Antiepileptic drugs for the acute and maintenance treatment of bipolar disorder
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Authors' objectives
To assess the efficacy of traditional and newer anti-epileptic drugs in the acute and maintenance treatment of bipolar disorder.

Searching
MEDLINE, PubMed, and PsycLIT were searched for studies reported in the English language. The keywords used were 'phenobarbital', 'primidone', 'phenytoin', 'valproate', 'carbamazepine', 'oxcarbazepine', 'lamotrigine', 'gabapentin', 'topiramate' and 'tiagabine' in combination with 'clinical trials', 'bipolar disorder' and 'mania'. The reference lists of the identified studies were also examined.

Study selection
Study designs of evaluations included in the review
Controlled trials, outcome reports, case series and anecdotal observations were eligible. Parallel-group and crossover non-randomised and randomised controlled trials (RCTs), double-blind non-randomised and RCTs, open-label studies, and reviews were included. The duration of the included studies ranged from 1 week to 14 years.

Specific interventions included in the review
Traditional and newer drugs anti-epileptic drugs were eligible. The following drugs were included in the review: phenobarbital, primidone, phenytoin, valproate, carbamazepine, oxcarbazepine, lamotrigine, gabapentin, topiramate and tiagabine. The control treatments included the above anti-epileptics plus placebo, lithium, haloperidol, antipsychotic agents or olanzapine. The cointervention drug therapies included lithium and antipsychotic agents. The anti-epileptics were used as monotherapy and as add-on therapy.

Participants included in the review
Patients in the acute and maintenance stages of bipolar disorders were eligible. Patients with the following characteristics were included: psychosis (bipolar, mania or schizoaffective disorder); acute mania and unresponsive to lithium; schizophrenic features; refractory bipolar disorder; depressive bipolar disorder; and unipolar depression. In- and out-patients were included.

Outcomes assessed in the review
Efficacy outcomes were eligible. The outcomes assessed in the primary studies were: response; Young Mania Rating Scale (YMRS); mean phase interval; Schedule for Affective Disorders and Schizophrenia (SADS), change version (SADS-C) and SADS Mania Rating Scale (SADS-MR); relapse index (number of relapses divided by the total months of treatment); drop-outs; time to relapse; the percentage of time ill with mania or depression; Mania Rating Scale; no relapse; Bech-Rafaelsen Mania Assessment Scale; Clinical Global Impression; and the Hamilton Depression Rating Scale.

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

Assessment of study quality
The validity of the primary studies was not formally assessed, though comment was made upon aspects of validity such as the sample size, study design, cointerventions, and differences in cointerventions between the treatment groups.

Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information were tabulated in the review: author, participants, sample size, study design, interventions compared, duration of study, and outcomes.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to the intervention drug and a narrative synthesis was undertaken. In addition, a summary table showed the number and type of studies providing supporting evidence on the efficacy of anti-epileptic agents in the acute and maintenance treatment of bipolar disorder.

How were differences between studies investigated?
Differences between the studies were discussed in the text of the review, particularly in relation to methodological flaws.

**Results of the review**

At least 41 studies (at least 1,987 patients) were included in the review, including 18 double-blind RCTs.

Phenobarbital, primidone and phenytoin.

Evidence for these classic anti-epileptic drugs in the treatment of acute mania was weak. No double-blind studies supported the efficacy of barbiturates, and the one single-blind trial that compared phenytoin plus haloperidol with placebo plus haloperidol was limited by the small sample size.

Valproate (10 controlled trials in 838 patients were presented).

One of the RCTs (n=30) found that valproate versus carbamazepine increased the proportion of patients that achieved a 50% or greater reduction on the YMRS (p=0.023). The other RCT (n=30) showed similar reductions in the YMRS when valproate was compared with haloperidol. Non-randomised comparisons of valproate versus placebo (7 comparisons) showed better response rates with valproate. The findings from 3 non-randomised comparisons of valproate versus lithium were inconsistent.

Two double-blind, placebo-controlled parallel-group trials (212 patients) of valproate showed that valproate was significantly better (assessed using YMRS and SADS-MR) than placebo in the treatment of acute mania.

The efficacy of valproate in the maintenance treatment of bipolar disorder was supported by two trials: one double-blind crossover trial involving 12 patients reported an average mean phase interval of 10 months before valproate versus 60 months on valproate; one double-blind, placebo-controlled parallel-group trial involving 372 patients reported a trend for longer duration of prophylaxis with valproate, compared with lithium (p<0.07).

