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TABLE OF CONTENTS

[Intervention Review]

Valproate preparations for agitation in dementia

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ABSTRACT

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 health care 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 mg/day to 1000 mg/day), duration of treatment (three weeks to six 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) score (range 0 to 108)

and with the BPRS agitation factor (range 0 to 18). They found that there was probably little or no effect of valproate treatment over six weeks (total BPRS: mean difference (MD) 0.23, 95% confidence interval (CI) -2.14 to 2.59; 202 participants, 2 studies; 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) were 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.

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

Analysis of adverse effects and serious adverse events (SAE) 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 to 3.14; 381 participants, 3 studies, low-quality evidence). Pooled analysis of the number of SAE 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 to 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 often frail group of people. Research would be better focused on effective non-pharmacological interventions for this patient group, or, for those situations where medication may be needed, further investigation of how to use other medications as effectively and safely as possible.

PLAIN LANGUAGE SUMMARY

Valproate preparations for the treatment of agitated behaviour in people with dementia

Background

Agitated behaviour is very common in the later stages of dementia. It can include verbal behaviours, such as shouting, and physical behaviours, such as wandering or physical aggression. It has been shown to worsen the stress experienced by family carers, increase the risk of injury, and increase the need for people with dementia to move into institutional care.

A type of medication that has been used to treat agitated behaviour in people who have dementia is valproate, which is available in several different preparations (valproic acid, divalproex sodium, sodium valproate, and valproate semi-sodium). These medications are not recommended in current guidelines (e.g. from the National Institute for Health and Care Excellence), but are sometimes still given to people with dementia to treat agitated behaviour.

Purpose of this review

We wanted to review the evidence about how effective and safe it is to give valproate preparations to people with dementia to treat agitation.

Studies included in this review

We searched medical databases up to December 2017 for studies that compared any preparation of valproate with a placebo (dummy tablet) to treat agitated behaviour in people diagnosed with dementia.

We included five studies with 479 participants who had various types of dementia and agitated behaviour. Most studies lasted for six weeks, although one was only three weeks long. The studies were generally well conducted, but the methods were not always fully

reported and one study was at high risk of bias because of the high number of people who dropped out from the valproate-treated group.

Key findings

Studies measured agitated behaviour with various scales and the reliability of the evidence for the different scales ranged from moderate to very low. Overall, we found no evidence that valproate preparations improved behaviour, or specifically, agitated behaviour. We found that valproate preparations probably had little or no effect on participants' ability to perform daily activities. We could not be sure whether they had an effect on cognition (thinking and remembering) because the reliability of the evidence was very low.

We found low-reliability evidence from three studies that participants taking valproate may be more likely than those taking placebo to experience harmful effects. We could not be as certain about differences in serious harms, such as serious illness or admission to hospital, but data from two studies suggested that these may be more common in the participants taking valproate. Some of the side effects associated with valproate were sleepiness, feeling sick, being sick, watery stools, and urinary tract infections.

Conclusions

We only identified five relatively small studies for inclusion in this review. They varied in their methods, type of medicine and its dose, duration of treatment, and scales used to make measurements. This limited our ability to pool data across studies. However, we could be moderately confident in the conclusion that valproate preparations do not improve agitated behaviour in dementia. They may also be associated with harmful effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Valproate preparations compared to placebo for agitation in dementia

Patient or population: people with agitation in dementia
Setting:
Intervention: valproate preparations
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with valproate preparations				
Agitation and aggression assessed with: Brief Psychiatric Rating Scale total score. Change from baseline at 6 weeks (ITT) Scale: 0-108 (higher score indicated higher level of dysfunction)	The mean change from baseline for agitation and aggression was -5.34 points	MD 0.23 higher (2.14 lower to 2.59 higher)	-	202 (2 RCTs)	⊕⊕⊕◯ **Moderate**[a,b]	-
Agitation and aggression assessed with: BPRS agitation factor. Change from baseline at 6 weeks (ITT) Scale: 0-18 (higher score indicated higher level of dysfunction)	The mean change from baseline for agitation and aggression was -1.88 points	MD 0.67 lower (1.49 lower to 0.15 higher)	-	202 (2 RCTs)	⊕⊕⊕◯ **Moderate**[a,b]	-

Agitation and aggression assessed with: Cohen-Mansfield Agitation Index total score. Change from baseline at 6 weeks (ITT) Scale: 0-216 (higher score indicated more agitated behaviour)	The mean change from baseline for agitation and aggression was -4.42 points	MD 1.84 lower (6.02 lower to 2.34 higher)	-	217 (3 RCTs)	⊕○○○ **Very low**[a,b,c,d]	-
Cognition assessed with: Mini-Mental State Examination total score. Change from baseline at 6 weeks (ITT) Scale: 0-30 (lower score indicated greater cognitive impairment)	The mean change from baseline for cognition was 0.46 points.	MD 0.7 lower (1.61 lower to 0.2 higher)	-	217 (3 RCTs)	⊕○○○ **Very low**[a,b,c,d]	-
Functional performance assessed with: Physical Self-Maintenance Scale total score. Change from baseline at 6 weeks (ITT) Scale: 6-30 (higher score indicated greater impairment in ADL)	The mean change from baseline for functional performance was 0.06 points	MD 1.19 higher (0.4 higher to 1.98 higher)	-	203 (2 RCTs)	⊕⊕⊕○ **Moderate**[a]	-
Any adverse event by 6 weeks	Study population		**OR 2.02** (1.30 to 3.14)	381 (3 RCTs)	⊕⊕○○ **Low**[c,d]	-
	602 per 1000	753 per 1000 (663 to 826)				

Serious adverse events by 6 weeks	Study population		**OR 4.77** (1.00 to 22.74)	228 (2 RCTs)	⊕◯◯◯ **Very low**[a,d]	-
	18 per 1000	79 per 1000 (18 to 291)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
ADL: activities of daily living; **CI:** confidence interval; **ITT:** intention to treat; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level for imprecision due to small number of participants.
[b]Downgraded in light of imprecision due to confidence intervals including the potential for harm or benefit.
[c]Downgraded one level due to inconsistency (heterogeneity between studies).
[d]Downgraded one level due to study limitations (risk of bias).

BACKGROUND

Description of the condition

Agitation is reported in up to 90% of people with dementia (Alzheimer's Society 2011a). A widely accepted definition of agitation is: "inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion per se" (Billig 1991; Cohen-Mansfield 1989). The descriptors of agitation include wandering, crying out, aggressiveness, repetitive movements, and unco-operative behaviour. Agitation in people with dementia worsens carer burden, increases the risk of injury, and adds to the need for institutionalisations (Livingstone 2014).

Description of the intervention

Current guidelines recommend that people with dementia who develop non-cognitive symptoms or behaviours that cause them distress or challenge those who provide their care should first have a comprehensive assessment to determine likely causative factors, such as physical illness, depression, pain, adverse effects of medication, personal or psychosocial factors, or aspects of their physical environment. Appropriate steps should then be taken to address those factors, and a period of 'watchful waiting' should be observed, if possible, as in many cases symptoms will improve or resolve over four to six weeks (Alzheimer's Society 2011a). The guidelines also suggest that consideration should be given to providing individualised interventions such as aromatherapy or multisensory stimulation as there is some evidence of their clinical effectiveness (Livingstone 2014; NICE 2006). In fact, research has shown that just 10 minutes of one-to-one time each day can reduce behavioural and psychological symptoms associated with dementia (BPSD) (Alzheimer's Society 2011b).

The National Institute for Health and Care Excellence (NICE) guideline on supporting people with dementia and their carers suggests that people with dementia who present with non-cognitive symptoms or challenging behaviour should be offered pharmacological intervention in the first instance "only if they are severely distressed or there is an immediate risk of harm to the person or others" and that a thorough assessment of possible causes of the behaviour should be carried out as soon as possible (NICE 2016). Drug treatment for the control of violence, aggression, and extreme agitation should be implemented with the aim of avoiding sedation and the use of high doses or combinations of drugs, and with careful monitoring of the person's physical condition and any adverse effects (NICE 2006).

If drug treatment of agitation is considered necessary, then the drug classes recommended by NICE, in order, are antipsychotics, acetylcholinesterase inhibitors, and memantine. There is some evidence of modest benefits of antipsychotics in around 50% of people with dementia, but they are associated with adverse effects such as sedation, parkinsonism, gait disturbance, dehydration, falls, chest infection, accelerated cognitive decline, and stroke, and they are associated with increased mortality in the long term (Alzheimer's Society 2011b; Maher 2011). The increased risk of cerebrovascular adverse events and death in this patient group resulted in a Medicines and Healthcare products Regulatory Agency (MHRA) warning that no antipsychotic should be used for this indication in dementia (except risperidone in some circumstances) (MHRA 2012). Risperidone is the only antipsychotic licensed for people with dementia, and guidelines recommend treatment should be used for no longer than 12 weeks. The evidence of benefit of other types of antipsychotics is more limited, and use for BPSD is off-label. Acetylcholinesterase inhibitors and memantine are licensed for the treatment of cognitive symptoms in Alzheimer's disease and there is some evidence that these medications may positively impact on agitated behaviour, although there is no evidence that they specifically improve agitation (NICE 2006).

Other medications that have been used to treat agitated behaviour in people with dementia include benzodiazepines, hypnotics, antidepressants, and anticonvulsants. There is no evidence of benefit of benzodiazepines for this indication, and they carry increased risk of adverse effects (Bierman 2007). There is relatively little evidence relating to antidepressants for agitated behaviour in dementia; findings on efficacy are mixed and there is evidence of adverse effects (Porteinsson 2014; Seitz 2011). Among anticonvulsants, carbamazepine and valproate preparations have both been used widely.

How the intervention might work

Various valproate preparations are available: valproic acid, divalproex, sodium valproate, and valproate semi-sodium. Suggested mechanisms by which valproic acid may have an impact on agitation include enhancement of the intracerebral neurotransmitting agent, gamma-butyric acid (GABA), antimanic action, and mood stabilising effect (Lon 1995). Since 1996, a more readily tolerated compound of valproate, divalproex, has been used. This drug differs slightly from valproic acid in that peak blood flow levels occur later (three to six hours, compared with three hours), but the dosage and half-life of this drug are identical to those of valproic acid. Sodium valproate is licensed for the treatment of epilepsy in standard-release oral preparations, and in modified-released preparations for various indications according to the preparation. Sodium valproate or valproate semi-sodium is licensed for the treatment of manic episodes in bipolar disorder. None of the valproate preparations are licensed for the management of agitated behaviour in people with dementia; therefore, use of for this purpose is off-label.

Adverse effects associated with valproate preparations include falls, gait disturbances, sedation, tremor, muscular weakness, depressed mood, gastrointestinal disorders (nausea, vomiting, constipation,

and diarrhoea), urinary tract infections (UTI), and thrombocytopenia. The current NICE advice on the use of valproate preparations for the management of aggression, agitation, and behavioural disturbances in dementia states that current evidence suggests that such medications are no more effective than placebo, and that adverse effects are also more common in people taking them (NICE 2015).

Why it is important to do this review

This is an update of a Cochrane Review first published in 2004, and previously updated in 2009.

One summary of evidence published by NICE suggests that valproate preparations are no more effective than placebo for agitation in dementia (NICE 2015). Despite this guidance, valproate preparations are still sometimes being used in this patient group, perhaps because other drug options are not always effective and may be associated with adverse effects. This update is intended to apply current Cochrane methods to synthesise the evidence concerning use of valproate for agitation in dementia, and to assess the quality of this evidence, in order to inform decision-making by carers, clinicians, researchers, and policy-makers.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised, placebo-controlled trials. We excluded interrupted time series trials. Where studies used a cross-over design, we included only data from the first part of the study.

Types of participants

We included participants of either sex and of any age, both inpatients and outpatients (with or without carers). Dementia should have been diagnosed according to the classifications provided by Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (APA 1994), International Classification of Diseases, 10th edition (ICD-10) (WHO 1991), Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) (APA 1980), or Diagnostic and Statistical Manual of Mental Disorders, 3rd revised edition (DSM-IIIR) (APA 1987). In the absence of these criteria, we also accepted other evidence of dementia such as the Mini-Mental State Examination (MMSE) (Folstein 1975), psychiatric evaluation, psychological evaluation, or a medical evaluation. We accepted definitions of agitation provided by individual investigators.

Because agitation is common in delirium, we had initially specified that all studies should have included clinical evaluation to rule out delirium and other treatable causes of agitation (e.g. pain, infection, drug effect, urinary or faecal retention) prior to entering people into the trial. However, reporting of baseline clinical evaluation was not always specific or detailed. Therefore, we took a pragmatic approach to avoid risking the loss of relevant evidence and included studies despite this information not being explicitly reported.

Types of interventions

We required at least one week of treatment with valproate preparations, of any dosage given by mouth, compared with placebo. People receiving stable therapy with other psychoactive medications, including cholinesterase inhibitors, memantine, and antidepressants, could be included if this was permitted in the study protocol.

Types of outcome measures

Primary outcomes

- Agitation, or one or more aspects of agitation as measured by a scale that specifically measured agitation, either exclusively or as one of its components. The scales included but were not limited to:
    - Cohen-Mansfield Agitation Inventory (CMAI; Cohen-Mansfield 1986);
    - Social Dysfunction and Agitation Scale (SDAS; Wistedt 1990);
    - Clinical Global Impression Scale for Aggression (CGI; Guy 1976);
    - "Nurse Observation" scale (Colenda 1991);
    - Behavior Observation Scale of Intramural Psychogeriatric Patients (GIP; Verstraten 1988);
    - Brief Psychiatric Rating Scale (BPRS; Overall 1962; Overall 1988);
    - Overt Aggression Scale (OAS; Yudofsky 1986).

Secondary outcomes

- Cognition.
- Functional performance.
- Overall clinical impression.

- Effect on carers (carers' psychological morbidity or burden).
- Incidence and severity of adverse effects.
- Dropouts, including dropouts due to adverse events.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), which is the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) Specialized Register on 2 October 2014. The search terms used were: valproic OR valproate OR divalproex.

The Information Specialists for the CDCIG maintain ALOIS, which contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy older populations. The studies are identified through:

- monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO, and Lilacs;
- monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the World Health Organization (WHO) portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
- quarterly searches of the Central Register of Controlled Trials (CENTRAL);
- six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses and Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL, and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Searching other resources

We performed additional searches in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.

We carried out the most recent search for this review on 7 December 2017. Previous searches were done in October 2016, July 2010, and February 2008.

