Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy


CRD summary
The authors concluded that adjunctive antipsychotic treatment is more effective than monotherapy with mood stabilisers for patients with acute bipolar mania who are already taking a mood stabiliser. A more cautious conclusion may have been more appropriate in view of the small number of studies with high drop-out rates and short-term follow-up.

Authors' objectives
To evaluate adjunctive drug treatments for patients with acute bipolar mania.

Searching
MEDLINE, EMBASE, PsycINFO and the Cochrane CENTRAL Register were searched from inception to March 2006 using the reported search strategy. In addition, reference lists in identified studies and reviews were screened and manufacturers of relevant drugs were contacted. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. The duration of follow-up ranged from 3 to 8 weeks in the included studies.

Specific interventions included in the review
Studies that compared adjunctive drug therapy with monotherapy, or an alternative adjunctive drug with drugs currently licensed in the UK or USA for the treatment of bipolar disorder, were eligible for inclusion (eligible drugs were listed). The included studies evaluated adjunctive treatment with quetiapine, loperidol, risperidone, olanzapine and ziprasidone. Mood tabilisers included lithium, valproate semisodium and carbamazepine.

Participants included in the review
Studies that reported results separately for patients with acute bipolar mania were eligible for inclusion. Studies of mixed populations had to have randomised patients by bipolar type. In all but one of the included studies patients were diagnosed with bipolar disorder using the American Psychiatric Association's DSM-IV or DSM-III criteria. All participants were currently manic or had mixed mania. With the exception of one study, which was in adolescents, the studies were in adults. In some of the included studies patients were taking a mood stabiliser at study entry.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the outcomes. The review assessed the following outcomes: changes in mania symptom scores on the Young Mania Rating Scale (YMRS); mania response (at least 50% improvement from baseline to end point on the YMRS); withdrawal for any reason, lack of efficacy or adverse event; extrapyramidal symptoms; and weight change.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies and resolved any disagreements on inclusion through recourse to a third author.

Assessment of study quality
Validity was assessed by considering the method of randomisation, allocation concealment, blinding of the investigators and participants, completeness of follow-up, and handling of withdrawals and drop-outs. The authors did not state how the validity assessment was performed.

Data extraction
Data were extracted onto a standardised form, but the authors did not state how many reviewers performed the extraction. Data were extracted for the longest follow-up period and, where possible, on an intention-to-treat basis.

**Methods of synthesis**

How were the studies combined?

The studies were grouped by outcome and combined using meta-analysis where there were sufficient data; otherwise, the studies were combined in a narrative. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated. A random-effects model was used when significant heterogeneity was found. A pooled mean difference (MD) and 95% CI were calculated for continuous data using the inverse variance method. Some pooled data were reported as the percentage difference in event rates between treatment groups.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic (p<0.01 indicated significant heterogeneity). A subgroup analysis was performed to examine the effects of individual atypical antipsychotics.

**Results of the review**

Eight RCTs (n=1,073) were included.

One study reported allocation concealment. Withdrawal rates were high (7 to 94%). Most studies used intention-to-treat analysis and carried forward the last observation to account for missing data.

**Effects on mania.**

Adjunctive treatment with quetiapine, haloperidol, risperidone and olanzapine was associated with a significant reduction in YMRS scores compared with monotherapy.

Compared to monotherapy with a mood stabiliser, adjunctive treatment with all atypical antipsychotics combined was associated with a significant reduction in YMRS scores (MD -4.41, 95% CI: -6.07, -2.74; based on 3 studies) and a significant increase in response rates (>50% or more improvement on the YMRS) (RR 1.53, 95% CI: 1.31, 1.80; based on 4 studies).

**Withdrawals.**

Little difference was found in the number of withdrawals between adjunct and monotherapy for haloperidol, olanzapine and quetiapine. However, adjunctive risperidone was associated with significantly lower withdrawal rates (for any reason) than monotherapy. There was no significant difference in withdrawal for any reason between all adjunctive atypical antipsychotics combined and monotherapy with a mood stabiliser.

Fewer withdrawals due to lack of efficacy were found with adjunctive haloperidol, quetiapine and risperidone compared with monotherapy. Adjunctive treatment with all atypical antipsychotics combined was associated with a significant reduction in withdrawal due to lack of efficacy compared to monotherapy with a mood stabiliser (RR 0.46, 95% CI: 0.27, 0.77; based on 5 studies). Adjunctive olanzapine was associated with significantly lower withdrawal rates due to lack of efficacy than monotherapy.

Adjunctive treatment with olanzapine was associated with a significant increase in withdrawal due to adverse events compared to monotherapy with a mood stabiliser (RR 6.28, 95% CI: 1.51, 26.04; based on 1 study). No significant between-group difference was found for adjunctive treatment with haloperidol, quetiapine or risperidone compared with monotherapy.

**Weight gain.**

Weight gain was greater with adjunctive olanzapine, quetiapine and risperidone compared to monotherapy with mood stabiliser.
stabilisers. There was little difference in weight gain between adjunctive haloperidol and monotherapy.

Extrapyramidal adverse events.

Adjunctive haloperidol and ziprasidone were associated with an increase in extrapyramidal adverse events compared with lithium monotherapy. There was little difference in extrapyramidal adverse events between adjunctive quetiapine and monotherapy.

Authors' conclusions
Adjunctive antipsychotic treatment is more effective than monotherapy with mood stabilisers for patients with acute bipolar mania who are already taking a mood stabiliser.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and study design. Although inclusion criteria for the outcomes were not specifically defined, the outcomes of interest were clearly stated. Several relevant sources were searched and attempts were made to minimise language bias. It is not clear whether unpublished studies were eligible, so the potential for publication bias cannot be assessed. Methods were used to minimise reviewer error and bias in the selection of studies, but it is not clear whether similar steps were taken at the validity assessment and data extraction stages. Validity was assessed using specified criteria and the results of the assessment were reported.

The studies were pooled, where appropriate, and the effects of individual drugs examined. The authors' conclusions appear to reflect the data presented, but the findings were based on a small number of studies with high drop-out rates and short-term follow-up (8 weeks or less) and a more cautious conclusion may therefore have been more appropriate.

One of the authors is an employee of Sanofi-Aventis.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that adequately powered studies are required to compare adjunctive antipsychotic treatment with monotherapy in patients with bipolar mania who are not already receiving mood stabilisers.

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