somewhat limited.

**Research:** The authors stated that further research was required on the impact of depression severity at baseline, antidepressant efficacy beyond the acute phase, efficacy/effectiveness when added to a mood stabiliser and long-term follow-up of side effects.

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