Data collection and analysis

Selection of studies

The Information Specialist of the CDCIG removed duplicates of the same references. Two review authors (ETL and JL) independently examined titles and abstracts against the prespecified inclusion criteria to exclude clearly ineligible studies. We examined any potentially eligible trial in full text. Two review authors (ETL and JL) independently evaluated full texts according to the eligibility criteria. We compared selections of trials and the review authors agreed the final list of studies. We explained final decisions for the exclusion of articles that we retrieved in full text in the Characteristics of excluded studies table.

Data extraction and management

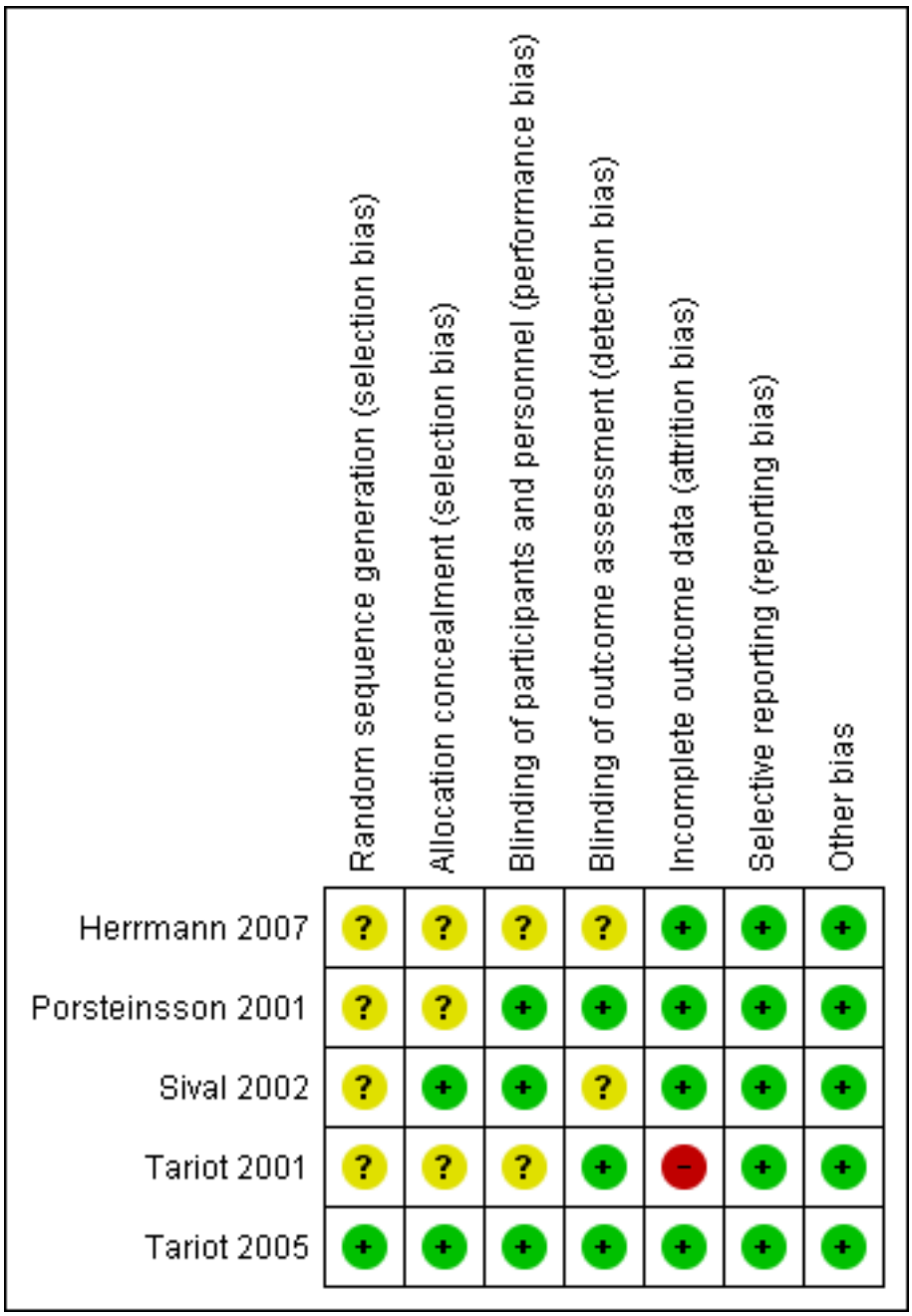
Two review authors (ETL and JL) extracted data from each study using a data collection form that was piloted by the team. For the purpose of this updated review, the data were entered into Review Manager 5 (Review Manager 2014). Two review authors (AC and SFB) checked the data for accuracy. We also extracted data about ongoing studies, including study name, methods, participants, interventions, outcomes, starting date, contact information, and notes.

Assessment of risk of bias in included studies

Two review authors (SFB and AC) independently assessed the risk of bias in accordance with Cochrane's tool for assessing methodological quality and risk of bias (Higgins 2011). This tool assesses how the randomisation sequence was generated, how allocation was concealed, the integrity of blinding (participants, raters, and personnel), the completeness of outcome data, selective reporting, and other biases. Where inadequate details of randomisation and other characteristics of the trials were provided, we contacted authors of the studies to obtain further information.

We described the risk of bias of all included studies in the Characteristics of included studies table and narratively. In addition, we provided an overall judgement of included studies in a 'Risk of bias' summary (see Figure 1). Where the two review authors disagreed on 'Risk of bias' decisions, the final rating was made by consensus discussion involving the third member of the review team.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We used the mean difference (MD) to measure the treatment effect. If the same outcome was assessed using different scales, then we used the standardised mean difference (SMD). We reported 95% confidence intervals (CI). We reported results of dichotomous outcomes as odds ratios (OR) with 95% CI.

Unit of analysis issues

We considered only participant-level outcomes. We analysed change in outcome measure from pre- to post-treatment. For crossover trials, we used data for the first period only (if available) because of the possibility of carry-over effects.

Dealing with missing data

To allow an intention-to-treat analysis, we sought data irrespective of compliance, whether or not the participant was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If intention-to-treat data were not available in the publications, we extracted 'on-treatment' data or the data of participants who completed the trial and indicated it as such. We did not use data from titration phases prior to the randomised phase to assess safety or efficacy.

Assessment of heterogeneity

We considered clinical heterogeneity between trials (participants, interventions, and outcomes) when deciding whether or not to synthesise data. Where we performed a meta-analysis, we used a standard Chi^2 test to check for heterogeneity. We also assessed the impact of heterogeneity on the meta-analysis using the I^2 statistic.

Assessment of reporting biases

We tried to minimise the impact of publication bias by searching for both published and unpublished trials. We compared conference abstracts and registered trials with published data. We contacted the responsible organisation or the researcher for more information when we found studies in trial registries that appeared to have been completed but not published (see Description of studies). We found too few studies to allow assessment of possible publication bias using funnel plots and Egger's test for asymmetry (Egger 1997).

Data synthesis

Where data were suitable for a meta-analysis, we presented the effect estimate from a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Due to the low number of included studies, subgroup analysis was not possible. Therefore, participants were combined into the category of 'dementia' regardless of subtype.

Sensitivity analysis

We did not conduct any sensitivity analyses.

'Summary of findings' table

We used the GRADE approach to assess the quality of the supporting evidence behind each estimate of treatment effect. We presented key outcomes in Summary of findings for the main comparison, including, for each outcome, a summary of the amount of data, the magnitude of the effect size, and the overall quality of the evidence (Schünemann 2011). The measures included were: change in agitation and aggression, cognition, functional performance, and incidence and severity of adverse effects.

RESULTS

Description of studies

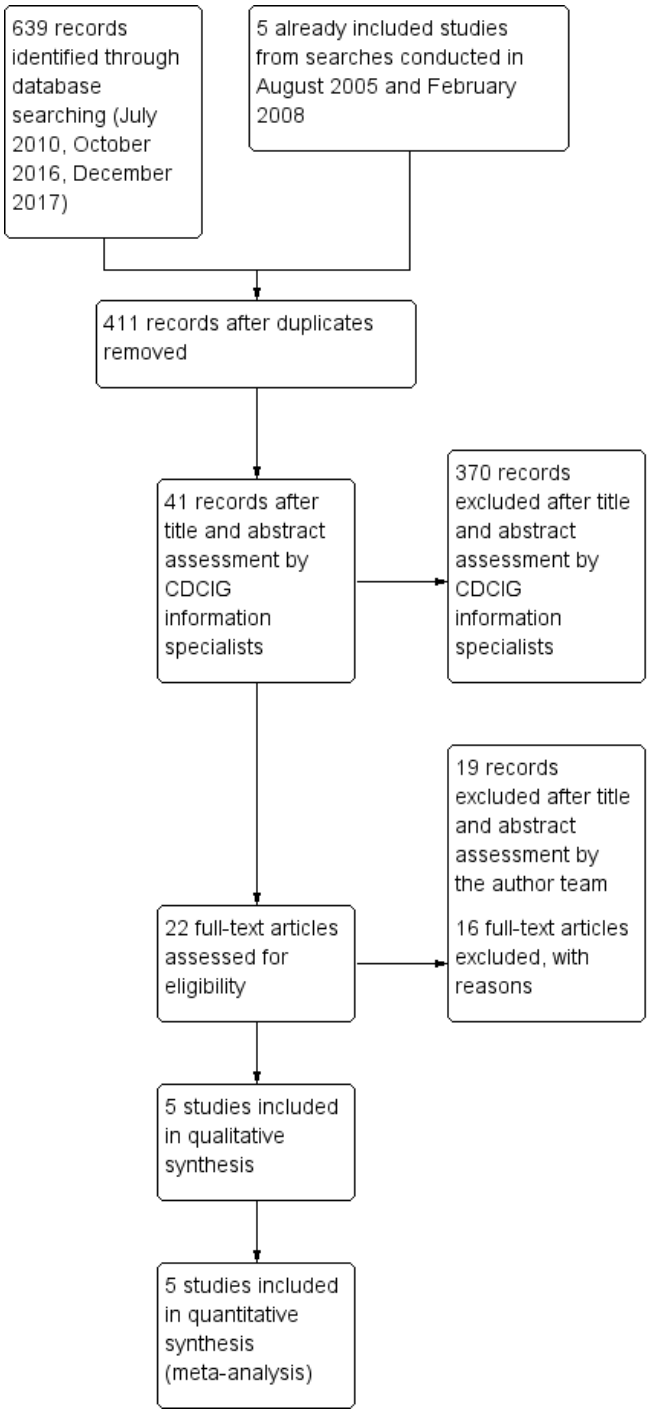
Results of the search

The initial search for eligible RCTs was completed in August 2005. This identified three studies for inclusion in the review (Porsteinsson 2001; Sival 2002; Tariot 2001). An updated search on 7 February 2008 retrieved two new studies (Herrmann 2007; Tariot 2005). Further updated searches on 30 July 2010, and 4 November 2016 identified no new studies for either inclusion or exclusion in the review. The most recent search was performed in December 2017.

After removal of duplicates and first assessment by the Information Specialist of the CDCIG based on a screening of titles and abstracts, these searches resulted in a total of 41 records being passed to the authors for further scrutiny.

See Figure 2 for the flow of studies for this review.

Figure 2. Study flow diagram.



Included studies

We identified five studies eligible for inclusion (Herrmann 2007; Porsteinsson 2001; Sival 2002; Tariot 2001; Tariot 2005). A detailed description of each study is given in the Characteristics of included studies table.

Design

Two studies were placebo-controlled crossover studies (Herrmann 2007; Sival 2002). In Sival 2002, there were two three-week treatment periods separated by a one-week washout period. In Herrmann 2007, the treatment periods lasted six weeks and there was a two-week washout period between treatments. The remaining three studies were parallel-group, placebo-controlled RCTs with six-week treatment periods (Porsteinsson 2001; Tariot 2001; Tariot 2005).

Sample size

The two crossover studies were the smallest with 14 (Herrmann 2007) and 43 (Sival 2002) participants. Porsteinsson 2001 had 56 participants, Tariot 2001 had 173, and Tariot 2005 had 153.

Setting

One study was conducted in Europe (Sival 2002), and another in Canada (Herrmann 2007). Three were multisite studies in the US (Porsteinsson 2001; Tariot 2001; Tariot 2005). All studies involved people who were institutionalised. In Sival 2002, the participants were from a short-stay ward at a psychiatric hospital; in the other studies, participants were resident in long-term care facilities.

Participants

See Table 1 for a description of the participants' characteristics at baseline in all studies.

All studies included participants with dementia, mostly with moderate-to-severe dementia. All studies used one or more standard methods to diagnose dementia, including Alzheimer's disease, vascular dementia, and mixed dementia (DSM-IV (APA 1994); National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann 1984)).

Sival 2002 used the Clinical Dementia Rating Scale (Hughes 1982), in which 2/42 participants were classified as "light," 24/42 participants as "moderate," and 14/42 participants as "severe." This same study used the MMSE (Folstein 1975), but 14 participants could not be scored because of low level of function. All other studies also used the MMSE. Mean scores at baseline were 7.4 (Tariot 2001), 6.8 (Porsteinsson 2001), 4.5 (Herrmann 2007), and 10.8 (range 4 to 24) (Tariot 2005).

Inclusion criteria relating to degree of agitated behaviour varied between studies, but all studies required included participants to exhibit minimum levels of agitation according to standardised measures (Neuropsychiatric Inventory (NPI), BPRS, Social Dysfunction and Aggression Scale-9).

- Herrmann 2007 required participants to display "significant BPSD" as indicated by a score of 8 or greater on the NPI.
- Porsteinsson 2001 required participants to have exhibited agitated behaviour for a minimum of two weeks "with sufficient intensity" to result in a BPRS score of three or more on items relating to tension, hostility, unco-operativeness, or excitement.
- Sival 2002 used Patel's criteria for aggressive behaviour (Patel 1993), and also required participants to score 3 or greater on at least one item of the Social Dysfunction and Aggression Scale-9.
- Tariot 2001 included participants who exhibited "manic symptoms" according to the Bech-Rafaelsen Mania Scale (BRMS) and six items of the BPRS. Participants were required to score 15 or greater on the BRMS and 3 or greater on two or more of the items of the BPRS relating to tension, grandiosity, hostility, suspiciousness, unco-operativeness, and excitement, with a total score of 15 or more.
- Tariot 2005 required participants to have at least a two-week history of agitation with a total score greater than 2 on the BPRS items relating to tension, hostility, unco-operativeness, or excitement.

