Treatment of psychotic symptoms in bipolar disorder with aripiprazole monotherapy: a meta-analysis

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CRD summary
The authors concluded that aripiprazole was useful for the treatment of psychotic symptoms during the acute manic/mixed and maintenance phases of bipolar illness. Given the high drop-out rates from trials, uncertainty over the quality of the included trials and potential for bias in the review, the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To assess the effectiveness of aripiprazole in the treatment of psychotic symptoms in patients with bipolar disorder.

Searching
MEDLINE was searched for relevant articles. Search terms were reported. Various other Internet sources were also searched, including Google, the Bristol-Myers Squibb website of clinical trials, ClinicalTrials.gov, ClinicalStudyResults.org, and Cochrane.org. Reference lists of relevant articles were manually searched.

Study selection
Randomised controlled trials (RCTs) that compared the efficacy of aripiprazole versus an active comparator or placebo in the treatment of psychotic symptoms in patients with bipolar disorder were eligible for inclusion.

Included trials were mainly of patients with moderate to severe manic episodes, with some patients also experiencing psychotic symptoms. Trials compared aripiprazole, using fixed or flexible treatment dosage, versus an active comparator (lithium and haloperidol) and/or placebo for the treatment of patients with acute mania/mixed episodes or acute bipolar depression. Trial durations ranged from three to 26 weeks. Patients in the maintenance phase (treated for an additional 26 weeks) were also assessed, with some patients receiving concomitant medication in the form of anticholinergics or lorazepam. Psychotic symptoms were measured using the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS). Side effects of treatments were also reported.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The authors did not state that they formally assessed study validity, but drop-out rates were reported.

Data extraction
One reviewer extracted or calculated mean changes and standard deviations for intervention and comparator groups to calculate effect sizes (Cohen’s d) and their 95% confidence intervals (CIs), corrected for sampling and measurement errors using the Hunter-Schmidt method.

Methods of synthesis
Mean changes and standard deviations were pooled using a fixed-effect model, or a random effects model where statistical heterogeneity was present. Statistical heterogeneity was assessed using the Cochran Q test and I² statistic.

Subgroup analyses were performed for each treatment group (aripiprazole, active comparator, and placebo) and for treatment comparisons (aripiprazole versus placebo, comparator versus placebo). RCTs reporting PANSS data were analysed separately; subgroup analyses were performed for PANSS subscales (PANSS-positive, PANSS-negative, PANSS-cognitive, and PANSS–hostility).

Results of the review
Seven RCTs were included in the review.
Acute mania/mixed episodes (six RCTs assessed aripiprazole): The authors stated that results were not available for one trial, which was halted prematurely 'because it was expected to produce negative results'. Four RCTs (n=1,640 participants) that assessed Positive and Negative Syndrome Scale (PANSS) scores were included in the meta-analyses. Drop-out rates at three weeks were 36.22% for aripiprazole, 43.62% for placebo, and 42.83% for the active comparator. At 12 weeks, drop-out rates were 56.81% for aripiprazole, and 62.87% for the comparator. The effect size for total PANSS scores comparing aripiprazole versus placebo was 0.14 (95% CI 0.03 to 0.25); this was corrected using Hunter-Schmidt method (d=0.18; 95% CI 0.176 to 0.184). There was a discrepancy in the figure reported in the text and the tables; the figures used in this abstract were reported in the tables. There was no evidence of statistical heterogeneity.

Maintenance phase (one RCT; n=161 patients who were stabilised on aripiprazole then randomised to aripiprazole or placebo): This RCT showed that the time to relapse was statistically significantly longer in patients receiving aripiprazole (p=0.02) compared with the placebo group. At 26 weeks, patients receiving aripiprazole showed statistically significant greater changes compared to placebo in the PANSS cognitive subscale score (d=0.38) and the PANSS hostility subscale score (d=0.71), but not for overall PANSS score (d=0.28). A similar trend was shown at 100 weeks follow-up. Adverse events occurring at a rate of 5% or more in aripiprazole groups during the maintenance phase were tremor (9.1%), akathisia (6.5%), vaginitis (6.4%), and pain extremity (5.2%).

There was no evidence on the depressive phase of bipolar illness.

Authors' conclusions
Aripiprazole was useful for the treatment of psychotic symptoms during the acute manic/mixed and maintenance phases of bipolar illness.

CRD commentary
The review question and supporting inclusion criteria were clearly defined. The search used one database and several other websites, which included a search for ongoing trials. It was unclear whether there were any language restrictions, so it was unclear whether there was a possibility for language bias. The authors did not undertake data extraction in duplicate, and did not state the process for study selection, which meant that reviewer error and bias was possible.

The authors did not formally assess the quality of the included trials, but the drop-out rates reported were high. Where possible, data were pooled and there was no evidence of statistical heterogeneity. However, data on patient characteristics and treatment regimens were lacking and it was unclear whether clinical or methodological heterogeneity may have been present. Some of the evidence was based on a small number of trials and the follow-up was only three months for acute mania/mixed episodes. The authors acknowledged the potential for bias due to trial sponsorship by the pharmaceutical industry, which may potentially lead to lack of reporting of negative trials, and highlighted that maintenance was only assessed in patients who responded to aripiprazole.

Given the high drop-out rates, uncertainty over the quality of the included trials and potential for bias in the review, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that the fixed dosage RCT showed negative findings, suggesting that aripiprazole should be prescribed at on an individual basis. They also stated that the generalisability of the findings may be limited.

Research: The authors did not state any implications for research.

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Not stated.

Bibliographic details

PubMedID
Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

MeSH
Antipsychotic Agents; Bipolar Disorder; Humans; Piperazines; Quinolones

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.