Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

CRD summary
This review concluded that antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine and haloperidol should be considered as being among the best available options for treatment of manic episodes. The review was generally well conducted and the conclusions appear likely to be reliable.

Authors' objectives
To assess the comparative efficacy and acceptability of antimanic drugs in the treatment of acute mania.

Searching
MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL) and trial databases of major regulatory agencies were searched from January 1980 to November 2010 without language restrictions. Full details of the search strategy were reported in an online appendix. Trials previously identified in Cochrane reviews were included. Manufacturers and authors were contacted to identify unpublished studies.

Study selection
Randomised controlled trials (RCTs) that compared an active antimanic drug at a therapeutic dose with either placebo or another antimanic drug in adults (aged over 18) with acute mania were eligible for inclusion. Only trials of oral therapies were considered. Fixed and flexible dose designs were permitted. Combination and augmentation trials were included. Patients had a primary diagnosis of bipolar I disorder (either manic or mixed episode) according to standard diagnostic criteria. Trials were required to be double-blinded. Primary outcomes were mean change scores on the Young Mania Rating Scale (efficacy) and treatment discontinuation (acceptability) defined as any patient leaving the study early during the first three weeks of treatment.

Included studies assessed the treatments aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine and ziprasidone. Seventeen studies had a combination design in which antimanic drugs were used in addition to lithium or valproate. Mean duration of studies was 3.4 weeks. Most patients in the included studies had moderate to severe manic symptoms; these were assessed using four different rating scales.

Three reviewers independently selected the studies for inclusion. Differences were resolved through consultation with another reviewer.

Assessment of study quality
Two independent reviewers assessed study validity. They used the Cochrane risk of bias tool to evaluate the adequacy of random allocation concealment and double blinding, and other elements that might have introduced bias; studies were graded as adequate, unclear or inadequate. Studies graded as adequate or unclear were included and those graded inadequate were not. Authors were contacted in case of insufficient detail. Disagreements were resolved with reference to another reviewer.

Data extraction
Data were extracted to enable calculation of odds ratios (OR) with 95% confidence intervals (CI) for dichotomous outcomes and mean differences with 95% CI for each pairwise comparison. Data previously extracted for Cochrane reviews conducted by the authors were utilised and independently checked by three reviewers. Data from additional trials were extracted using a standardised data extraction form; it was not clear how many reviewers were involved in this stage. Risperidone was combined with paliperidone and considered as a single treatment. Acute treatment was defined as three-week treatment; where this was unavailable, data at two to six weeks were used.

Methods of synthesis
Pairwise comparisons between treatments were assessed by calculation of pooled odds ratios and standardised mean differences (SMD) with 95% CIs using a random-effects model. Heterogeneity was assessed by visual inspection of forest plots and use of I^2. A Bayesian multiple-treatments meta-analysis was conducted using a random-effects model to calculate effect sizes and 95% credible intervals (CrI). Where possible, inconsistency was assessed through calculation of differences between indirect and direct estimates. The model was fitted with and without consistency assumptions and the two were compared for fit and parsimony. Clinical and methodological variables were investigated as potential sources of heterogeneity where significant inconsistency was detected.

A sensitivity analysis that excluded combination or augmentation studies was conducted. A further sensitivity analysis was used to assess the impact of combining risperidone with paliperidone. Comparative efficacies of antimanic drugs were expressed using placebo as a reference.

**Results of the review**

Sixty-eight studies (n=16,073 participants) were included in the review; 54 of these were two-armed and 14 were three-armed. The overall quality of studies was rated as good, although around three-quarters of the studies were rated as having unclear adequacy of allocation concealment.

All treatments except gabapentin, lamotrigine and topiramate were more effective than placebo. Haloperidol showed more significant differences from comparators than any other treatment and showed superior efficacy to all other active treatments except risperidone and olanzapine. Risperidone and olanzapine showed similar efficacy profiles and both had statistically superior efficacy compared to five other treatments (valproate, ziprasidone, lamotrigine, topiramate and gabapentin).

Efficacy results compared to placebo using the mean change in score on the Young Mania Rating Scale were: haloperidol (SMD -0.56, 95% CrI -0.68 to -0.43), risperidone (SMD -0.50, 95% CrI -0.63 to -0.38) and olanzapine (SMD -0.43, 95% CrI -0.54 to -0.32); these treatments had the highest probability of being the most effective treatment.

Olanzapine, risperidone and quetiapine led to significantly fewer discontinuations than lithium, lamotrigine, placebo, topiramate and gabapentin; haloperidol was also inferior to olanzapine. Results of pairwise meta-analyses were reported.

Statistical heterogeneity was generally moderate, although there were wide confidence intervals for most comparisons. Four of the pairwise analyses showed an I^2 value above 75%, which indicated very high levels of heterogeneity. Inconsistency was low and found in only three of 33 loops for efficacy as a continuous outcome and in none of the 34 acceptability loops or the 18 binary efficacy loops. Sensitivity analyses did not significantly alter the results.

**Authors’ conclusions**

Antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine and haloperidol should be considered as being among the best available options for treatment of manic episodes.

**CRD commentary**

The review question and inclusion criteria were clear. The authors searched several relevant databases and other sources, which reduced the chances that relevant studies were omitted. It appeared that the authors used methods designed to reduce bias and error at all stages of the review process. Validity was assessed using relevant criteria and the results were used as additional inclusion criteria. The synthesis was appropriate and included evaluation and exploration of heterogeneity. The authors acknowledged some limitations in the way that drug acceptability was assessed.

The authors’ conclusions reflect the results of the review and appear likely to be reliable.

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

**Practice:** The authors stated that risperidone, olanzapine and haloperidol should be considered as being among the best
available options for treatment of manic episodes; the results of this study applied only to short-term treatment of the acute manic phase.

**Research:** The authors stated that these results should be considered in the development of clinical practice guidelines. Further studies were required to assess the efficacy and acceptability of chlorpromazine for treatment of acute mania.

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