Interventions

Divalproex sodium

One study treated participants with divalproex sodium delayed-release tablets or placebo (Tariot 2001). Dosage started at 125 mg twice daily and was titrated to 20 mg/kg/day to 30 mg/kg/day, to be reduced if intolerable adverse effects appeared. The median dose for treated participants at the end of six weeks was 1000 mg/day. One study treated participants with rapid-acting divalproex sodium at an initial dose of 375 mg/day which was titrated upwards to a mean dose of 826 mg/day (Porsteinsson 2001). In this trial, a non-blinded supervising physician, who had no contact with the blinded researchers, altered drug dosage by 125 mg/day, depending on written reports by the researchers of response and adverse effects. In Tariot 2005, participants commenced sprinkle formulation divalproex sodium 125 mg twice daily for three days, which was increased in 125 mg increments every three days to 750 mg/day or up to a maximum dose 1000 mg/day. Researchers

decreased the dose by 125 mg/day if a participant experienced adverse effects. The mean dose at the end of the treatment period was 800 mg/day.

Sodium valproate

In Sival 2002, study participants received sodium valproate 240 mg twice daily for three weeks. Participants in Herrmann 2007 received valproate 125 mg liquid suspension twice daily, increased to 500 mg twice daily over the first two weeks. The dose could then be increased to a maximum of 1500 mg/day or decreased based on efficacy and tolerability as determined by a blinded study physician.

All studies permitted short-term use of short-acting psychotropics. Porsteinsson 2001 used chloral hydrate. Tariot 2001 permitted short-term use of lorazepam, oxazepam, or chloral hydrate as needed. Sival 2002 allowed oxazepam for severe anxiety or insomnia. Tariot 2005 permitted zolpidem or lorazepam (or both) for severe agitation or sleep-induction. Herrmann 2007 permitted loxapine as a rescue medication.

Outcomes

All included studies aimed to assess the effect of valproate treatments on agitation, aggression, mania, and overall function of people with dementia.

The instruments used to measure the outcomes in each study are given in Table 2.

Agitation and aggression

The included studies used several different scales to assess change in agitated and aggressive behaviour.

Four studies used the CMAI scale to measure agitation and aggression (Herrmann 2007; Porsteinsson 2001; Tariot 2001; Tariot 2005). It was not clear which version of the CMAI was used, although three gave the same source reference for the scale (Herrmann 2007; Porsteinsson 2001; Tariot 2005). Tariot 2005 stated that they used a 36-item version of CMAI, whereas the most commonly used version is the 29-item version. Information obtained from the author suggested that they actually used the 29-item version of the scale. Herrmann 2007 and Porsteinsson 2001 did not state specifically which version of the CMAI they used in their studies. We attempted to contact these authors to clarify the scale version and scoring used. Tariot 2001 used a different version of the scale specifically designed for nursing home residents (Cohen-Mansfield 1989).

Three studies used the BPRS to assess disturbed behaviour (Porsteinsson 2001; Tariot 2001; Tariot 2005), and two studies also used the agitation and hostility subscales of the BPRS as outcome measures (Porsteinsson 2001; Tariot 2005). All three studies used the 18-item scale but two studies rated items 0 to 6 (Tariot 2001; Tariot 2005), whereas one study rated items 1 to 7 (Porsteinsson 2001). While this would lead to disparity in total scores in each study, analysis of change in score in each study were still comparable. Information relating to the scoring of the agitation and hostility subscales of the BPRS was not available from the authors of the studies which used them, and could not be found through a further literature search.

Tariot 2001 used the BRMS to assess manic symptoms. Porsteinsson 2001 used the OAS to measure aggression. Herrmann 2007 used the NPI and its agitation subscale at their primary outcome measure. Sival 2002 used the Social Dysfunction and Aggression-9 Scale (SDAS-9), and the "Nurse Observation" scale, to measure incidence of aggression; the CGI to rate clinical impression of aggressive behaviour; and GIP to measure other types of disturbed behaviour.

- The CMAI examines 29 types of agitated behaviour, including pacing, verbal or physical aggression, screaming, and restlessness. The frequency of these behaviours is measured on a 29-item scale with each item rated from 0 (never occurs) to 6 (occurs several times an hour) and scores for physical and verbal aggression and overall aggression may be aggregated.
- The BPRS measures physical and verbal aggression, hallucinatory behaviour, and abnormal thought content. The scale comprises 18 items each scored on a 7-point scale with a higher score indicating higher level of dysfunction.
- The CGI uses a 7-point scale with scores ranging from 1 (no aggressive behaviour) to 7 (severely aggressive behaviour). It is also used to measure overall response to treatment.
- The BRMS is an 11-item observer-based scale that rates the severity of manic symptoms on a 5-point scale (Bech 1978).
- The OAS quantifies aggressive verbal and physical behaviours and includes the number, specific nature, and intervention response.
- The NPI is a 12-item scale, designed to assess the severity and frequency of behavioural symptoms in people with dementia (Cummings 1994).
- The SDAS-9 measures several aspects of behaviour to do with patient interaction with other people, and physical and verbal aggression. The scale is a 9-point observation scale covering outward aggressive behaviour, with total sores ranging from 0 to 36).
- The "Nurse Observation" scale assesses the incidence of aggressive behaviour at the moment the behaviour occurs.
- The GIP consists of 14 observational scales to describe agitated and aggressive behaviour.

Cognition

Herrmann 2007; Porsteinsson 2001; and Tariot 2005 assessed cognitive functioning using the MMSE.

Functional performance

Porsteinsson 2001 and Tariot 2005 assessed participants' functional performance using the Physical Self-Maintenance Scale (PSMS) (Lawton 1969).

Overall clinical impression

Three studies included a rating of global clinical response of the participants using the CGI, a 7-point scale with scores ranging from "very much improved" to "very much worse" (Porsteinsson 2001; Tariot 2001; Tariot 2005). Tariot 2001 reported this as mean change and Tariot 2005 as number of participants showing improvement. Porsteinsson 2001 reported CGI separately for therapeutic effect and adverse effects using a different Likert type scale for each.

Adverse effects

All five studies examined the tolerability, adverse effects, and safety of valproate preparations.

- Four studies used check-lists of adverse effects (e.g. drowsiness, nausea, vomiting, diarrhoea, confusion, disturbance in speech, disturbance of co-ordination, tremor, seizures, oedema, fever thrombocytopenia), which were reviewed at regular intervals by interviewing participants and nursing staff; and by reviewing chart entries (Herrmann 2007; Porsteinsson 2001; Sival 2002; Tariot 2005).
- Tariot 2001 measured adverse events based on the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART 1989).

Effect on carers (carers psychological morbidity)

None of the included studies assessed any aspect of carer burden or well-being.

Excluded studies

We excluded most studies on the basis of the study design (e.g. not RCTs). The studies that were excluded, with reasons for exclusion, are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

See Figure 1.

Allocation

All studies included in this review indicated that participants were randomly allocated to treatments groups. However, four studies did not report the process of random sequence generation and we considered them to be at unclear risk of bias in this domain (Herrmann 2007; Porsteinsson 2001; Sival 2002; Tariot 2001). For three of these studies, there was also no specific information about allocation concealment, but Sival 2002 stated that the "code was not available to the investigators" and so we rated its risk of bias due to allocation concealment to be low. Tariot 2005 had a low risk of allocation bias.

Blinding

Two studies failed to state explicitly whether all staff involved in the study were blind to the treatment allocation of the participants (unclear risk of bias; Herrmann 2007; Tariot 2001), and two failed to state whether research staff completing the outcome measures were blinded (unclear risk of bias; Herrmann 2007; Sival 2002).
In Porsteinsson 2001, although the physicians having direct responsibility for participant care and researchers completing study assessments were blinded, a non-blinded physician, who had no direct contact with these physicians, adjusted divalproex sodium dosage based on reports from the blinded raters. Similarly, in Sival 2002, a pharmacist and independent physician reviewed out-of-range laboratory results, including valproate levels. These staff had no contact with participants, investigators, the ward team or participant's relatives so we considered that the risk of introducing bias due to unblinding was low.
Tariot 2001 was described as a double-blind study but total serum valproate levels were measured weekly and monitored by nursing staff. It was not stated whether these nursing staff were involved in the study, so we judged this to pose an unclear risk of performance bias.

Incomplete outcome data

In Tariot 2001, 54% of the valproate-treated participants dropped out compared with 29% of control participants; 22% of all participants dropped out because of adverse effects, and the study had to be discontinued prematurely. Further, since participants had been on therapy for varying periods of time when the study was terminated, interpretation of the effects of treatment was difficult. We considered this study at high risk of attrition bias.
Porsteinsson 2001 included data in the analysis from participants who dropped out of the study, and gave the reasons for the participants dropping out (two from the divalproex group, and four from the placebo group; low risk of attrition bias).
In Tariot 2005, 11/75 participants in the divalproex group and 14/78 participants in the placebo group dropped out of treatment early, but the reasons for discontinuation were not given. However, all participants who discontinued prematurely completed final assessments which were included in the analysis, so we considered the risk of attrition bias to be low.
In Herrmann 2007, two participants dropped out during each treatment phase but reasons for this were not stated. The study

authors stated that they conducted an intention-to-treat analysis, but data for all participants was not included in the results table. We included only the results from the first part of the study in this review and obtained first-phase data from the study authors for all participants; for this reason, we considered the risk of attrition bias to be low.

In Sival 2002, three participants dropped out of the study due to adverse events in either the placebo or washout periods and these data were included in the analysis. One participant was excluded from the analysis due to protocol violation (low risk of attrition bias).

Selective reporting

We found no published protocols for the included studies. However, for all included studies, the results of the primary and secondary outcome measures that were specified in the methods sections of the papers were reported, as well as the frequency of adverse events. Therefore, we judged all the studies to be at low risk of selective reporting bias.

Other potential sources of bias

Sival 2002 had a cross-over design. No results from the first phase of the study were available. The statistical analysis did not take account of the paired nature of the data ("the t-test for independent samples is used to analyse the two-period cross-over trial").

We noted that three of the included studies were supported by grants from Abbott laboratories - a company which may have had a vested interest in the efficacy of the treatment - but we did not rate this as a source of bias (Porsteinsson 2001; Tariot 2001; Tariot 2005).

Effects of interventions

See: **Summary of findings for the main comparison** Valproate preparations compared to placebo for agitation in dementia

The included studies varied in the type of valproic acid preparation, dosage, and duration of therapy. The methods of evaluating the participants also varied between the studies, with use of different scales to assess agitation and aggression, and response to therapy. Tariot 2001 was discontinued due to the disproportionate number of dropouts in the treatment group (54%) as well as a high proportion in the placebo group (29%), with the results that not all participants received treatment for the full study period. Many of these dropouts occurred in the first three weeks (11/47 participants). Due to the high risk of attrition bias caused by the high dropout rate, we decided to exclude the data from the pooled analysis in this review. Sival 2002 was a cross-over design and first-phase data were not available from the published paper, or from the authors, and so data from this study was also not included in our analyses.

Agitation and aggression

We were able to pool data on agitation/aggression measured with the BPRS from two studies and the CMAI from three studies.

A meta-analysis of agitated behaviour, assessed with total BPRS scores in two studies, showed that there was probably no difference between valproate and placebo group in total BPRS after six weeks of treatment (MD 0.23, 95% CI -2.14 to 2.59; 202 participants, 2 studies; Analysis 1.1; moderate-quality evidence, downgraded due to imprecision) (Porsteinsson 2001; Tariot 2005). A pooled analysis of agitation measured with the agitation factor of the BPRS confirmed that there was probably no effect of treatment specifically on agitation (MD -0.67, 95% CI -1.49 to 0.15; 202 participants, 2 studies; Analysis 1.2; moderate-quality evidence, downgraded due to imprecision). The quality of evidence on agitation measured with the CMAI was lower, but meta-analysis of three studies that reported the change in total CMAI score between baseline and six weeks also suggested no effect on agitated behaviour (MD -1.84, 95% CI -6.02 to 2.34, 217 participants, 3 studies; I^2 = 52%; Analysis 1.3; very low-quality evidence, downgraded due to risk of bias, inconsistency, and imprecision) (Herrmann 2007; Porsteinsson 2001; Tariot 2005). Herrmann 2007 and Porsteinsson 2001 did not state specifically which version of the CMAI they used in their studies, we made the assumption that they used the standard 29-item scale. Information from Tariot 2005 indicated that they also used the 29 item scale despite the paper stating they used a 36 item version of the scale. In light of the uncertainty regarding which version Tariot 2005 used, we repeated the pooled analysis of change in total CMAI score after excluding data from Tariot 2005 (MD 1.96, 95% CI -6.18 to 10.10; 70 participants, 2 studies; very low-quality evidence, downgraded due to risk of bias, inconsistency, and imprecision).

Single studies only reported the other outcome measures. Porsteinsson 2001 found that there was probably little or no effect of divalproex on the hostility factor of the BPRS (MD 0.10, 95% CI -1.12 to 1.32; 55 participants, 1 study; Analysis 1.4; moderate-quality evidence, downgraded due to imprecision) or the Overt aggression total score (MD 0.10, 95% CI -3.42 to 3.62; 55 participants, 1 study; Analysis 1.5; moderate-quality evidence, downgraded due to imprecision). Herrmann 2007 used the NPI. This showed a clinically important difference in behavioural symptoms as measured by the NPI total score, favouring the placebo group, but there was a great deal of uncertainty about this result (MD 15.28, 95% CI -5.19 to 35.75; 14 participants, 1 study; Analysis 1.6; very low-quality evidence, downgraded one level due to risk of bias and two levels due to imprecision). There was similarly a high level of uncertainty about the result on the NPI agitation/aggression subscale, which showed no clear evidence of a difference between groups (MD 1.43, 95% CI -2.48 to 5.34; 14 participants, 1 study; Analysis 1.7; very low-quality evidence, downgraded one level due to risk of bias and two levels due to imprecision).

Cognition

Three studies assessed cognitive functioning using the MMSE (Herrmann 2007; Porsteinsson 2001; Tariot 2005). The quality of this evidence was very low. but pooled analysis of the data indicated that there may have been little or no effect of valproate on the change in MMSE score over the six-week treatment period (MD -0.70, 95% CI -1.61 to 0.20; 217 participants, 3 studies; Analysis 1.8; very low-quality evidence, downgraded due to risk of bias, inconsistency, and imprecision).

Functional performance

Porsteinsson 2001 and Tariot 2005 assessed functional ability using the PSMS. Pooled analysis of the change in total PSMS score indicated that there was probably little or no effect of valproate on this outcome (MD 1.19, 95% CI 0.40 to 1.98; 203 participants, 2 studies; Analysis 1.9; moderate-quality evidence, downgraded due to imprecision).

