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## Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania: a systematic review and meta-analysis

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### CRD summary

The authors concluded that, compared with mood stabilisers, second-generation antipsychotics may be preferable for initial monotherapy treatment of acute mania. Minimal quality assessment of included trials and lack of patient information mean that the applicability and reliability of the authors' conclusions are unclear.

### Authors' objectives

To evaluate the efficacy and acceptability of mood stabilisers versus second-generation antipsychotics, as monotherapy treatment for acute mania.

### Searching

EMBASE (1974 to date) and MEDLINE (1950 to date) were searched; search terms were reported. Reference lists of resulting articles were searched manually. Identification of unpublished and grey literature was attempted by electronic searches of clinical trials websites, pharmaceutical industry trial registers, and communication with trial authors. Searches were restricted to papers published in English.

### Study selection

Randomised double-blind trials that compared mood stabilisers versus second-generation antipsychotics as monotherapy drug treatment for acute mixed or manic episodes were eligible for inclusion. Drugs had to be administered for a minimum of three weeks, at clinically relevant doses and/or blood levels. Eligible outcome measures were changes in symptom severity, responder rate (50% reduction in symptom severity by endpoint, according to the scale employed) and number of drop-outs. Trials that lacked treatment outcome information or that contained treatment-resistant patients were excluded.

The included trials compared mood stabilisers versus second-generation antipsychotic monotherapy drug treatment in patients with acute mania. Some trials also included patients with mixed mania (27% to 48% of the population of these trials). Mood stabilizers investigated were lithium or valproate. Second-generation antipsychotics investigated were aripiprazole, olanzapine, quetiapine, and risperidone. Drug doses and/or blood levels were reported by all included trials. The outcome measures reported included mean changes in symptom severity rating scales from baseline to endpoint, responder rates, and numbers of drop-outs. Trial duration ranged from three to four weeks.

Full papers were screened for eligibility by two reviewers; discrepancies were resolved by their consensus.

### Assessment of study quality

Consideration of trial quality was demonstrated by inclusion criteria that specified randomised double blind study designs. The authors stated that a standardised data extraction form was used for quality assessment, but no further details were provided.

Two reviewers independently conducted quality assessment of the individual trials; any discrepancies were resolved by their consensus.

### Data extraction

Mean baseline symptom severity ratings and change by endpoint were extracted to calculate standard errors and standardised mean differences (SMDs) with 95% confidence intervals (CIs). Responder rates (proportion of participants with 50% or more reduction in symptom rating compared with baseline) and number of drop-outs per trial were extracted to calculate risk differences (RDs) with 95% confidence intervals.

Data were extracted by two independent reviewers, using a standardised data extraction form. Corrections were agreed between the two reviewers.

## Methods of synthesis

The generic inverse variance method was used to pool standardised mean differences, estimated with a 95% confidence interval. The Mantel-Haenszel method was utilised to pool risk differences for responder rates and number of drop-outs, with 95% confidence intervals. Random-effects models were used for meta-analyses (where reported). Number needed to treat was calculated for responder rates; small-sample and publication biases were assessed using funnel plots.

Heterogeneity was assessed in all main analyses using  $X^2$  and  $I^2$ . Exploratory analysis was conducted to investigate standardised mean differences representing change in symptom severity. Subanalyses included: lithium alone versus second-generation antipsychotics; valproate versus second-generation antipsychotics; olanzapine versus second-generation antipsychotics; other second-generation antipsychotics versus mood stabilisers; trials with mixed mania patients enrolled; trials without mixed mania patients enrolled.

## Results of the review

Nine trials were included in the review (1,661 patients).

A statistically significant difference, favouring second-generation antipsychotics over mood stabilisers, was found for change in symptom severity ratings (SMD -0.22, 95% CI -0.32 to -0.12;  $I^2=0%$ ; nine trials). Small-sample bias was not evident on the corresponding funnel plot (data not shown).

Statistically significant differences, favouring second-generation antipsychotics over mood stabilisers, were found for drop-out rates (RD -0.05, 95% CI -0.10 to -0.01;  $I^2=23%$ ; nine trials) and responder rates (RD -0.07, 95% CI -0.13 to -0.01;  $I^2=28%$ ; six trials). Number needed to treat for responder rates (50% reduction in patient symptom severity by endpoint) was 17 patients (95% CI 9 to 122).

In exploratory analyses, the statistically significant difference that favoured second-generation antipsychotics over mood stabilisers was maintained when analysing lithium (SMD -0.23, 95% CI -0.40 to -0.07) and valproate (SMD -0.20, 95% CI -0.36 to -0.05) separately. Statistically significant differences were also maintained with subanalyses for trials that investigated olanzapine versus mood stabilisers (SMD -0.24, 95% CI -0.38 to -0.10) and for trials that enrolled mixed mania patients (SMD -0.25, 95% CI -0.38 to -0.13). Similar trends were shown with the other subanalyses, but they were not statistically significant. No substantial heterogeneity was indicated in any of the subanalyses.

## Authors' conclusions

As monotherapy treatment for acute mania, second-generation antipsychotics demonstrated statistically significant advantages over mood stabilisers for efficacy and acceptability. Second-generation antipsychotics may be considered preferable when selecting initial monotherapy treatment for acute mania.

## CRD commentary

The review question and inclusion criteria were clear. The search included attempts to locate unpublished data and grey literature, so the risk of publication bias was reduced. Language bias may have been present due to the English language restriction imposed during the searches. Screening, quality assessment and data extraction were all performed by more than one reviewer, which reduced the risk of reviewer bias and error.

Minimal quality assessment details (randomised double-blind study designs) were provided; these results were not incorporated into the statistical analyses. There was a lack of patient characteristic information (such as age, gender, medical history) reported; this meant that the comparability of the populations and qualities of individual trials for meta-analysis was ambiguous and generalisation was difficult. However, statistical analyses appeared to have been appropriate for the data presented and did not indicate substantial heterogeneity.

Minimal quality assessment and lack of patient characteristic information mean that the generalisability and reliability of the authors' conclusion is unclear.

## Implications of the review for practice and research

**Practice:** The authors stated that second-generation antipsychotics might be preferable to mood stabilisers as the first-

line monotherapy treatment for acute mania, unless patients had previously demonstrated intolerance to second-generation antipsychotics.

**Research:** The authors stated that further research was required to compare the effectiveness of second-generation antipsychotic monotherapy versus combined mood stabiliser/second-generation antipsychotic treatment of acute mania.

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