Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis
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Authors' objectives
To determine the efficacy of lithium versus valproic acid and carbamazepine as a pharmacologic treatment of manic-depressive illness.

Searching
The authors searched the MEDLINE database (dates of search and keywords used were not reported). The authors also made an informal search through Index Medicus. References from published studies were checked for additional relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with double-blind evaluation of treatment outcome where the dose of lithium was within an acceptable therapeutic range of 0.4 to 1.5 mmol/l. Study duration ranged from 7-21 days to 12 months.

Specific interventions included in the review
Lithium (dosages ranging from 0.6 to 1.5 mmol/l), carbamazepine (various doses ranging from 38-51 micrograms/ml) and valproic acid (various doses ranging from 37 to 126 micrograms/ml or 1041 micromol/l) or placebo.

Participants included in the review
Patients with manic-depressive illness, as diagnosed by diagnostic criteria for manic disorder or American Psychiatric Association criteria for bipolar disorder (DSM-III) or acute manic episodes and/or bipolar disorder (DSM-III-R). In some of the studies, participants were excluded if they had positive results on toxicology screening tests, significant or acute systemic medical problems, abnormal EEG, liver function or haematological findings, focal neurological abnormalities, evidence or history of seizure disorder, previously received >250 mg valproate, evidence of any progressive neurological disorder, or contraindications to lithium or carbamazepine.

Outcomes assessed in the review
The outcome measures (good/poor) were ratings of global evaluation as indicated by the assessment measures (e.g. use of ratings scales and behavioural observations).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

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

Data extraction
The authors do not state who, or how many of the reviewers, performed the data extraction. Data was extracted for the categories of study identification, number of participants, inclusion criteria, exclusion criteria, drop-outs or premature termination and serum level of intervention or control. Authors were contacted for further details on studies where necessary.
Methods of synthesis
How were the studies combined?
Data was combined using the Mantel-Haenszel odds ratio (OR) with 95% confidence intervals (CIs).

How were differences between studies investigated?
The chi-square test, the Breslow-Day test and the Zelen's exact test were used to test for homogeneity.

Results of the review
Seven RCTs were included with 391 participants.

The combined OR for lithium versus other treatments (5 studies) was 1.14 (95% CI: 0.68, 1.91) which was not statistically significant.

For the 5 studies of lithium versus other treatments, the chi-square test was not statistically significant; the Breslow-Day statistic was 7.07, p = 0.13, df = 4; and the Zelen statistic was 0.004, p = 0.14.

One study reported on valproic acid versus placebo with an OR = 0.16 (95% CI: 0.04, 0.60).

Four studies reported on adverse events which included vomiting (lithium 25%, valproic acid 14%, and placebo 4%, p-value less than or equal to 0.05), fever (lithium 14%, valproic acid 1%, and placebo 4%, p-value less than or equal to 0.05), pain (lithium 3%, valproic acid 19%, and placebo 20%, p-value less than or equal to 0.05), twitching (lithium 8%, valproic acid 3%, and placebo 0%, p-value less than or equal to 0.05), weight gain in 27% of the lithium patients (p-value not statistically significant), hepatotoxicity in 7% of the carbamazepine patients, non-compliance/toxicity in 26% of the lithium patients, sedation or fatigue (2 groups reporting 20% for valproic acid versus 4.3% placebo and 10% for valproic acid versus 0% for placebo, (p-value not statistically significant)).

Authors' conclusions
This meta-analysis indicates that valproic acid and carbamazepine are as effective as lithium in the acute pharmacological management of manic-depressive illness.

CRD commentary
The authors have clearly stated their research question and their inclusion and exclusion criteria. The literature search is limited in its use of keywords and may have missed studies published outside the United States by focusing the search on only the MEDLINE database. The authors do not report whether there were any language restrictions on their search or whether they sought unpublished data. The data extraction is reported in tables and text and the statistical analysis was appropriate. The quality of the included studies was not assessed and the authors have not reported how the articles were selected, or how many of the reviewers were involved in the data extraction.

The authors conducted several tests for homogeneity and have acknowledged several drawbacks about the quality and design of the included studies. Their conclusions appear to follow from the results.

Implications of the review for practice and research
Practice: The authors state that the choice of the appropriate drug therapy requires an important understanding of each patient's drug tolerance and social quality-of-life aspects, as well as long-term drug effects.

Research: The authors state that further well-controlled clinical studies are needed to clarify and confirm the therapeutic benefit of carbamazepine and valproic acid in comparison with lithium in the manic depressive patient population.

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