Centre for Reviews and Dissemination

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Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials

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CRD summary

The review found that most commonly used anti-manic treatments were at least moderately effective in reducing symptoms. There was no clear evidence that any one agent or drug class was superior. These conclusions require cautious interpretation due to a lack of formal quality assessment of the primary trials and variation between the trials.

Authors' objectives

To evaluate the efficacy of drugs for treating acute mania.

Searching

PubMed, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Current Controlled Trials and EMBASE were searched to January 2010. Search terms were reported. Proceedings of meetings of the American and European Colleges of Neuro-psychopharmacology, American Psychiatric Association, American College of Psychiatry and International Conference on Bipolar Disorder were searched (1990 onward). References from all sources were checked. Researchers in the field and relevant pharmaceutical companies were consulted.

Study selection

Randomised controlled trials (RCTs) that compared a single drug versus placebo or a standard comparator for treatment of acute mania or mixed manic depressive states of adult bipolar I disorder were eligible for inclusion. Participants were required to be diagnosed using established diagnostic criteria (specified in the review). The primary outcome was change in manic symptoms measured at baseline and during treatment using specific rating scales (named in the review). The secondary outcome was response rate. Studies that used psychotropic agents other than moderate doses of benzodiazepines or chloral hydrate were excluded. Placebo-controlled trials were required to be double-blinded. Unblinded head-to-head trials were eligible for inclusion in secondary analyses.

Most participants in the included studies had acute mania and nearly 30% overall had psychotic symptoms at study entry. More than 25% of participants were considered to be in a mixed manic depressive state. About half of the participants in the included studies were men. Participants had a mean age of 39 years. Interventions included a first-generation antipsychotic (haloperidol), eight different second-generation antipsychotics, tamoxifen, two mood-stabilising anticonvulsants and lithium. Interventions were compared with each other or with placebo. Most studies defined response as a reduction in mania score of at least 50%. Most studies were sponsored by drug manufacturers. Most studies had multiple sites (mean=30). Study duration was usually three weeks.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality

The authors did not state that they assessed validity. Some aspects of quality (such as blinding and use of validated measures) formed part of the review inclusion criteria. Drop-out rates were reported.

Data extraction

Mean change scores from baseline and 95% confidence intervals (CIs) were extracted or calculated for each group for continuous outcomes. Risk ratios (RRs) with 95% confidence intervals (CIs), absolute differences in response rate and numbers need to treat (NNT) were calculated for dichotomous outcomes. Where necessary, standard deviations were estimated using established methods.

Two reviewers extracted data. Disagreements were resolved by consensus. Primary researchers and pharmaceutical companies were contacted for more information where required.

Methods of synthesis

Studies were combined to calculate standardised mean differences in change scores (SMDs, Hedge's adjusted g) and pooled risk ratios, with 95% conffidence intervals, using random-effects models. Heterogeneity was assessed with X^2 and I^2.

Subgroup analyses were conducted by drug class. Meta-regression was conducted to investigate the impact of the number of study sites, sample size and baseline symptom severity in studies that reported positive effects for the intervention.

Publication bias was assessed using a funnel plot, calculation of a fail-safe statistic and a trim-and-fill approach.

Results of the review
It appeared that the review included 51 RCTs. Drop-out rates ranged from 11% to 83%. Double-blinding was used in 94% of head-to-head comparisons.

Drug versus placebo (35 RCTs, 56 comparisons, 10,800 participants):

Thirteen of 17 drugs tested reduced symptoms significantly more than placebo (SMD 0.42, 95% CI 0.36 to 0.48; 48 RCTs) with significant heterogeneity (I^2=70%, p<0.0001). Aripiprazole, asenapine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, valproate and ziprasidone had effect sizes that ranged from 0.26 to 0.46. Larger effect sizes (0.51 to 2.32) were found for carbamazepine, cariprazine, risperidone and tamoxifen, although data were limited.

For effective drugs, the overall responder rate was significantly higher in the intervention group (RR 1.52, 95% CI 1.42 to 1.62, response rate 17%, NNT=6; 46 RCTs). Licarbazepine, verapamil, lamotrigine (each with one RCT) and topiramate (four RCTs) did not reduce symptoms significantly more than placebo. There was no evidence of significant publication bias.

Head-to-head comparisons (27 RCTs, 33 comparisons, 6,710 participants):

Second-generation antipsychotics reduced symptoms significantly more than mood stabilisers (SMD 0.17, 95% CI 0.07 to 0.28; eight RCTs) and all antipsychotics (SMD 0.18, 95% CI 0.08 to 0.28; 10 RCTs), but did not differ significantly from haloperidol alone. Valproate and lithium did not differ significantly (four RCTs).

In meta-regression, smaller treatment effects were associated with higher number of study sites and larger samples. Higher baseline severity of mania symptoms was associated with greater response to the intervention.

Authors' conclusions
Most commonly used anti-manic treatments were at least moderately effective in reducing symptoms. There was no clear evidence that any one agent or drug class was superior.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies. It was unclear whether the search was restricted by language. Steps were taken to minimise risks of reviewer bias and error by having more than one reviewer extract data; the process used for study selection was not described. Blinding and drop-out rates were reported; it was unclear whether other aspects of study quality (such as allocation concealment) were formally assessed.

Appropriate methods were used to combine data, assess statistical heterogeneity and publication bias, and explore differences between the trials. Results from heterogeneity tests in individual drug-placebo comparisons were not presented. There was significant heterogeneity for the primary analysis and it was unclear how much this was explained by variables explored in subgroup analysis, as heterogeneity in subgroups was not reported. The authors noted that sample numbers for some comparisons were small, duration of treatment was generally inadequate and the included trials only evaluated the effect of short-term treatment.

The authors' conclusions require cautious interpretation due to a lack of formal quality assessment and heterogeneity between the studies.

Implications of the review for practice and research
Practice: The authors stated that there was limited evidence that antipsychotic agents (second-generation antipsychotics and haloperidol) may be more effective or act more rapidly than mood stabilisers (such as carbamazepine, lithium, valproate). They noted the need to consider side-effects and the possibility that the most effective anti-manic agents may not be the best to prevent a switch into depression.

Research: The authors stated that there was a need to develop more effective anti-manic drugs with improved long-term and short-term tolerability. Further studies were needed to compare existing drugs head-to-head. Future studies should ensure adequate duration of follow-up.

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