Valproate in the treatment of PTSD: systematic review and meta analysis

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CRD summary
The authors concluded that limited evidence suggested that valproate may be effective for the treatment of post-traumatic stress disorder and that further research is required. There were limitations to this review, but overall the authors' conclusions reflected limited evidence from a small number of poor quality studies.

Authors' objectives
To evaluate the effects of the anticonvulsant valproate in patients with post-traumatic stress disorder (PTSD).

Searching
MEDLINE, CINAHL, EMBASE, PsycINFO, the National PTSD Centre Pilots Database (published and unpublished studies) and the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register were searched. Search terms were reported. No language restrictions were applied. In addition, reference lists of identified studies were handsearched. The manufacturer of valproate (Sanofi-Aventis) also conducted a search for unpublished studies that had been presented at conferences. Searches were updated to June 2005.

Study selection
Any studies that evaluated valproate for treatment of any severity or duration of post-traumatic stress disorder (using any criteria) were eligible for inclusion. Participants were included regardless of co-morbid disorders. Studies had to assess medication response outcomes on continuous measures, post-traumatic stress disorder (PTSD) total symptoms or symptom cluster mean and standard deviations for interval outcomes.

Most studies involved patients with combat-induced PTSD. In included studies, most patients were male (89%) and ages ranged from 25 to 72 years (mean 43). Daily doses of valproate or divalproex ranged from 250 to 2500 mgs daily; some studies included concomitant drugs. Treatment duration ranged from two weeks to 17 months; most regimens lasted eight weeks or less. Studies assessed outcomes using clinician-rated DSM (Diagnostic and Statistical Manual of Mental Disorders) based PTSD scales and self-rated scales. Studies included in meta-analyses used different measures to assess PTSD symptoms. The review also assessed co-morbid symptoms such as depression. The review included trials with no control groups and case reports.

The authors did not state how papers were selected for the review, or how many reviewers performed the selection. One author apparently selected studies for inclusion in meta-analyses.

Assessment of study quality
Three reviewers independently assessed validity using the Cochrane Collaboration Depression, Anxiety and Neurosis Quality of Research Scale; disagreements were resolved by discussion. This scale assessed sample size, duration of intervention, inclusion and exclusion criteria, blinding, statistical data, and handling of withdrawals.

Data extraction
Data were extracted onto a spreadsheet but the authors did not state how many reviewers performed the data extraction. For studies included in the meta-analyses, values of outcome measures at baseline and after eight weeks were presented with means, standard errors and levels of statistical significance. The standardised mean difference was calculated as Hedge’s g. Authors of original studies were contacted by e-mail for missing data.

Methods of synthesis
Studies were initially combined in a narrative synthesis. Studies that were considered comparable with respect to outcome measure, study design and valid control measure were combined using meta-analysis. Pooled effect sizes (Hedge’s g) were calculated for symptoms of PTSD and depression using fixed-effect and random-effects meta-analysis. Heterogeneity was assessed using the $\chi^2$ statistic, with a p value less than 0.10 interpreted as evidence of
heterogeneity.

**Results of the review**
One single-blinded study (n=16 patients), four open-label studies (n=63 patients) and three case reports (n=4 patients) were included. Overall studies 34% (28/83) dropped out. Reasons for dropouts included intolerable side-effects (n=14 patients) and non-compliance (n=4 patients). Studies scored between 22 and 25.5 out of 46 points for quality, indicating poor to moderate quality. Methodological problems included small sample size, absence of control groups, attrition bias, and limited generalisability of results.

Meta-analysis was based on four studies (one single-blinded trial and three open label trials, 63 patients total before treatment, 38 after eight weeks). Valproate was associated with a statistically significant reduction in PTSD symptoms at eight weeks compared to baseline, Hedge's g -0.982 (95% CI: -1.499 to -0.465 using random-effects model), and a significant reduction in depression from baseline, Hedge's g -0.775 (95% CI: -1.274 to -0.276 using random-effects model). No significant heterogeneity was found for either analysis (p=0.274 for PTSD and p=0.286 for depression). Results for fixed-effect models were similar.

All three case reports described improvements in hyper-arousal symptoms post-treatment with valproate.

**Authors' conclusions**
Limited evidence suggested that valproate may be effective for the treatment of post-traumatic stress disorder. Further research is required.

**CRD commentary**
The review question was clearly stated and inclusion criteria were defined for participants, outcome and intervention. The criteria for study design were broad, which appeared appropriate given the paucity of identified studies. Several relevant sources were searched and attempts were made to minimise publication and language bias. Study validity was assessed using defined criteria and, although results were mainly reported as an aggregate score, some methodological flaws were summarised in the discussion, including the problem of attrition bias when calculating before and after effect size from aggregate data. Appropriate methods were used to minimise reviewer error and bias in the assessment of study validity, but it was not clear if similar methods were used to select studies for inclusion in the review or extract data. In view of the clinical heterogeneity among studies, particularly with respect to outcome measures, it was questionable if pooling data statistically was appropriate. There were limitations to this review, but overall the authors’ cautious conclusions reflected limited evidence from a small number of poor quality studies.

**Implications of the review for practice and research**

**Practice:** The authors stated that in view of the limitations of the existing evidence, valproate cannot be recommended as monotherapy for post-traumatic stress disorder.

**Research:** The authors stated that there is a need for double-blind controlled studies to initially compare valproate with placebo and then compare valproate with selective serotonin re-uptake inhibitors in patients with post-traumatic stress disorder.

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