Overall clinical impression

Three studies included a measure of global clinical change, but we excluded data from Tariot 2001 due to the very high risk of attrition bias. Tariot 2005 used the CGI as an index of clinical efficacy, measuring change in participants' overall clinical condition on a 7-point scale (0 marked improvement to 6 marked worsening). The number of participants showing improvement was reported not to differ significantly between the two groups. Porsteinsson 2001 used the CGI to rate "therapeutic effect" on a 4-point scale, and the presence and clinical significance of adverse effects on a 7-point scale (from very much improved to very much worse). They reported no difference between groups in CGI ratings. Because of the different ways in which the CGI was used was used in these two studies, we were unable to pool data.

Incidence and severity of adverse effects

Meta-analysis of three studies, all of which used divalproex sodium, found there may have been a higher rate of adverse effects among participants treated with divalproex sodium than among participants in the control group (OR 2.02, 95% CI 1.30 to 3.14; 381 participants, 3 studies; Analysis 2.27; low-quality evidence, downgraded due to imprecision and inconsistency) (Porsteinsson 2001; Tariot 2001; Tariot 2005). A fourth study reported that the mean incidence of adverse effects was low during three weeks of observation in both sodium valproate (0.17) and placebo (0.02) groups, but the study provided no description of the types of adverse reactions or actual numbers of adverse events experienced, so we could not include this study in the meta-analysis (Sival 2002). Data on adverse effects during the first treatment phase of Herrmann 2007 were not available in the published data or from the authors, but over the course of both treatment phases, 12 participants experienced at least one adverse event while taking valproate compared to eight participants while taking placebo. The mean number of adverse events from valproate was significantly greater than with placebo.

The descriptions of adverse effects which study authors used varied making pooled analysis of all adverse effects difficult. However, pooled analysis of adverse effects that were reported in more than one study indicated that sedation (OR 2.66, 95% CI 1.44 to 4.92; 228 participants, 2 studies; Analysis 2.1; moderate-quality evidence, downgraded due to imprecision), 'nausea, vomiting and diarrhoea' (OR 6.92, 95% CI 2.13 to 22.49; 381 participants, 3 studies; Analysis 2.2; moderate-quality evidence, downgraded due to imprecision), and UTIs (OR 3.07, 95% CI 1.05 to 8.97; 228 participants, 2 studies; Analysis 2.3; moderate-quality evidence, downgraded due to imprecision) were more frequently reported among valproate-treated participants than placebo-treated participants. Falls, respiratory, skin or joint problems, and infections (other than UTI) were no more frequent in valproate-treated than in placebo-treated participants.

One study reported thrombocytopenia in 6/87 participants in the valproate group and 0/85 participants in the placebo group (Tariot 2001). One study reported thrombocytopenia in 2/14 participants during the treatment phase and none in the placebo phase (Herrmann 2007). In Porsteinsson 2001, 2/28 participants in the divalproex group had developed a significant decrease in platelet count, but not to the level of thrombocytopenia. Sival 2002 monitored blood counts, but reported no instances of a drop in platelet count.

Serious adverse events

The included studies varied in the reporting of serious adverse events (SAE) during their treatment period. Sival 2002 did not report the incidence of SAE during their study. Herrmann 2007 did not report numbers of participants who experienced SAE clearly, but the study stated that two participants in the treatment phase had falls that rated as SAEs. There was no indication given about whether these falls were considered related to the study medication and it was not clear whether these were the only SAEs to occur. Tariot 2005 also did not report specifically on numbers of SAEs although there was one death in the drug-treatment group which was not considered related to the study drug. The authors stated that most adverse events were rated as mild to moderate in severity and were judged as not related to the study drug. Porsteinsson 2001 reported four SAEs, one in the placebo group (worsening of chronic renal failure) and three in the divalproex group (one with seizure, cerebrovascular accident, and pneumonia; one with seizure; and one with small bowel obstruction). Tariot 2001 reported one SAE due to hyponatraemia in the divalproex group, which was thought probably to be related to the study drug. Six other participants experienced SAEs, five in the divalproex group and one in the placebo group. These SAEs were four hospitalisations (for cellulitis, dehydration, pneumonia, myocardial infarc-

tion, and constipation) and one cerebrovascular accident; all were considered to be unrelated to the study drug.

Pooled analysis of the number of SAEs for the two studies which did report data indicated that participants treated with valproate were more likely to experience SAEs (OR 4.77, 95% CI 1.00 to 22.74; 228 participants, 2 studies; Analysis 2.28; very low-quality evidence, downgraded due to risk of bias, inconsistency, and imprecision) (Porsteinsson 2001; Tariot 2001).

Dropouts

All included studies reported that there were participants who dropped out during the study period. For most studies, the number of dropouts were not disproportionate between the treatment and the placebo groups (Porsteinsson 2001: 7% divalproex versus 14% placebo; Sival 2002: 0% valproate versus 5% placebo; Tariot 2005: 15% divalproex versus 18% placebo; Herrmann 2007: 7% valproate versus 7% placebo). However, in the study by Tariot 2001, a disproportionate number of participants in the treatment group dropped out of the study (54% divalproex versus 29% placebo), with 22% from the treatment group compared to only 4% of the placebo group withdrawing due to adverse events. These adverse events were predominantly related to somnolence but also included hyponatraemia, accidents, and weight loss. Due to this disproportionate level of withdrawal in the divalproex group, the study was terminated early.

DISCUSSION

Summary of main results

We found no evidence of a beneficial effect of valproate on our primary outcome of agitation or closely related behavioural outcomes, measured using several outcome scales. Neither did we find evidence of any important effect on any of our secondary efficacy outcomes. However, participants taking valproate may have been at higher risk of adverse effects, including SAEs. These findings are described in Summary of findings for the main comparison.

Specifically, our results showed that there was probably little or no effect on agitated and aggressive behaviours as measured by the BPRS. There was very low-quality evidence using other scales, but results were consistent with this finding. Pooled analysis also indicated probably slightly worse function in the valproate-treated group, on functional ability assessed with the PSMS, of uncertain clinical importance. We found very low-quality evidence of no effect on cognition assessed with the MMSE.

Pooled analysis of the numbers of participants who experienced any adverse effect was limited to three of the included studies (Porsteinsson 2001; Tariot 2001; Tariot 2005), but indicated that participants treated with valproate preparations may have been more likely to experience adverse effects than participants taking placebo. Likewise, participants treated with valproate preparations were more likely to experience SAEs, although the quality of this evidence was very low (data from two studies; Porsteinsson 2001; Tariot 2001). Individual adverse effects which were found in one or more studies to be more frequent in the valproate-treated group were sedation, gastrointestinal symptoms, and UTI.

Overall completeness and applicability of evidence

The small number of included studies, some of which involved small numbers of participants, limited the evidence available. This was further limited since one study closed prematurely and that separate first-phase data were not available from the cross-over trials for inclusion in the review analysis (Herrmann 2007 for some data; Sival 2002).

Because of the limited number of participants, it was not possible to analyse secondary objectives such as the effect of valproate therapy on individual manifestations of agitation (e.g. crying out, wandering) or the influence of age, gender, or degree and type of dementia on the response to therapy. The small number of included studies also meant it was not possible to analyse how the response to valproate preparations was influenced by dose and duration of treatment.

The premature termination of one study, in which 47 (54%) treated participants dropped out before the protocol could be completed, severely limited the confidence that could be placed on the conclusion of the study authors that divalproex sodium improved agitation of people with dementia (Tariot 2001). Because so many of the participants did not complete the study treatment period, we did not include data from this study in the pooled efficacy analyses.

Quality of the evidence

We only identified five studies for inclusion in this review and most varied in the outcome measures used to assess impact of treatment with valproate preparations on agitated behaviour thus making comparisons of study outcomes difficult. We found the quality of evidence for most outcomes measures used to be of low or very low quality primarily due to risk of bias, imprecision, and inconsistency in the included studies (because of poorly described methodology, small sample sizes, and heterogeneity of sample groups and treatments used).

Methodological and clinical diversity limited opportunities for pooling data. Specifically, variations in method, type of medication, dosage, duration of treatment, and use of different outcome measures in these studies made it difficult to apply meta-analysis. For example, it was difficult to compare directly studies that employed short-acting sodium valproate (Sival 2002) or longer-acting

divalproex sodium (Porsteinsson 2001; Tariot 2001), and in which the dosage varied more than two-fold (Sival 2002, mean dose 480 mg/day; Tariot 2001, median dose 1000 mg/day; Porsteinsson 2001, mean dose 875 mg/day).

We did not include data from Sival 2002 because we could not obtain first period data as our protocol required. We considered that there was a risk of carryover effects. We also considered that there was a unit of analysis error in the analysis reported in the paper, which failed to account for the cross-over design.

Potential biases in the review process

It is possible that pooling of clinically diverse studies may have concealed important benefits or harms.

Agreements and disagreements with other studies or reviews

The conclusions of this updated review were in keeping with the NICE evidence summary on the use of valproate preparations for agitation and aggression in dementia which stated that such medications were no more effective than placebo, and that adverse effects were more common in people taking them (NICE 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Robust randomised controlled trial evidence regarding valproate preparations for aggression in people who have dementia is limited, and we identified only five studies for inclusion in this review. Evidence from the five trials, including limited pooled analysis of data, did not support the use of valproate preparations to manage agitation in people with dementia, and demonstrated increased frequency of several types of adverse effect, including serious adverse effects.

From the information available, valproate preparations cannot be recommended for the treatment of people with dementia with agitation.

Implications for research

The quality of evidence in this review ranged from moderate to very low on a range of different outcome measures and overall did not indicate any benefit of valproate for the treatment of agitation in people with dementia. As the limited evidence that was available showed no signal of benefit, further investigation may not be justified, particularly in light of the increased risk of adverse effects in this often frail group of people. Research would be better focused on effective non-pharmacological interventions for this patient group, or, for those situations where the behaviours present immediate risk, further evaluation of how other medications, such as antipsychotics, can be used most effectively and safely.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Herrmann 2007

Methods	Randomised, double-blind, placebo-controlled trial. Cross-over design, of 6-week treatment with valproate/placebo, with 2-week washout interval
Participants	Setting: residents of 2 long-term care facilities associated with university-affiliated general hospitals in Canada Diagnosis: AD Inclusion criteria: DSM-IV criteria for primary degenerative dementia, and NINCDS-ADRDA criteria for probable AD of ≥ 1 year's duration; aged > 55 years; MMSE score < 15 (i.e. moderate-to-severe cognitive impairment); NPI total score ≥ 8 Exclusion criteria: significant medical or neurological conditions that could account for cognitive impairment; Hachinski Ischemic Scale score 3; neuroimaging inconsistent with diagnosis of AD; presence of premorbid or current psychiatric diagnoses. No stated clinical evaluation to exclude acute medical illness such as delirium Total number of participants: 14 (12 participants completed, 1 dropout during each treatment phase. 2 additional participants discontinued placebo early but competed all study assessments.) Baseline characteristics • Age: mean 85.6 years (SD 4.5) • Women: 43% • MMSE: mean 4.5 (SD 4.6) • NPI total score: mean 33.4 (SD 23.6) • NPI agitation/aggression score: mean 6.4 (SD 3.5) • CMAI total score: mean 53.4 (SD 15.7) • Number of participants with antidepressant drugs at screening (%): 2 withdrawn from antidepressants before study • Use of cholinesterase inhibitors: not reported • Use of memantine: not reported
Interventions	6 weeks of valproate/placebo followed by 2 weeks of washout period followed by 6 weeks of valproate/placebo Titration of valproate, with a mean daily dose of 1134.6 mg (SD 400.1) Participants underwent a placebo washout of all psychotropic drugs before randomisation
Outcomes	Primary: • Agitation measured with NPI agitation subscale score mean change at 6 weeks Secondary: • BPSD measured by NPI total score, change at 6 weeks • Agitation measured with CMAI, change at 6 weeks • Safety and tolerability
Notes	Cross-over design and small number of participants urge caution in the interpretation of the results of this study
Risk of bias	

Herrmann 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised…." (p. 117) Insufficient information about the sequence generation process to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Initial 1 week of single-blind placebo washout, then "double-blind crossover design" (p. 117) Quote: "patients randomised to receive valproate liquid suspension or an identical placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information. No explanation given regarding who completed outcome measures. Given that the study was described as double-blind, it was likely that the rater was blind to treatment allocation but this is not stated explicitly
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/16 participants dropped out prior to randomisation and were not included in analysis. 1 dropped out during each treatment phase (reasons not stated). 2 additional participants discontinued treatment with placebo early (reasons not stated), but completed all study assessments. Study authors stated that intention-to-treat analysis was completed using last observation carried forward, but incomplete data reported in results table
Selective reporting (reporting bias)	Low risk	Results of the primary and secondary outcome measures specified in methods were reported, as well as frequency of adverse events, but no study protocol was available to determine the prespecified outcome measures
Other bias	Low risk	No other potential source of bias identified.

Porsteinsson 2001

Methods	Multicentre, randomised, double-blind, placebo-controlled study of 6-week treatment placebo/divalproex sodium
Participants	Setting: 7 long-term care facilities in New York Diagnosis: AD, VaD, or mixed dementia Inclusion criteria: probable or possible AD (by DSM-IV and NINCDS-ADRDA criteria or VaD (by DSM-IV) or mixed dementia (by DSM-IV); aged > 60 years; agitation for a minimum of 2 weeks; BPRS score ≥ 3 on items rating tension, hostility, uncooperativeness, or excitement Exclusion criteria: acute medical illness as reflected by history, examination, and laboratory testing. Acute medical illness excluded Best efforts exerted to identify and implement non-pharmacological interventions for the agitation prior to study consideration Total number of participants: 56 (1 dropped out between randomisation and treatment because of agitation, but was included in the analysis) Baseline characteristics • Mean age: placebo: 84.7 (SD 6.0) years; divalproex: 85.3 (SD 8.1) • Women: placebo: 22/28 (79%); divalproex: 17/28 (61%) • Diagnosis: placebo: AD 75%, VaD 18%, mixed 7%; divalproex: AD 68%, VaD 18%, mixed 14% • Number of participants on psychotropic drugs at screening (%): placebo: 79%; divalproex: 68% • Use of cholinesterase inhibitors: not reported • Use of memantine: not reported
Interventions	Divalproex sodium: titrated to mean dose of 826 mg/day; 6-week course Placebo Choral hydrate 250-500 mg given on an as-needed basis. Psychotropic medication was withdrawn before randomisation.
Outcomes	Primary: • BPRS total score, change over 6 weeks • BPRS agitation factor, change over 6 weeks • BPRS hostility factor, change over 6 weeks • CGI, change over 6 weeks Secondary: • Overt Aggression Scale score, change over 6 weeks • CERAD BRSD weighted, change over 6 weeks • CMAI total score, change over 6 weeks • Physical Self-maintenance score, change over 6 weeks • Safety and tolerability
Notes	A physician monitor who did not have access to participants or study personnel determined the optimal dose of divalproex based on written reports from the blinded raters

Risk of bias

Bias	Authors' judgement	Support for judgement

Porsteinsson 2001 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomisation was blocked by site, but no specific information regarding sequence generation process given to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	No information given. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to treatment condition with the exception of a physician-monitor and a pharmacist, neither of whom had contact with the participant, care team, family, or laboratory personnel. The participant's optimal dose was determined by the non-blinded physician on the basis of written reports of adverse effects from the blinded raters, written reports describing change in baseline behavioural target symptoms received from blinded raters, and confidential laboratory data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measures were completed by blinded raters.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant was dropped between randomisation and treatment because of agitation, this participant was included in analysis. 2 participants dropped out from the divalproex group, due to bowel obstruction, and due to respiratory and urinary tract infections, delirium, and seizures. 4 participants dropped out from the placebo group, due to increased agitation. Data from participants who dropped out were included in analysis. Efficacy data were analysed according to intention-to-treat principles, using last observation carried forward for subjects who dropped out after randomisation
Selective reporting (reporting bias)	Low risk	Results of the primary and secondary outcome measures specified in methods were reported, as well as frequency of adverse events, but no study protocol was available to determine the prespecified outcome measures

Porsteinsson 2001 (*Continued*)

Other bias	Low risk	Study supported by "an unrestricted investigator-initiated grant from Abbott Laboratories. Divalproex Sodium was donated by Abbott Park Laboratories."

