Quetiapine for acute mania in bipolar disorder

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Authors’ objectives
To evaluate the safety and efficacy of quetiapine as a treatment for acute mania in bipolar disorder.

Searching
MEDLINE, Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, Cochrane Controlled Trials Registry and International Pharmaceutical Abstracts databases were searched to 2006. Search terms were reported. Manufacturers' websites were searched for unpublished and ongoing trials.

Study selection
Randomised double-blind placebo-controlled trials (RCTs) of quetiapine for the treatment of acute mania were eligible for inclusion.

The included studies evaluated quetiapine as monotherapy (400 mg/day to 800 mg/day). Some studies compared quetiapine with another pharmacological agent, such as lithium (serum concentration 0.6 meq/L to 1.4 meq/L) and haloperidol (4 mg/day to 8 mg/day), or placebo. Other studies compared quetiapine as adjunct therapy (50 mg/day to 800 mg/day) augmenting lithium (serum concentration 0.7 to 1.0 meq/L) or divalproex (serum concentration 50 µg/ml to 100 µg/ml or 80 mg/dL to 130 mg/dL) compared to placebo augmenting lithium and divalproex. The duration of monotherapy studies was 12 weeks. Adjunct therapy study duration ranged from three weeks to six weeks. The primary outcome was the change in Young Mania Rating Scale (YMRS) scores from baseline to day 21. Scores from this scale range from 0 to 60 (higher scores indicating more severe symptomatology). Other outcomes included changes in total Young Mania Rating Scale scores from baseline to end of trial, Young Mania Rating Scale response and Young Mania Rating Scale remission. Remission was defined as a total Young Mania Rating Scale score of 12 or less. Other scales used in the included studies to assess effectiveness included Clinical Global Impression-Bipolar Severity of Illness Scale, Montgomery-Asberg Depression Rating Scale (MADRS), Positive and Negative Symptom Scale (PANSS) and subscales, and Global Assessment Scale. Most studies did not report detailed participant characteristics. One study included hospitalised adolescents with ages ranging from 12 to 18 years; other studies did not report age of participants.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

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

Data extraction
The authors stated neither how data were extracted nor how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a narrative synthesis. Each study was described in the text and additional descriptive information was presented in tables.

Results of the review
Five RCTs (n=1,034) were included in the review.

Quetiapine as monotherapy: There was evidence of comparable efficacy for quetiapine and lithium compared to placebo for change in Young Mania Rating Scale points, response and remission rates at days 21 and 84 (one RCT, n=302). However, lithium concentrations may have been suboptimal.

Participants (one RCT, n=302) receiving haloperidol showed a greater improvement at day 21 for the Young Mania Rating Scale total scores (minus 15.71 points) compared to those receiving quetiapine (minus 12.29 points) or placebo (minus 8.32 points). However, efficacy at day 84 was similar for haloperidol and quetiapine. There were no significant
differences between quetiapine or haloperidol and placebo groups for remission rates at day 21. However, remission rates were better at day 84 for patients receiving haloperidol (63.3 per cent) and quetiapine (61.4 per cent) compared to placebo (38 per cent, p<0.001 for both comparisons).

Quetiapine as adjunctive therapy: One RCT (n=191) found a greater reduction in Young Mania Rating Scale scores at 21 days for patients receiving quetiapine (minus 13.76 points) than placebo (minus 9.93 points) as adjunct therapy to lithium or divalproex for adults with acute mania. However, there were no significant differences between groups for remission rates. A second RCT (n=209) found no significant differences at 21 days between groups receiving quetiapine or placebo as adjunct therapy to lithium or divalproex for change in Young Mania Rating Scale scores.

Quetiapine was found to be more effective than placebo as an adjunct to divalproex for the treatment of adolescents with mania (one RCT, n=30, Young Mania Rating Scale scores: minus 23 for quetiapine; minus 15 for placebo).

Adverse effects: The most common adverse effects experienced by participants receiving quetiapine were somnolence (34 per cent as monotherapy, 66 per cent as adjunct therapy) and dry mouth (33 per cent as monotherapy and 38 per cent as adjunct therapy). Higher rates of asthenia were reported for participants taking quetiapine as adjunct therapy (19 per cent) compared to placebo (eight per cent). Weight increases of seven per cent or more were found in 21 per cent to 39 per cent of patients receiving quetiapine as monotherapy compared to 9.5 per cent to 14 per cent of participants taking placebo. A similar weight gain was found for participants taking quetiapine as adjunct therapy (21 per cent) compared to participants taking placebo (7 per cent).

Authors' conclusions
Although the results demonstrated evidence of efficacy for treatment of quetiapine for acute mania the robustness of the evidence was questionable.

CRD commentary
The inclusion criteria were clear for intervention, study design and outcomes, but were not explicitly defined in terms of participants. Several relevant sources were searched and some attempts were made to locate unpublished studies, thus limiting the possibility of publication bias. It was not clear whether any language limitations had been applied and so the potential for language bias could not be assessed. Methods used to select studies and extract data were not described and so it was not known whether efforts were made to reduce reviewer errors and bias. Only RCTs were included, but their quality was not assessed further and so results from these studies and any synthesis may not be reliable. Some characteristics of the included studies were presented in tables, but details of participants were not reported either in the text or the tables, therefore, it was not possible to assess the generalisability of the results. A narrative synthesis was appropriate given the differences between studies. Although the main outcome was a reduction in Young Mania Rating Scale scores, the ages of participants were not reported for all the studies, however, results appeared to be reported for both adults and adolescents. The authors appropriately discussed the limitations of the included studies and reported discrepancies between published data and web-based data. The authors' cautious conclusion was an accurate reflection of the results of the review, but it should be borne in mind that the review was based on a small number of studies.

Implications of the review for practice and research
Practice: The authors stated that using quetiapine as a first-line therapy for the treatment of acute mania was not recommended due to a lack of evidence and the cost considerations. However, quetiapine may be used as second-line therapy when sensitivity to extrapyramidal symptoms limits other treatment options.

Research: The authors stated that further research was needed to evaluate the efficacy of quetiapine for treatment of mixed mania and as a long-term maintenance treatment for bipolar disorder.

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Bibliographic details
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The review concluded that there was evidence of efficacy for treatment of quetiapine for acute mania in bipolar disorder, but that the robustness of the evidence was questionable. The authors' conclusions were an accurate reflection of the results of the review, but it should be borne in mind that the review was based on a small number of studies.

**MeSH**
Acute Disease; Antimanic Agents /adverse effects /therapeutic use; Antipsychotic Agents /adverse effects /therapeutic use; Bipolar Disorder /drug therapy; Dibenzothiazepines /adverse effects /therapeutic use; Drug Interactions; Drug Therapy, Combination; Haloperidol /therapeutic use; Humans; Lithium Compounds /therapeutic use; Quetiapine Fumarate; Valproic Acid /therapeutic use

**Record Status**
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.