COCHRANE CORNER

Valproate preparations for agitation in dementia†

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†This review is an abridged version of a Cochrane review previously published in the *Cochrane Database of Systematic Reviews*, 2018, October 5, Issue 10: CD003945 (doi: 10.1002/14651858.CD003945.pub4) (see www.Cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

We thank the Cochrane Review Group for their support in publishing these reviews.

See commentary in this issue.

Background

Agitation has been reported in up to 90% of people with dementia. Agitation in people with dementia worsens carer burden, increases the risk of injury, and adds to the need for institutionalisation. Valproate preparations have been used in an attempt to control agitation in dementia, but their safety and efficacy have been questioned.

Objectives

To determine the efficacy and adverse effects of valproate preparations used to treat agitation in people with dementia, including the impact on carers.

Search methods

We searched ALOIS – the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 7 December 2017 using the terms: valproic OR valproate OR divalproex. ALOIS contains records from all major healthcare databases (the Cochrane Library, MEDLINE, Embase, PsycINFO, CINAHL, LILACS) as well as from many trials databases and grey literature sources.

Selection criteria

Randomised placebo-controlled trials that assessed valproate preparations for agitation in people with dementia.

Data collection and analysis

Two review authors independently screened the retrieved studies against the inclusion criteria and extracted data and assessed methodological quality of the included studies. If necessary, we contacted trial authors to ask for additional data, including relevant subscales, or for other missing information. We pooled data in meta-analyses where possible. This is an update of a Cochrane Review last published in 2009. We found no new studies for inclusion.

Main results

The review included five studies, with 430 participants. Studies varied in the preparations of valproate, mean doses (480–1000 mg/day), duration of treatment (3–6 weeks) and outcome measures used. The studies were generally well conducted although some methodological information was missing and one study was at high risk of attrition bias.

The quality of evidence related to our primary efficacy outcome of agitation varied from moderate to very low. We found moderate-quality evidence from two studies that measured behaviour with the total Brief Psychiatric Rating Scale (BPRS) total score (range 0–108) and with the BPRS agitation factor (range 0–18). They found that there was probably little or no effect of valproate treatment over 6 weeks (total BPRS: mean difference (MD) = 0.23, 95% CI –2.14 to 2.59; BPRS agitation factor: MD = –0.67, 95% CI –1.49 to 0.15; 202 participants, 2 studies). Very low-quality evidence from three studies which measured agitation with the Cohen–Mansfield Agitation Index (CMAI) was consistent with a lack of effect of valproate treatment on agitation. There was variable quality evidence on other behaviour outcomes reported in single studies of no difference between groups or a benefit for the placebo group.

The three studies that measured cognitive function using the Mini-Mental State Examination (MMSE) found little or no effect of valproate over 6 weeks, but we were uncertain about this result because the quality of the evidence was very low. The two studies that assessed functional ability using the Physical Self-Maintenance Scale (PSMS) (range 6–30) found that there was probably slightly worse function in the valproate-treated group and it was of uncertain clinical importance (MD = 1.19, 95% CI 0.40–1.98; 203 participants, 2 studies; moderate-quality evidence).

Analysis of adverse effects and serious adverse events (SAEs) indicated a higher incidence in valproate-treated participants. A meta-analysis of three studies showed that there may have been a higher rate of adverse effects among valproate-treated participants than among controls (odds ratio (OR) = 2.02, 95% CI 1.30–3.14; 381 participants, 3 studies; low-quality evidence). Pooled analysis of the number of SAEs for the two studies that reported such data indicated that participants treated with valproate preparations were more likely to experience SAEs (OR = 4.77, 95% CI 1.00–22.74; 228 participants, 2 studies), but the very low quality of the data made it difficult to draw any firm conclusions regarding SAEs. Individual adverse events that were more frequent in the valproate-treated group included sedation, gastrointestinal symptoms (nausea, vomiting and diarrhoea) and urinary tract infections.

Authors' conclusions

This updated review corroborates earlier findings that valproate preparations are probably ineffective in treating agitation in people with dementia but are associated with a higher rate of adverse effects and possibly of SAEs. On the basis of this evidence, valproate therapy cannot be recommended for management of agitation in dementia. Further research may not be justified, particularly in light of the increased risk of adverse effects in this group of often frail people. Research would be better focused on effective non-pharmacological interventions for this patient group or, for situations where medication may be needed, further investigation of how to use other medications as effectively and safely as possible.