Authors' objectives
To critically review the available data on the use of valproate for the treatment of nonbipolar patients with aggressive and violent behaviours.

Searching
MEDLINE and PsycLIT were searched from 1987 to 1998 using the keywords 'aggression', 'violence', 'valproate' and the names of all commercial preparations of valproate available in the United States, i.e. 'valproic acid' ('Depakene'), 'divalproex sodium' ('Depakote') or 'sodium valproate'.

Study selection
Study designs of evaluations included in the review
Any designs were considered, although only case reports with a clear diagnostic description were included. The duration of the studies ranged from 2 to 34 weeks.

Specific interventions included in the review
Valproic acid. A very wide range of 250 to 4,000 mg/day valproate was used; the mean maximum dose of valproate was 1,393.5 mg/day. The mean reported plasma valproate level was 62.44 microg/mL (range: 13 - 111 microg/mL).

In 12 of the 17 studies, participants were taking concurrent medications such as benzodiazepines, neuroleptics, antidepressants and other mood stabilisers.

Participants included in the review
Patients with aggressive or violent behaviour were classified according to four categories:

1. Dementia.
2. Organic brain syndromes including brain injuries.
3. Mental retardation.
4. Other diagnoses associated with aggressive behaviours, such as schizophrenia and schizo-affective and bipolar disorders.

The participants ranged in age from 8 to 97 years, with a mean age of 53.81 years.

Reports of patients with aggression and bipolar diagnosis were excluded since the efficacy of valproate for that indication has been well documented. Studies in patients with aggression in the context of an acute organic delirium were also excluded, because of the multitude of medical factors and concomitant medications usually involved that would make it difficult to draw valid conclusions.

Outcomes assessed in the review
Response to treatment, measured as a reduction in aggressive and violent behaviours generally by global clinical impressions. Six studies used a rating scale to measure aggression, four of which used the Overt Aggression Scale (OAS). Side-effects were also reported.

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 reviewers performed the selection.
Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Data were extracted for the categories of: study identification and date of publication, number of patients, mean age range, diagnosis, study design, duration of treatment, dose, plasma valproate level, concurrent medication (yes or no) and outcome.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative analysis reporting on the outcome measures and discussing possible influences on study results.

How were differences between studies investigated?
The authors did not assess heterogeneity.

Results of the review
Seventeen reports were included in the review with 164 participants: 10 were case reports with a total of 31 participants, 3 were retrospective chart reviews with 83 participants, and 3 were open-label prospective studies with a total of 34 participants. No double-blind, placebo-controlled trials were found. Only one pilot double-blind study examined the effectiveness of valproate in 16 participants with borderline personality disorder.

An overall response rate of 77.1% was calculated when response was defined as a 50% reduction of target behaviour. The anti-aggressive response usually occurred in conjunction with other psychotropic medication. The dose and plasma valproate level required for response appeared identical to those for the treatment of seizure disorders.

In the majority of cases, patients diagnosed with dementia and treated with valproate showed improvement on global measures of aggression and behavioural agitation. The results were comparable when the patients were treated with valproate alone or with concomitant medication. The improvement seems to be unrelated to the dose of concomitant psychotropic medications.

Two studies of patients (27 participants) with borderline personality disorder who were treated with valproate yielded encouraging results, although in both studies the OAS measurements were non significant.

One study (35 participants) reporting on schizophrenic, schizo-affective and bipolar patients treated with valproate, used an indirect measure of aggressive behaviour, i.e. the number of hours per week spent in seclusion, to measure change in behaviour. The mean number of hours spent in seclusion fell significantly from 18 hours per week at baseline to 2 hours per week after 2 weeks of treatment. Patients most likely to respond were those with atypical or mixed bipolar disorder and those with abnormal electroencephalogram results. Concurrent other psychotropic medications did not have a significant effect on treatment response.

Overall, side-effects were very low: only a minority of patients were reported to have experienced sedation, tremor or gait disturbances. No patients experienced hepatic transaminase elevation, thrombocytopenia or pancreatitis.

Authors’ conclusions
The authors state that while the general anti-aggressive effect of valproate is promising, in the absence of controlled data, conclusions are limited at this time. The effect appeared to be non-specific diagnostically, although the best responses appeared to occur in patients with bipolar disorder, and organic disorders such as dementia and brain injuries. The dose and plasma level of valproate required for response appeared identical to those for the treatment of
bipolar and seizure disorders. Few side-effects were observed.

**CRD commentary**
The authors have stated the research question but the predetermined inclusion and exclusion criteria were limited. The literature search was reasonably thorough, although it was not stated whether the search was restricted to English language publications or whether unpublished information was sought. There were no tests for publication bias.

The quality of the included studies was not formally assessed, and the authors have not reported how the articles were selected or who performed the selection and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were not statistically combined. Study details are described in the text, with the outcomes for each study presented individually without a brief overview.

The authors' conclusions appear to follow from the results, but should be viewed with much caution because of limitations in the quality of the review process, specifically the lack of quality assessment and the many differences in intervention and participant characteristics.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors state that further research, in the form of randomised, double-blind, controlled trials, is needed to confirm a specific anti-aggressive effect for this medication. Specific recommendations for study design were stated.

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