Sival 2002

Methods	Randomised, double-blind, placebo-controlled, cross-over design study of sodium valproate
Participants	Setting: psychogeriatric short-stay ward at a psychiatric teaching hospital in the Netherlands Diagnosis: dementia (by DSM-IV and NINCDS-ADRDA criteria) Inclusion criteria: people with aggressive behaviour and senile dementia according to the criteria of the DSM-IV and NINCDS-ADRDA and who met Patel's criteria and also had a score of 3 on ≥ 1 of the items of the SDAS-9. Aggressive behaviour was defined according to Patel's description (Patel 1993): aggressive behaviour is an overt act, involving the delivery of noxious stimuli to (but not necessarily aimed at) another object, organism, or self, which is clearly not accidental Exclusion criteria: another diagnosis besides dementia at Axis 1 of the DSM-IV; epilepsy or epileptic activity according to EEG; myocardial infarction < 3 months prior to the study, cardiac arrhythmia requiring acute medical treatment; liver insufficiency, renal failure, myelodysplasia, and blood dyscrasias; using sodium valproate previously; alcohol or substance abuse, or both; using depot antipsychotics or fluoxetine within 30 days before the start of the trial. No stated clinical evaluation to exclude acute medical illness such as delirium Total number of participants: 43 (1 participant excluded due to protocol violation, and 3 participants dropped out) Baseline characteristics • Age: mean80.4 years (SD 6.8) • Women: 59.5% • Diagnosis: AD 54.8%, VaD 9.5%, dementia in PD 2.4%, mixed 31%, other dementia 2.4% • MMSE: 11.4 (SD 5.0) • CDR: light 4.8%, moderate 57.1%, severe 38.1% • Number of participants on psychotropic drugs at screening (%): not reported • Use of cholinesterase inhibitors: not reported • Use of memantine: not reported
Interventions	Sodium valproate 240 mg twice daily. Oxazepam 10-30 mg/day given if required for severe anxiety. Baseline extended by 1 week where SDAS-9 score was not > 2 Psychotropic medication was withdrawn before randomisation. Baseline period (1 week), placebo period (3 weeks), washout period with placebo (1 week), and treatment period with sodium valproate (3 weeks) - sequence of the treatment periods was assigned at random

Outcomes	Primary: • SDAS-9, mean change at end of each treatment period • CGI scale, mean change at end of each treatment period Secondary: • GIP scale, mean change at end of each treatment period • Safety and tolerability
Notes	Participants who withdrew from the study were excluded from analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the sequence of the treatment periods was assigned at random. The code was not accessible for the investigators" (p. 581) No specific information regarding sequence generation process given to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Low risk	Quote: "The code was not accessible for the investigators" (p. 581)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study design. Used a placebo suspension, identical to the active medication in appearance, quantity, smell, and taste. Participants and investigators blinded to treatment allocation. A pharmacist and an independent physician dealt with laboratory values, including peak valproate levels, outside the normal range. They had no contact with the participants, investigators, the ward team, or participant's relatives
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind study. Outcome assessments made by geriatrician and research nurse, but not explicitly stated if they were blind to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants were considered dropouts and excluded from analysis in case of severe adverse reactions or in case of violation of the protocol. 1/43 participants left out of analysis due to protocol violation, and there were 2 dropouts during placebo period, and 1 dropout during washout period (reasons given and not associated with valproate treatment) and not included in anal-

Sival 2002 (*Continued*)

		ysis
Selective reporting (reporting bias)	Low risk	Results of the primary and secondary outcome measures specified in methods were reported, as well as frequency of adverse events, but no study protocol was available to determine the prespecified outcome measures
Other bias	Low risk	No other potential source of bias identified.

Tariot 2001

Methods	6-week randomised, double-blind, placebo-controlled, parallel-group, multicentre study
Participants	Setting: nursing home residents in USA Diagnosis: probable or possible AD type or VaD Inclusion criteria: residents of long-term care facilities, aged ≥ 65 years; diagnosis that met DSM-IV criteria for DAT or VaD, or both; exhibited manic symptoms. Manic symptoms defined using the Bech-Rafaelsen Mania Scale and 6 items of the BPRS. Participants were required to have a BRMS total score ≥ 15; BPRS score ≥ 3 on ≥ 2 of the following items: tension, grandiosity, hostility, suspiciousness, unco-operativeness, and excitement; and BPRS total score ≥ 15; people had to be able to take oral medications; expected to remain in the same facility throughout the study Exclusion criteria: dementia other than DAT or VaD, or both; delirium; seizure disorders; uncontrolled gastrointestinal, renal, hepatic, endocrine, cardiovascular, pulmonary, immunological, or haematological disease; history of alcohol abuse or substance abuse; history of, or current, hepatitis A, B, or C infection or pancreatitis; and platelet count < 100×10^9/L prior to randomisation; acute systemic medical disorders that could confound interpretation of results or affect compliance; medical conditions requiring the continuous use of medication that would interfere with the assessment of safety or efficacy of divalproex sodium; delirium Total number of participants: 173 (87 divalproex, 85 placebo). 1 participant excluded after randomisation as they could not swallow the study medication Baseline characteristics • Mean age: divalproex: 83.1 (SD 6.7) years, placebo: 83.6 (SD 7.5) years • Women: divalproex: 66%, placebo: 64% • MMSE: divalproex: 7.1 (SD 0.75), placebo: 7.7 (SD 0.77) • Number of participants on psychotropic drugs at screening (%): not reported • Use of cholinesterase inhibitors: allowed, if on stable dose • Use of memantine: not reported
Interventions	Divalproex sodium: starting dose 125 mg twice daily, titrated in increments of 125 mg/day to target dose of 20-30 mg/kg. Median dose 1000 mg/day Psychotropic medication was withdrawn at least 7 days before randomisation. Lorazepam, oxazepam, or chloral hydrate were permitted as needed

Tariot 2001 (*Continued*)

Outcomes	Primary: • BRMS (11-item observer-based scale that rates the severity of manic symptoms), change at end point • CMAI, change at end point • CMAI verbally agitated behaviour subscale, change at end point • CMAI aggressive behaviour subscale, change at end point • CMAI physically non-aggressive behaviour subscale, change at end point • BPRS, change at end point • CGI, change at end point Secondary: • Safety and tolerability
Notes	Study terminated prematurely due to a high number of dropouts in the active treatment group compared to placebo. 54% of divalproex sodium-treated participants dropped out compared to 29% of placebo-treated participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Following screening/washout period patients were randomly assigned in a 1:1 ratio" (p. 54). Insufficient information about the sequence generation process to permit judgement of low risk or high risk
Allocation concealment (selection bias)	Unclear risk	No information given. Insufficient information to permit judgement of low risk or high risk
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as a double-blind study but explicit statement that all staff were blinded to allocation not made except for the fact that the clinicians completing the outcome assessment measures were blinded. Total serum valproate levels were measured weekly and monitored by nursing staff - it was not stated whether these nursing staff were involved with the study/blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinician who completed the outcome assessment measures were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Based on an interim analysis indicating a disproportionate number of dropouts (due to adverse events) in the active-treatment group versus the placebo group, the trial

Tariot 2001 (*Continued*)

		was suspended (47/87 participants in divalproex group and 25/85 participants in placebo group withdrew prematurely. 22% of participants in divalproex group vs 4% in participants in placebo group due to adverse effects. Intention-to-treat analysis carried out using last observation carried forward method. For those participants who discontinued early, final assessment carried out on the last day they were in the study. The previous assessment was used as an estimate of the missing assessment
Selective reporting (reporting bias)	Low risk	Results of the primary and secondary outcome measures specified in methods were reported, as well as frequency of adverse events, but no study protocol was available to determine the prespecified outcome measures
Other bias	Low risk	This study was supported by a grant from Abbott Laboratories

Tariot 2005

Methods	Prospective, multicentre, randomised, double-blind, placebo-controlled, parallel-arm, flexible-dose study
Participants	Setting: nursing home residents in USA Diagnosis: AD Inclusion criteria: diagnosis of probable or possible AD according to the NINCDS-ADRDA criteria; MMSE score 4-24; aged > 49 years; residing in a nursing home; and having at least a 2-week history of agitation associated with a total score > 14 on the 18-item BPRS and score > 2 on items assessing tension, hostility, unco-operativeness, or excitement at screening and baseline. People were ambulatory or ambulatory-aided, and in stable medical condition Exclusion criteria: clinically significant active medical conditions, other psychiatric or CNS disorders; modified Hachinski Ischemia Score. Excluded "clinically significant active medical conditions, other psychiatric or CNS disorders." Total number of participants: 153 (75 divalproex sodium, 78 placebo) Baseline characteristics • Mean age: placebo: 83.9 (SD 5.9) years, divalproex: 84.2 (SD 6.6) years • Women: placebo: 73%, divalproex: 63% • MMSE: placebo: 10.8 (SD 5.4), divalproex: 10.5 (SD 4.9) • BPRS agitation score, mean: placebo: 8.2 (SD 3.3), divalproex: 8.3 (SD 3.0) • BPRS total score, mean: placebo: 33.4 (SD 10.0), divalproex: 35.0 (SD 9.1) • CMAI total score, mean: placebo: 36.4 (SD 15.8), divalproex: 35.6 (SD 16.4) • PSMS score, mean: placebo: 17.8 (SD 5.0), divalproex: 17.5 (SD 5.2) • Number of participants on psychotropic drugs at screening (%): not reported

Tariot 2005 (*Continued*)

	• Use of cholinesterase inhibitors: permitted • Use of memantine: not reported
Interventions	Divalproex sodium delayed-release tablets or placebo given for 6 weeks. Dosage titrated to 500-1000 mg/day All psychoactive drugs stopped 7 days prior to randomisation Psychotropic medication was withdrawn at least 7 days before randomisation. Zolpidem or lorazepam (or both) were permitted for severe agitation or sleep-induction as needed
Outcomes	Primary: • BPRS, change in agitation factor (items relating to anxiety, tension, and excitement) Secondary: • ADCS • CGIC (index of clinical efficacy), change between baseline and 3 and 6 weeks • CMAI, change between baseline and 3 and 6 weeks • PSMS, change between baseline and 6 weeks • MMSE, change between baseline and 6 weeks • Frequency of rescue medication • Safety and tolerability
Notes	Study represents the extension of an earlier pilot study that investigated the safety and tolerability of divalproex (Porsteinsson 2001). The authors concluded that diarrhoea and decreased platelet counts were more common among divalproex-treated participants and that divalproex sodium offered no advantage, compared with placebo, in the management of people with dementia with agitation and should not be used as a first-line treatment for this condition

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were assigned to one of two treatment groups in permuted blocks of 4, in accordance with a randomisation list created and maintained by the ADCS data management centre. Investigators sequentially assigned a randomisation number to each participant. No individual randomisation code was revealed during the trial" (p. 2)
Allocation concealment (selection bias)	Low risk	The randomisation list was created and maintained by the ADCS data management centre. No individual randomisation code was revealed during the trial

Tariot 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were assigned to double-blind treatment. All investigators blinded to treatment allocation. Drug and placebo tablets were visually identical. Masked valproate levels were obtained
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators blinded, study authors stated that no individual randomisation code was broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/75 participants in divalproex group and 14/78 participants in placebo group discontinued treatment early (specific reasons for discontinuation not given). Participants who discontinued prematurely were seen for a final evaluation. Primary analysis performed according to intention-to-treat principle
Selective reporting (reporting bias)	Low risk	Results of the primary and secondary outcome measures specified in methods were reported, as well as frequency of adverse events, but no study protocol was available to determine the prespecified outcome measures
Other bias	Low risk	Quote: "Laboratories Inc provided unrestricted supplemental and material support for this study."