Carbamazepine and oxcarbazepine (7 double-blind RCTs of maintenance treatment in 346 patients). There was limited evidence on the use of carbamazepine in maintenance treatment. The interpretation of the results was hindered by methodological flaws. These included: small and heterogeneous samples; concomitant use of other medications during manic or depressive episodes; differences between the groups in the type of rescue medication; high drop-out rates; insufficient medication; sudden switch from one medication to another; selection bias; and loss of patients’ blinding to treatment. The treatment was started during remission and/or during an episode of illness. One double-blind RCT (22 patients) compared carbamazepine with placebo and found no significant difference for carbamazepine versus placebo at 1 year: carbamazepine was effective in 60%, compared with 22% for placebo (p<0.10). Five double-blind RCTs (324 patients) compared carbamazepine and lithium. None of the RCTs appeared to show any consistent significant difference between carbamazepine and lithium.

Lamotrigine (5 double-blind RCTs in 490 patients). Two studies lacked a placebo control group, while another study had low YMRS scores at the beginning of each treatment phase. All three of the placebo-controlled studies reported
greater improvement on lamotrigine than on placebo. Three double-blind RCTs compared lamotrigine with placebo. The duration of these RCTs ranged from 6 weeks to 6 months. Two RCTs appeared to find that lamotrigine was significantly better than placebo but p-values for comparisons between the treatments were not reported consistently.

Two double-blind RCTs compared lamotrigine with lithium for 4 weeks. There appeared to be no significant difference between lamotrigine and lithium.

Gabapentin, topiramate and tiagabine.

There was limited information on the clinical usefulness of gabapentin, topiramate and tiagabine. Gabapentin (9 open-label prospective studies in 306 patients): the study results were confounded by concurrent administration of other agents, heterogeneous patient populations, widely varying drug doses, open trials and small sample sizes. Topiramate (5 studies in 145 patients, including 3 open-label add-on studies, 1 open-label monotherapy study and 1 chart review of add-on therapy): no controlled studies were identified. Tiagabine (3 very small open-label add-on studies in 13 patients): one study reported a case of generalised tonic-clonic seizure in a patient with no history of epilepsy, and one case of severe nausea and vomiting. The evidence was limited.

Authors’ conclusions
Despite considerable interest in these drugs, data are still limited. A comparison of clinical responses to the various mood stabilisers, and the determination of their mechanism of action, could help to improve the treatment of bipolar disorder.

CRD commentary
The aims of the review were stated. The inclusion criteria were defined precisely in terms of the intervention, and broadly in terms of the study design, participants and outcomes. In particular, the criteria for the diagnosis of bipolar disorder and for the outcome of relapse were not defined a priori, and the actual definitions used in the primary studies were not described. The lack of clarity in the results resulted from an absence of strict inclusion criteria for the study design. Three relevant databases were searched, but the dates searched were not reported and the methods used to select the studies were not described. The omission of an attempt to locate unpublished material raises the possibility of publication bias.

Validity was not assessed systematically, and it is uncertain whether the crossover studies were analysed appropriately. Methodological flaws in some of the primary studies were mentioned in the text of the review. Relevant data were extracted and details of some, but not all, of the included studies were presented in tabular format. The methods used to extract the data were not described. A narrative synthesis was appropriate given the small number of studies per intervention drug and the heterogeneity of study design. It was unclear how many of the studies met the inclusion criteria or contributed to the results on which the conclusions were based. Many of the included studies were methodologically flawed and used study designs that were open to bias. Conclusions based on such inadequate evidence should be interpreted with caution.

The evidence presented does not support the author's conclusions.

Implications of the review for practice and research
Practice: The author states that valproate is superior to placebo and similar to lithium, haloperidol and carbamazepine in the treatment of acute mania, and is effective in the maintenance of bipolar illness. In addition, carbamazepine is better than placebo and similar in efficacy to lithium and antipsychotics. The author further states that tiagabine may cause potentially dangerous side-effects when the dosage is increased quickly, and is probably not indicated in the treatment of acute mania when rapid onset of action is desirable.

Research: The author states that further research is required into lamotrigine (either as an adjunct or alternative medication), gabapentin, topiramate and tiagabine. The author advises that the use of crossover designs and sophisticated statistical techniques may circumvent some of the difficulties of research into bipolar disorder. There is also a need to elucidate the cellular and molecular mechanisms underlying the action of mood stabilisers.
Bibliographic details

PubMedID
11553525

Indexing Status
Subject indexing assigned by NLM

MeSH
Acetates /therapeutic use; Amines; Anticonvulsants /therapeutic use; Bipolar Disorder /drug therapy; Carbamazepine /analogs & derivatives /therapeutic use; Cyclohexanecarboxylic Acids; Fructose /analogs & derivatives /therapeutic use; Humans; Nipecotic Acids /therapeutic use; Triazines /therapeutic use; Valproic Acid /therapeutic use; gamma-Aminobutyric Acid

AccessionNumber
12001004673

Date bibliographic record published
28/02/2003

Date abstract record published
28/02/2003

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.