Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis
Smith LA, Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, Bowden CL

CRD summary
The authors concluded that valproate was effective for reducing depressive symptoms in acute bipolar depression and was well-tolerated. The authors’ conclusions appeared to reflect the evidence, but the small number of patients in the few relatively short-term included trials should be taken into account when interpreting these conclusions.

Authors' objectives
To evaluate the efficacy and tolerability of valproate for the treatment of acute bipolar depression.

Searching
MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and PsycINFO were searched from inception to October 2008 for studies in any language. ClinicalTrials.gov was searched. Reference lists were screened. Experts were contacted for information about unpublished studies. Studies reported as abstracts or conference posters were only included if they reported adequate information.

Study selection
Randomised controlled trials (RCTs) that compared valproate semisodium with placebo in patients with an acute bipolar depressive or mixed episode were eligible for inclusion.

The primary review outcomes were changes in depression symptoms using a validated scale and response to treatment (defined as a 50% or greater improvement in depressive symptoms). Secondary outcomes included switch to mania, anxiety, withdrawals, lack of efficacy, adverse events, and 10 pre-specified adverse events.

Included trials evaluated different dosing regimens of valproate; initial doses started from 250mg daily with doses increased to achieve mean serum levels ranging from 61.5 to 83mcg/mL. Half of the included trials used an extended release form of valproate.

Patients were moderately to severely depressed (Diagnostic and Statistical Manual of mental disorders DSM-IV criteria for bipolar disorder I or II with and without rapid cycling). The mean age of participants ranged from 35 to 41 years; the percentage of males ranged from 38 to 89%. Trials used different scales to assess depressive symptoms (details were reported).

The authors did not state how papers were selected for the review.

Assessment of study quality
Trial validity was assessed using: randomisation method, allocation concealment; blinding of patients and investigators; and use of intention-to-treat analysis.

Information on trial methods was extracted by one reviewer and checked by second reviewer. Disagreements were resolved by consensus.

Data extraction
Means and standard deviations of changes from baseline or final scores were extracted for depression rating scales and used to calculate risk ratios (RRs), odds ratios (ORs), standardised mean differences (SMDs) and their 95% confidence intervals (CIs). Where possible, data were extracted on an intention-to-treat basis (with patients lost to follow-up for any reason classed as treatment failures). Authors were contacted if additional information was required.

Data were extracted onto a standardised form by one reviewer and checked by second reviewer. Disagreements were
resolved by consensus.

Methods of synthesis
Pooled risk ratios with 95% confidence intervals were calculated for dichotomous data; standardised mean differences with 95% confidence intervals were calculated for continuous data. The DerSimonian and Laird random-effects model was used.

Heterogeneity was quantified using the $I^2$ statistic. The number needed-to-treat (NNT) was also calculated.

For rare outcomes, a Peto odds ratio was calculated.

Results of the review
Four RCTs were included in the review (n=142 patients). Sample size ranged from 18 to 54. All of the trials were double-blind and all used last observation carried forward methods to deal with missing data. Trial completion rates ranged from 48 to 67%. Two trials reported adequate allocation concealment.

Treatment duration was either four or eight weeks.

Effects on depression: Valproate was associated with a statistically significant improvement in depression rating scores (SMD -0.35, 95% CI -0.69 to -0.02) and response to treatment (RR 2.00, 95% CI 1.13 to 3.53; NNT 5) compared with placebo. No heterogeneity was found for either analysis.

Anxiety symptoms: There was no statistically significant difference between valproate and placebo in anxiety symptoms (three RCTs, n=97 patients), switch to mania (three RCTs, n=117 patients), withdrawal due to any reason (four RCTs, n=142 patients, lack of efficacy, adverse events, or any of the 10 specified adverse events.

Authors’ conclusions
Valproate was effective for the reduction of depressive symptoms of acute bipolar depression and was well tolerated.

CRD commentary
The review question was clearly stated. Inclusion criteria were appropriately defined. Several relevant sources were searched and some attempts were made to minimise publication and language bias. Methods were used to minimise reviewer errors and bias in the extraction of data and probably the assessment of validity, but it was not clear whether similar steps were taken in study selection.

Trial quality was assessed and the results were reported. Relevant information was provided about the included trials. Appropriate methods were used for the meta-analyses; heterogeneity was assessed.

The authors’ conclusions appeared to reflect the evidence, but the small number of patients in the few relatively short-term included trials should be taken into account when interpreting these conclusions.

Implications of the review for practice and research
Practice: The authors stated that clinicians should exercise caution when considering prescribing valproate for women of reproductive age and should discuss the potential teratogenic risks with their patients.

Research: The authors stated that larger controlled studies are required to confirm the findings of this review.

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