AD: Alzheimer's disease; ADCS: Alzheimer's Disease Cooperative Study Activities ; BPRS: Brief Psychiatric Rating Scale; BPSD: behavioural and psychological symptoms associated with dementia; CDR: Clinical Dementia Rating; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CMAI: Cohen-Mansfield Agitation Index; CNS: central nervous system; DAT: dementia of the Alzheimer type; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EEG: electroencephalograph; GIP: Behavior Observation Scale of Intramural Psychogeriatric Patients; MMSE: Mini-Mental State Examination; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NPI: Neuropsychiatric Inventory; PD: Parkinson's disease; SD: standard deviation; SDAS-9: 9-item Social Dysfunction and Agitation Scale; VaD: vascular dementia.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Forester 2007	Not randomised, no concealed allocation
Goldberg 1999	Not randomised placebo controlled
Gupta 1998	Not randomised placebo controlled
Haas 1997	Not randomised placebo controlled
Horne 1995	Not randomised placebo controlled
Kasckow 1997	Not randomised placebo controlled
Lott 1995	Not randomised placebo controlled
Mazure 1992	Not randomised placebo controlled
Mellow 1993	Not randomised placebo controlled
Narayan 1997	Not randomised placebo controlled
Niedermier 1998	Not randomised placebo controlled
Porsteinsson 1997	Not randomised placebo controlled
Sandborn 1995	Not randomised placebo controlled
Sival 1994	Not randomised placebo controlled
Takahashi 1996	Not randomised placebo controlled
Tariot 2002	Not randomised placebo controlled

DATA AND ANALYSES

Comparison 1. Valproate preparations versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Brief Psychiatric Rating Scale (BPRS) total score. Change from baseline at 6 weeks (intention to treat (ITT))	2	203	Mean Difference (IV, Fixed, 95% CI)	0.23 [-2.14, 2.59]
2 BPRS agitation factor. Change from baseline at 6 weeks (ITT)	2	203	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.49, 0.15]
3 Cohen-Mansfield Agitation Index. Total Score. Change from baseline at 6 weeks (ITT)	3	217	Mean Difference (IV, Fixed, 95% CI)	-1.84 [-6.02, 2.34]
4 BPRS hostility factor. Change from baseline at 6 weeks (ITT)	1	55	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.12, 1.32]
5 Overt Aggression Scale total score. Change from baseline at 6 weeks (ITT)	1	55	Mean Difference (IV, Fixed, 95% CI)	0.10 [-3.42, 3.62]
6 Neuropsychiatric Inventory total score. Change from baseline at 6 weeks (ITT)	1	14	Mean Difference (IV, Fixed, 95% CI)	15.28 [-5.19, 35.75]
7 Neuropsychiatric Inventory Agitation/Aggression subscore. Change from baseline at 6 weeks (ITT)	1	14	Mean Difference (IV, Fixed, 95% CI)	1.43 [-2.48, 5.34]
8 Mini-Mental State Examination total score. Change from baseline at 6 weeks (ITT)	3	217	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.61, 0.20]
9 Physical Self-Maintenance Scale total score. Change from baseline at 6 weeks (ITT)	2	203	Mean Difference (IV, Fixed, 95% CI)	1.19 [0.40, 1.98]

Comparison 2. Divalproex versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total number of participants with sedation at 6 weeks	2	228	Odds Ratio (M-H, Fixed, 95% CI)	2.66 [1.44, 4.92]
2 Total number of participants with nausea, vomiting, or diarrhoea at 6 weeks	3	381	Odds Ratio (M-H, Fixed, 95% CI)	6.92 [2.13, 22.49]

3 Total number of participants with a urinary tract infection by 6 weeks	2	228	Odds Ratio (M-H, Fixed, 95% CI)	3.07 [1.05, 8.97]
4 Total number of participants who had falls by 6 weeks	2	209	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.71, 2.79]
5 Total number of participants with general disorders by 6 weeks	1	153	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [1.05, 4.36]
6 Total number of participants with postural instability by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	4.5 [0.47, 43.09]
7 Total number of participants with weakness by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	10.47 [0.54, 204.32]
8 Total number of participants with cardiovascular problems by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [0.18, 24.31]
9 Total number of participants with oedema by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	7.82 [0.39, 158.87]
10 Total number of participants with a fever by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	7.82 [0.39, 158.87]
11 Total number of participants with a respiratory problem by 6 weeks	2	209	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.33, 2.46]
12 Total number of participants with ataxia at 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.28, 6.87]
13 Total number of participants with a skin problem at 6 weeks	3	381	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.55, 1.91]
14 Total number of participants with trauma (other than falls) by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.10, 4.17]
15 Total number of participants with thrombocytopenia by 6 weeks	1	172	Odds Ratio (M-H, Fixed, 95% CI)	13.64 [0.76, 245.98]
16 Total number of participants with joint problems by 6 weeks	2	209	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.35, 2.05]
17 Total number of participants with other infection by 6 weeks	3	381	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.70, 2.45]
18 Total number of participants with hallucinations by 6 weeks	1	56	Odds Ratio (M-H, Fixed, 95% CI)	3.11 [0.12, 79.64]
19 Total number of participants with accidental injury by 6 weeks	2	325	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.84, 2.50]
20 Total number of participants with anorexia by 6 weeks	1	172	Odds Ratio (M-H, Fixed, 95% CI)	2.53 [0.92, 6.92]
21 Total number of participants with weight loss by 6 weeks	1	172	Odds Ratio (M-H, Fixed, 95% CI)	2.77 [0.71, 10.81]
22 Total number of participants with dehydration by 6 weeks	1	172	Odds Ratio (M-H, Fixed, 95% CI)	3.63 [0.73, 18.01]
23 Total number of participants with metabolism and nutritional disorders by 6 weeks	1	153	Odds Ratio (M-H, Fixed, 95% CI)	3.30 [0.65, 16.92]

24 Total number of participants with psychiatric disorders by 6 weeks	1	153	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.71, 3.66]
25 Total number of participants with other gastrointestinal problem by 6 weeks	2	208	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.70, 2.97]
26 Total numbers of participants with nervous system disorders by 6 weeks	1	153	Odds Ratio (M-H, Fixed, 95% CI)	2.42 [1.01, 5.80]
27 Total number of participants with any adverse event by 6 weeks	3	381	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.30, 3.14]
28 Total number of participants with serious adverse events by 6 weeks	2	228	Odds Ratio (M-H, Fixed, 95% CI)	4.77 [1.00, 22.74]

Analysis 1.1. Comparison 1 Valproate preparations versus placebo, Outcome 1 Brief Psychiatric Rating Scale (BPRS) total score. Change from baseline at 6 weeks (intention to treat (ITT)).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 1 Brief Psychiatric Rating Scale (BPRS) total score. Change from baseline at 6 weeks (intention to treat (ITT))

Study or subgroup	Divalproex N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Porsteinsson 2001	28	-6.9 (8.2)	28	-5.9 (6.6)		36.8 %	-1.00 [-4.90, 2.90]
Tariot 2005	72	-4.19 (9.3)	75	-5.13 (9.1)		63.2 %	0.94 [-2.04, 3.92]
Total (95% CI)	**100**		**103**			**100.0 %**	**0.23 [-2.14, 2.59]**

Heterogeneity: $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Valproate preparations versus placebo, Outcome 2 BPRS agitation factor. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 2 BPRS agitation factor. Change from baseline at 6 weeks (ITT)

Study or subgroup	Divalproex N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Porsteinsson 2001	28	-3.6 (2.9)	28	-2.3 (2.5)		33.3 %	-1.30 [-2.72, 0.12]
Tariot 2005	72	-2.08 (3.1)	75	-1.72 (3.1)		66.7 %	-0.36 [-1.36, 0.64]
Total (95% CI)	**100**		**103**			**100.0 %**	**-0.67 [-1.49, 0.15]**

Heterogeneity: Chi^2 = 1.13, df = 1 (P = 0.29); I^2 =11%

Test for overall effect: Z = 1.61 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Valproate preparations versus placebo, Outcome 3 Cohen-Mansfield Agitation Index. Total Score. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 3 Cohen-Mansfield Agitation Index. Total Score. Change from baseline at 6 weeks (ITT)

Study or subgroup	Divalproex N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Herrmann 2007	7	11.7 (13.9)	7	-2.7 (17)		6.6 %	14.40 [-1.87, 30.67]
Porsteinsson 2001	28	-9.5 (22.2)	28	-7.3 (12.3)		19.8 %	-2.20 [-11.60, 7.20]
Tariot 2005	72	-6.7 (15.6)	75	-3.5 (14.5)		73.6 %	-3.20 [-8.07, 1.67]
Total (95% CI)	**107**		**110**			**100.0 %**	**-1.84 [-6.02, 2.34]**

Heterogeneity: $Chi^2 = 4.13$, df = 2 (P = 0.13); $I^2 = 52\%$

Test for overall effect: Z = 0.86 (P = 0.39)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Valproate preparations versus placebo, Outcome 4 BPRS hostility factor. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 4 BPRS hostility factor. Change from baseline at 6 weeks (ITT)

Study or subgroup	Divalproex N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Porsteinsson 2001	28	-1.5 (2.5)	27	-1.6 (2.1)		100.0 %	0.10 [-1.12, 1.32]
Total (95% CI)	**28**		**27**			**100.0 %**	**0.10 [-1.12, 1.32]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.16 (P = 0.87)

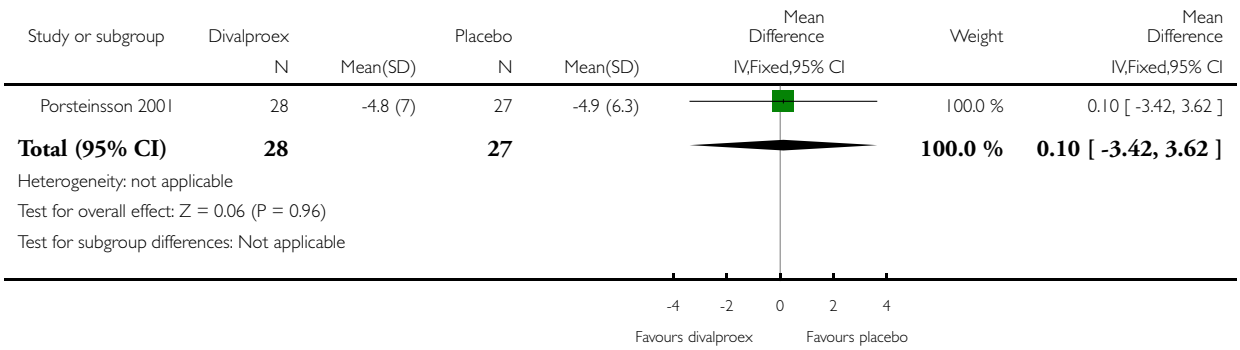
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Valproate preparations versus placebo, Outcome 5 Overt Aggression Scale total score. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 5 Overt Aggression Scale total score. Change from baseline at 6 weeks (ITT)



Analysis 1.6. Comparison 1 Valproate preparations versus placebo, Outcome 6 Neuropsychiatric Inventory total score. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

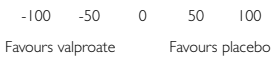
Outcome: 6 Neuropsychiatric Inventory total score. Change from baseline at 6 weeks (ITT)

Study or subgroup	Valproate N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Herrmann 2007	7	11.14 (16.24)	7	-4.14 (22.36)		100.0 %	15.28 [-5.19, 35.75]
Total (95% CI)	**7**		**7**			**100.0 %**	**15.28 [-5.19, 35.75]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Valproate preparations versus placebo, Outcome 7 Neuropsychiatric Inventory Agitation/Aggression subscore. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

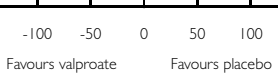
Outcome: 7 Neuropsychiatric Inventory Agitation/Aggression subscore. Change from baseline at 6 weeks (ITT)

Study or subgroup	Valproate N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Herrmann 2007	7	1 (3.51)	7	-0.43 (3.95)		100.0 %	1.43 [-2.48, 5.34]
Total (95% CI)	**7**		**7**			**100.0 %**	**1.43 [-2.48, 5.34]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Valproate preparations versus placebo, Outcome 8 Mini-Mental State Examination total score. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 8 Mini-Mental State Examination total score. Change from baseline at 6 weeks (ITT)

Study or subgroup	Valproate/divalproex		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Herrmann 2007	7	1.71 (4.57)	7	-2.29 (3.64)		4.4 %	4.00 [-0.33, 8.33]
Porsteinsson 2001	28	-1.8 (5.6)	28	-1.6 (6.3)		8.4 %	-0.20 [-3.32, 2.92]
Tariot 2005	72	-0.85 (2.8)	75	0.14 (3.2)		87.2 %	-0.99 [-1.96, -0.02]
Total (95% CI)	**107**		**110**			**100.0 %**	**-0.70 [-1.61, 0.20]**

Heterogeneity: Chi^2 = 4.97, df = 2 (P = 0.08); I^2 =60%

Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Valproate preparations versus placebo, Outcome 9 Physical Self-Maintenance Scale total score. Change from baseline at 6 weeks (ITT).

Review: Valproate preparations for agitation in dementia

Comparison: 1 Valproate preparations versus placebo

Outcome: 9 Physical Self-Maintenance Scale total score. Change from baseline at 6 weeks (ITT)

Study or subgroup	Valproate/divalproex N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Porsteinsson 2001	28	0.4 (2.6)	28	-0.2 (2.2)		39.2 %	0.60 [-0.66, 1.86]
Tariot 2005	72	1.73 (3.5)	75	0.16 (2.7)		60.8 %	1.57 [0.56, 2.58]
Total (95% CI)	**100**		**103**			**100.0 %**	**1.19 [0.40, 1.98]**

Heterogeneity: Chi^2 = 1.38, df = 1 (P = 0.24); I^2 =28%

Test for overall effect: Z = 2.95 (P = 0.0032)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Divalproex versus placebo, Outcome 1 Total number of participants with sedation at 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 1 Total number of participants with sedation at 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	11/28	3/28		14.1 %	5.39 [1.31, 22.25]
Tariot 2001	31/87	17/85		85.9 %	2.21 [1.11, 4.41]
Total (95% CI)	**115**	**113**		**100.0 %**	**2.66 [1.44, 4.92]**

Total events: 42 (Divalproex), 20 (Placebo)

Heterogeneity: Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =18%

Test for overall effect: Z = 3.13 (P = 0.0018)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Divalproex versus placebo, Outcome 2 Total number of participants with nausea, vomiting, or diarrhoea at 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 2 Total number of participants with nausea, vomiting, or diarrhoea at 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	7/28	2/28		52.0 %	4.33 [0.81, 23.10]
Tariot 2001	6/87	1/85		32.7 %	6.22 [0.73, 52.83]
Tariot 2005	7/75	0/78		15.3 %	17.19 [0.96, 306.53]
Total (95% CI)	**190**	**191**		**100.0 %**	**6.92 [2.13, 22.49]**

Total events: 20 (Divalproex), 3 (Placebo)

Heterogeneity: $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 3.22 (P = 0.0013)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Divalproex versus placebo, Outcome 3 Total number of participants with a urinary tract infection by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 3 Total number of participants with a urinary tract infection by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	5/28	3/28		57.6 %	1.81 [0.39, 8.44]
Tariot 2001	9/87	2/85		42.4 %	4.79 [1.00, 22.86]
Total (95% CI)	**115**	**113**		**100.0 %**	**3.07 [1.05, 8.97]**

Total events: 14 (Divalproex), 5 (Placebo)

Heterogeneity: Chi^2 = 0.76, df = 1 (P = 0.38); I^2 =0.0%

Test for overall effect: Z = 2.05 (P = 0.040)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Divalproex versus placebo, Outcome 4 Total number of participants who had falls by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 4 Total number of participants who had falls by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	7/28	5/28		27.2 %	1.53 [0.42, 5.58]
Tariot 2005	16/75	13/78		72.8 %	1.36 [0.60, 3.05]
Total (95% CI)	**103**	**106**		**100.0 %**	**1.40 [0.71, 2.79]**

Total events: 23 (Divalproex), 18 (Placebo)

Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.87); I^2 =0.0%

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

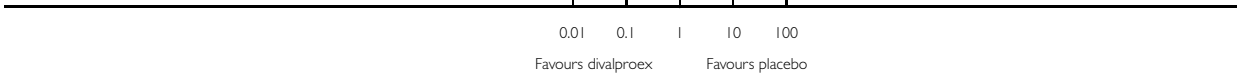
Analysis 2.5. Comparison 2 Divalproex versus placebo, Outcome 5 Total number of participants with general disorders by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 5 Total number of participants with general disorders by 6 weeks

Study or subgroup	Divalproex n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2005	28/75	17/78		100.0 %	2.14 [1.05, 4.36]
Total (95% CI)	**75**	**78**		**100.0 %**	**2.14 [1.05, 4.36]**
Total events: 28 (Divalproex), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.09 (P = 0.037)					
Test for subgroup differences: Not applicable					



Analysis 2.6. Comparison 2 Divalproex versus placebo, Outcome 6 Total number of participants with postural instability by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 6 Total number of participants with postural instability by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	4/28	1/28		100.0 %	4.50 [0.47, 43.09]
Total (95% CI)	**28**	**28**		**100.0 %**	**4.50 [0.47, 43.09]**
Total events: 4 (Divalproex), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
Test for subgroup differences: Not applicable					

Analysis 2.7. Comparison 2 Divalproex versus placebo, Outcome 7 Total number of participants with weakness by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 7 Total number of participants with weakness by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	4/28	0/28		100.0 %	10.47 [0.54, 204.32]
Total (95% CI)	**28**	**28**		**100.0 %**	**10.47 [0.54, 204.32]**
Total events: 4 (Divalproex), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
Test for subgroup differences: Not applicable					

Analysis 2.8. Comparison 2 Divalproex versus placebo, Outcome 8 Total number of participants with cardiovascular problems by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 8 Total number of participants with cardiovascular problems by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	2/28	1/28		100.0 %	2.08 [0.18, 24.31]
Total (95% CI)	**28**	**28**		**100.0 %**	**2.08 [0.18, 24.31]**
Total events: 2 (Divalproex), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: Not applicable					

Analysis 2.9. Comparison 2 Divalproex versus placebo, Outcome 9 Total number of participants with oedema by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 9 Total number of participants with oedema by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	3/28	0/28		100.0 %	7.82 [0.39, 158.87]
Total (95% CI)	**28**	**28**		**100.0 %**	**7.82 [0.39, 158.87]**
Total events: 3 (Divalproex), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
Test for subgroup differences: Not applicable					

Analysis 2.10. Comparison 2 Divalproex versus placebo, Outcome 10 Total number of participants with a fever by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 10 Total number of participants with a fever by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	3/28	0/28		100.0 %	7.82 [0.39, 158.87]
Total (95% CI)	**28**	**28**		**100.0 %**	**7.82 [0.39, 158.87]**
Total events: 3 (Divalproex), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
Test for subgroup differences: Not applicable					

Analysis 2.11. Comparison 2 Divalproex versus placebo, Outcome 11 Total number of participants with a respiratory problem by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 11 Total number of participants with a respiratory problem by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	5/28	0/28		5.0 %	13.34 [0.70, 253.89]
Tariot 2005	2/75	8/78		95.0 %	0.24 [0.05, 1.17]
Total (95% CI)	**103**	**106**		**100.0 %**	**0.90 [0.33, 2.46]**
Total events: 7 (Divalproex), 8 (Placebo)					
Heterogeneity: Chi^2 = 5.90, df = 1 (P = 0.02); I^2 =83%					
Test for overall effect: Z = 0.21 (P = 0.84)					
Test for subgroup differences: Not applicable					

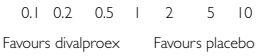
Analysis 2.12. Comparison 2 Divalproex versus placebo, Outcome 12 Total number of participants with ataxia at 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 12 Total number of participants with ataxia at 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	4/28	3/28		100.0 %	1.39 [0.28, 6.87]
Total (95% CI)	**28**	**28**		**100.0 %**	**1.39 [0.28, 6.87]**
Total events: 4 (Divalproex), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Not applicable					

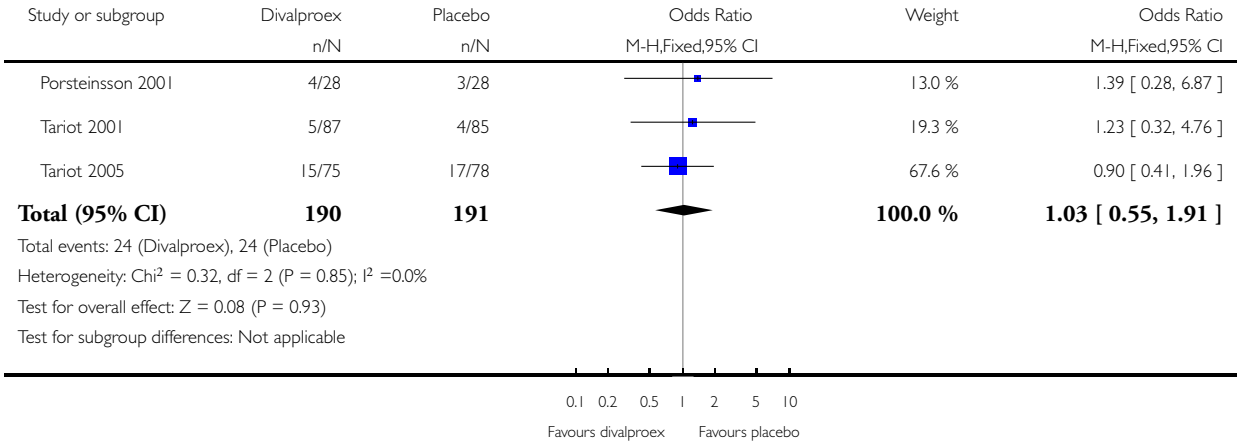


Analysis 2.13. Comparison 2 Divalproex versus placebo, Outcome 13 Total number of participants with a skin problem at 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 13 Total number of participants with a skin problem at 6 weeks

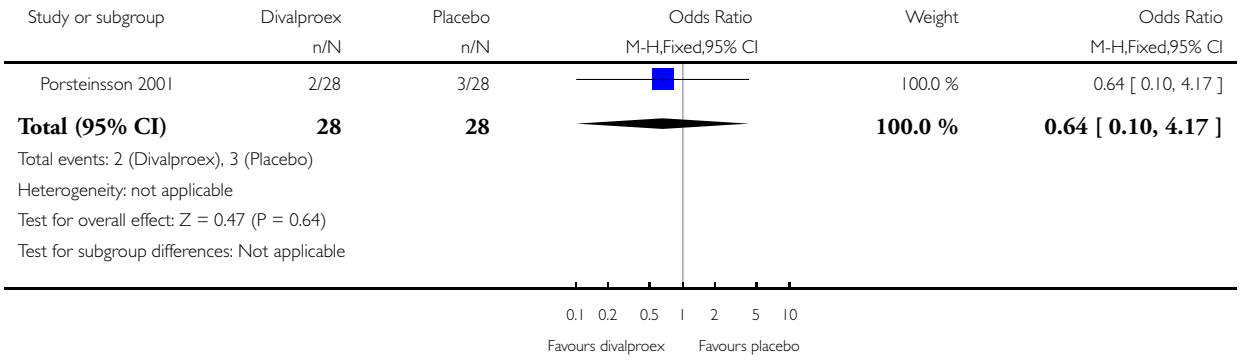


Analysis 2.14. Comparison 2 Divalproex versus placebo, Outcome 14 Total number of participants with trauma (other than falls) by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 14 Total number of participants with trauma (other than falls) by 6 weeks



Analysis 2.15. Comparison 2 Divalproex versus placebo, Outcome 15 Total number of participants with thrombocytopenia by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 15 Total number of participants with thrombocytopenia by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2001	6/87	0/85		100.0 %	13.64 [0.76, 245.98]
Total (95% CI)	**87**	**85**		**100.0 %**	**13.64 [0.76, 245.98]**
Total events: 6 (Divalproex), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.077)					
Test for subgroup differences: Not applicable					

Analysis 2.16. Comparison 2 Divalproex versus placebo, Outcome 16 Total number of participants with joint problems by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 16 Total number of participants with joint problems by 6 weeks

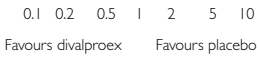
Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	1/28	3/28		27.1 %	0.31 [0.03, 3.16]
Tariot 2005	9/75	9/78		72.9 %	1.05 [0.39, 2.80]
Total (95% CI)	**103**	**106**		**100.0 %**	**0.85 [0.35, 2.05]**

Total events: 10 (Divalproex), 12 (Placebo)

Heterogeneity: $Chi^2 = 0.90$, df = 1 (P = 0.34); $I^2 = 0.0\%$

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable



Analysis 2.17. Comparison 2 Divalproex versus placebo, Outcome 17 Total number of participants with other infection by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 17 Total number of participants with other infection by 6 weeks

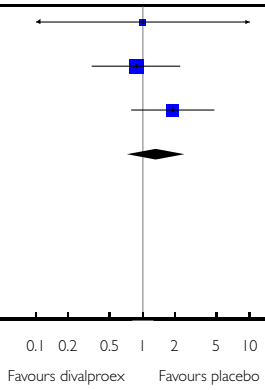
Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	1/28	1/28		5.6 %	1.00 [0.06, 16.82]
Tariot 2001	9/87	10/85		53.1 %	0.87 [0.33, 2.25]
Tariot 2005	15/75	9/78		41.3 %	1.92 [0.78, 4.69]
Total (95% CI)	**190**	**191**		**100.0 %**	**1.31 [0.70, 2.45]**

Total events: 25 (Divalproex), 20 (Placebo)

Heterogeneity: Chi^2 = 1.45, df = 2 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 0.84 (P = 0.40)

Test for subgroup differences: Not applicable



Analysis 2.18. Comparison 2 Divalproex versus placebo, Outcome 18 Total number of participants with hallucinations by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 18 Total number of participants with hallucinations by 6 weeks

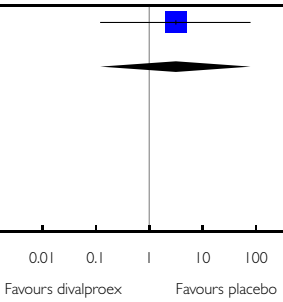
Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	1/28	0/28		100.0 %	3.11 [0.12, 79.64]
Total (95% CI)	**28**	**28**		**100.0 %**	**3.11 [0.12, 79.64]**

Total events: 1 (Divalproex), 0 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable



Analysis 2.19. Comparison 2 Divalproex versus placebo, Outcome 19 Total number of participants with accidental injury by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 19 Total number of participants with accidental injury by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2001	29/87	21/85		65.3 %	1.52 [0.78, 2.96]
Tariot 2005	11/75	9/78		34.7 %	1.32 [0.51, 3.39]
Total (95% CI)	**162**	**163**		**100.0 %**	**1.45 [0.84, 2.50]**

Total events: 40 (Divalproex), 30 (Placebo)

Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 1.35 (P = 0.18)

Test for subgroup differences: Not applicable

Analysis 2.20. Comparison 2 Divalproex versus placebo, Outcome 20 Total number of participants with anorexia by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 20 Total number of participants with anorexia by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2001	14/87	6/85		100.0 %	2.53 [0.92, 6.92]
Total (95% CI)	**87**	**85**		**100.0 %**	**2.53 [0.92, 6.92]**

Total events: 14 (Divalproex), 6 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.80 (P = 0.072)
Test for subgroup differences: Not applicable

Analysis 2.21. Comparison 2 Divalproex versus placebo, Outcome 21 Total number of participants with weight loss by 6 weeks.

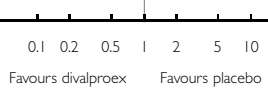
Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 21 Total number of participants with weight loss by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2001	8/87	3/85		100.0 %	2.77 [0.71, 10.81]
Total (95% CI)	**87**	**85**		**100.0 %**	**2.77 [0.71, 10.81]**

Total events: 8 (Divalproex), 3 (Placebo)
Heterogeneity: not applicable
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

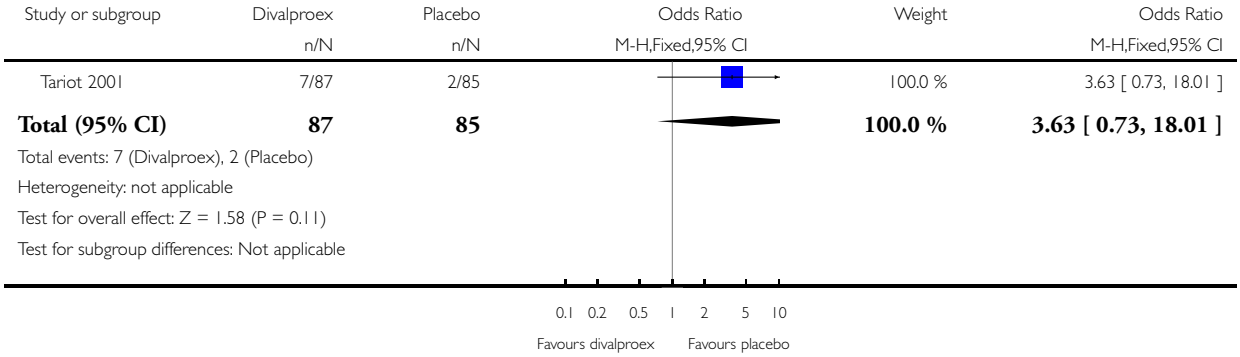


Analysis 2.22. Comparison 2 Divalproex versus placebo, Outcome 22 Total number of participants with dehydration by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 22 Total number of participants with dehydration by 6 weeks

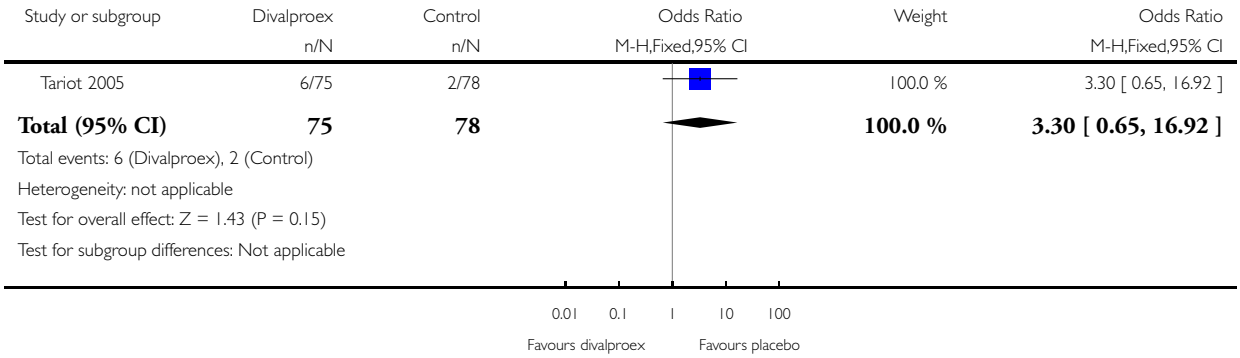


Analysis 2.23. Comparison 2 Divalproex versus placebo, Outcome 23 Total number of participants with metabolism and nutritional disorders by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 23 Total number of participants with metabolism and nutritional disorders by 6 weeks



Analysis 2.24. Comparison 2 Divalproex versus placebo, Outcome 24 Total number of participants with psychiatric disorders by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 24 Total number of participants with psychiatric disorders by 6 weeks

Study or subgroup	Divalproex n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2005	17/75	12/78		100.0 %	1.61 [0.71, 3.66]
Total (95% CI)	**75**	**78**		**100.0 %**	**1.61 [0.71, 3.66]**
Total events: 17 (Divalproex), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.14 (P = 0.25)					
Test for subgroup differences: Not applicable					

Analysis 2.25. Comparison 2 Divalproex versus placebo, Outcome 25 Total number of participants with other gastrointestinal problem by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 25 Total number of participants with other gastrointestinal problem by 6 weeks

Study or subgroup	Divalproex n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	4/28	2/27		14.1 %	2.08 [0.35, 12.45]
Tariot 2005	17/75	14/78		85.9 %	1.34 [0.61, 2.96]
Total (95% CI)	**103**	**105**		**100.0 %**	**1.44 [0.70, 2.97]**
Total events: 21 (Divalproex), 16 (Placebo)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.00 (P = 0.32)					
Test for subgroup differences: Not applicable					

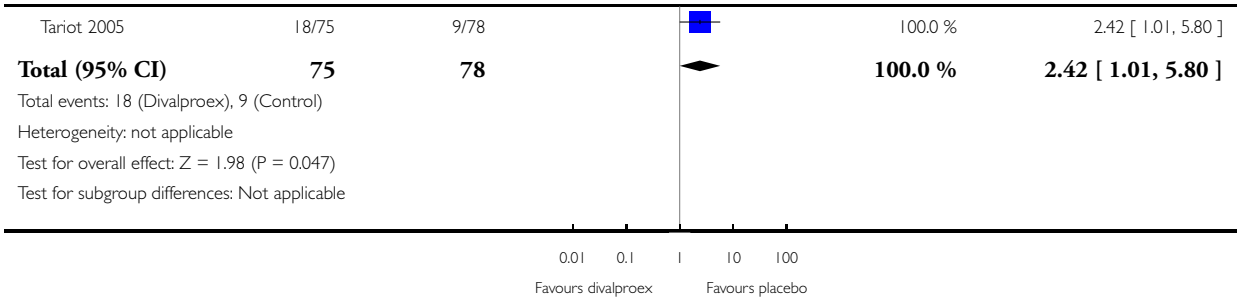
Analysis 2.26. Comparison 2 Divalproex versus placebo, Outcome 26 Total numbers of participants with nervous system disorders by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 26 Total numbers of participants with nervous system disorders by 6 weeks

Study or subgroup	Divalproex n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Tariot 2005	18/75	9/78		100.0 %	2.42 [1.01, 5.80]
Total (95% CI)	**75**	**78**		**100.0 %**	**2.42 [1.01, 5.80]**
Total events: 18 (Divalproex), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.047)					
Test for subgroup differences: Not applicable					



Analysis 2.27. Comparison 2 Divalproex versus placebo, Outcome 27 Total number of participants with any adverse event by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 27 Total number of participants with any adverse event by 6 weeks

Study or subgroup	Divalproex n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Porsteinsson 2001	19/28	9/28		10.3 %	4.46 [1.45, 13.68]
Tariot 2001	72/87	53/85		32.9 %	2.90 [1.43, 5.89]
Tariot 2005	52/75	53/78		56.8 %	1.07 [0.54, 2.11]
Total (95% CI)	**190**	**191**		**100.0 %**	**2.02 [1.30, 3.14]**

Total events: 143 (Divalproex), 115 (placebo)

Heterogeneity: Chi^2 = 6.27, df = 2 (P = 0.04); I^2 =68%

Test for overall effect: Z = 3.12 (P = 0.0018)

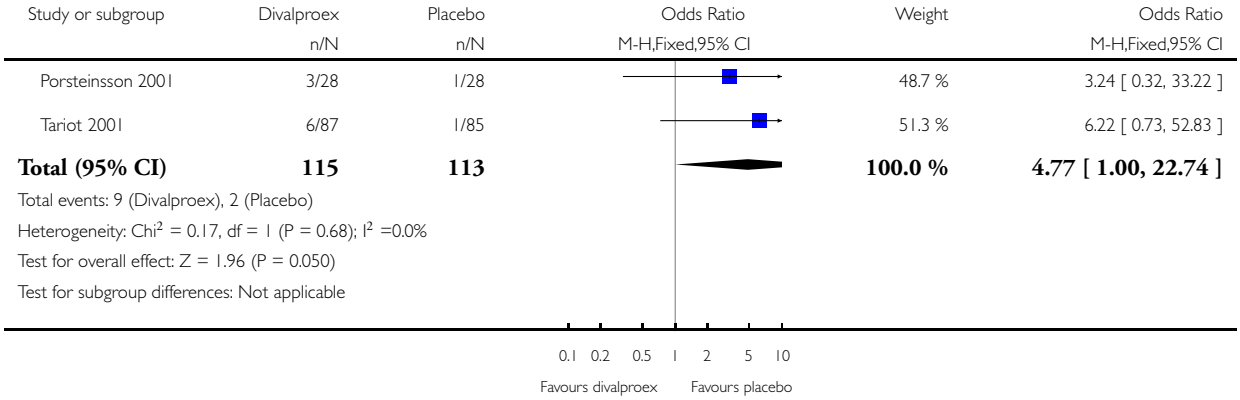
Test for subgroup differences: Not applicable

Analysis 2.28. Comparison 2 Divalproex versus placebo, Outcome 28 Total number of participants with serious adverse events by 6 weeks.

Review: Valproate preparations for agitation in dementia

Comparison: 2 Divalproex versus placebo

Outcome: 28 Total number of participants with serious adverse events by 6 weeks



ADDITIONAL TABLES

Table 1. Baseline characteristics

Name	Country	Population	Mean age (years)	% Women	Intervention	Diagnoses and baseline assessments	Mean MMSE
Herrmann 2007	Canada	Multi-centric, insti-tutionalised; Alzheimer's disease	85.6	42.8	Valproate (n = 14) Placebo (n = 13) Valproate titrated to 1500 mg/day 6-week course	AD: NIND-CDS-ADRDA criteria Agitation/ aggression: CMAI	< 15
Porsteinsson 2001	US	Multi-centric, insti-tutionalised; AD, VaD, and other demen-tias	85.0	61.0	Valproic acid (n = 28) Placebo (n = 28). Divalproex sodium titrated to mean 826	Dementia: MMSE; DSM-IV; NICDS-ADRDA Agitation: CMAI Aggression:	6.8

Table 1. Baseline characteristics (*Continued*)

					mg/day 6-week course	CMAI subscale Global: CGI	
Sival 2002	The Netherlands	Institutionalised, AD, VaD, and other dementias	80.4	59.5	Valproate (n = 42) Placebo (n = 42) Sodium valproate 480 mg/day 3-week course	Dementia: MMSE; DSM-IV; NINCDS-ADRDA; Clinical Dementia Rating Scale Agitation: BPRS subset Aggression: Patel's method; SDAS-9 subscale; CGI; GIP Global: CGI	-
Tariot 2001	US	Multicentric, institutionalised; AD, VaD, and other dementias	83.3	64.0	Valproic acid (n = 87) Placebo (n = 85) Divalproex sodium (delayed release); titrated to target dose of 20 mg/kg/day; median dose 1000 mg/day 6-week course	Dementia: MMSE; DSM-IV Agitation: CMAI Aggression: CMAI subscale Global: CGI	7.4
Tariot 2005	US	Multicentric, institutionalised, AD	84.0	68.6	Divalproex (n = 48) Placebo (n = 78) Titrated to target dose 750 mg/day 6-week course	Dementia (probable or possible): NINDCDS-ADRDA Agitation, hostility, and unco-operativeness: BPRS	10.8

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression Scale; CMAI: Cohen-Mansfield Agitation Inventory; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GIP: Behavior Observation Scale of Intramural Psychogeriatric Patients; MMSE: Mini-Mental State Examination; n: number of participants; NINDCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; SDAS-9: 9-item Social Dysfunction and Agitation Scale; VaD: vascular dementia.

Table 2. Outcomes, instruments, and studies

Outcomes	Instruments	Studies
Agitation and aggression	CMAI	Herrmann 2007; Porsteinsson 2001; Tariot 2001; Tariot 2005
	BPRS or agitation and hostility subscale, or both	Porsteinsson 2001
	BPRS	Tariot 2001; Tariot 2005
	Neuropsychiatric Inventory (NPI)	Herrmann 2007
	Social Dysfunction and Aggression-9 Scale (SDAS-9)	Sival 2002
	Clinical Global Impression Scale (CGI)	Sival 2002
	Nurse Observation Scale	Sival 2002
	Patel's Method	Sival 2002
	Overt Aggression Scale	Porsteinsson 2001
Other types of disturbed behaviour	Behavior Scale for Intramural Psychogeriatric Patients (GIP)	Sival 2002
Cognition	MMSE	Herrmann 2007; Porsteinsson 2001; Tariot 2005
Functional performance	PSMS	Porsteinsson 2001
		Tariot 2005
Overall clinical impression	CGI	Porsteinsson 2001; Tariot 2001; Tariot 2005
Adverse effects	Number of Adverse Reactions (checklist)	Herrmann 2007; Porsteinsson 2001; Sival 2002; Tariot 2005
	Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART 1989)	Tariot 2001

BPRS: Brief Psychiatric Rating Scale; CMAI: Cohen-Mansfield Agitation Inventory; MMSE: Mini-Mental State Examination; PSMS: Physical Self-Maintenance Scale.

APPENDICES

Appendix 1. Sources searched and search strategies

Source	Search strategy	Hits
MEDLINE (OvidSP) [Most recent search: 7 December 2017]	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/ 5. dement*.mp. 6. alzheimer*.mp. 7. (lewy* adj2 bod*).mp. 8. deliri*.mp. 9. (chronic adj2 cerebrovascular).mp. 10. ("organic brain disease" or "organic brain syndrome").mp 11. ("normal pressure hydrocephalus" and "shunt*").mp. 12. "benign senescent forgetfulness".mp. 13. (cerebr* adj2 deteriorat*).mp. 14. (cerebral* adj2 insufficient*).mp. 15. (pick* adj2 disease).mp. 16. (creutzfeldt or jcd or cjd).mp. 17. huntington*.mp. 18. binswanger*.mp. 19. korsako*.mp. 20. or/1-19 21. Valproic Acid/ 22. valproic*.ti,ab. 23. valproate.ti,ab. 24. divalproex*.ti,ab. 25. or/21-24 26. 20 and 25 27. randomised controlled trial.pt. 28. controlled clinical trial.pt. 29. randomized.ab. 30. placebo.ab. 31. drug therapy.fs. 32. randomly.ab. 33. trial.ab. 34. groups.ab. 35. or/27-34 36. (animals not (humans and animals)).sh. 37. 35 not 36 38. 26 and 37 39. (2008* or 2009* or 2010*).ed. 40. 38 and 39	July 2010: 44 October 2016: 14 December 2017: 5

(*Continued*)

Embase (OvidSP) [Most recent search: 7 December 2017]	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/ 6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp. 10. (chronic adj2 cerebrovascular).mp. 11. ("organic brain disease" or "organic brain syndrome").mp 12. "supranuclear palsy".mp. 13. ("normal pressure hydrocephalus" and "shunt*").mp. 14. "benign senescent forgetfulness".mp. 15. (cerebr* adj2 deteriorat*).mp. 16. (cerebral* adj2 insufficient*).mp. 17. (pick* adj2 disease).mp. 18. (creutzfeldt or jcd or cjd).mp. 19. huntington*.mp. 20. binswanger*.mp. 21. korsako*.mp. 22. CADASIL.mp. 23. or/1-22 24. valproic acid/ 25. valproic*.ti,ab. 26. valproate.ti,ab. 27. divalproex*.ti,ab. 28. or/24-27 29. 23 and 28 30. randomised controlled trial/ 31. controlled clinical trial/ 32. randomi?ed.ab. 33. placebo.ab. 34. randomly.ab. 35. trial.ab. 36. groups.ab. 37. or/30-36 38. 29 and 37 39. (2008* or 2009* or 2010*).em. 40. 38 and 39	July 2010: 128 October 2016: 32 December 2017: 76
PsycINFO (OvidSP) [Most recent search: 7 December 2017]	1. exp Dementia/ 2. exp Delirium/ 3. exp Huntingtons Disease/ 4. exp Kluver Bucy Syndrome/ 5. exp Wernickes Syndrome/ 6. exp Cognitive Impairment/	July 2010: 37 October 2016: 11 December 2017: 21

(*Continued*)

	7. dement*.mp. 8. alzheimer*.mp. 9. (lewy* adj2 bod*).mp. 10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp. 16. (cerebr* adj2 deteriorat*).mp. 17. (cerebral* adj2 insufficient*).mp. 18. (pick* adj2 disease).mp. 19. (creutzfeldt or jcd or cjd).mp. 20. huntington*.mp. 21. binswanger*.mp. 22. korsako*.mp. 23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 24. or/1-23 25. Valproic Acid/ 26. valproic*.ti,ab. 27. valproate.ti,ab. 28. divalproex*.ti,ab. 29. or/25-28 30. 24 and 29 31. (2008* or 2009* or 2010*).up. 32. 30 and 31	
CINAHL (EBSCOhost) [Most recent search: 7 December 2017]	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd	July 2010: 15 October 2016: 2 December 2017: 8

(*Continued*)

	S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 (MH "Valproic Acid") S21 TX valproic* S22 TX valproate S23 TX divalproex* S24 S20 or S21 or S22 or S23 S25 S19 and S24 S26 EM 2008 S27 EM 2009 S28 EM 2010 S29 S26 or S27 or S28 S30 S25 and S29	
Web of Knowledge (all databases) [Most recent search: 7 December 2017]	Topic=(dement* OR alzheimer* OR AD OR lewy) AND Topic=(valproic* OR valproate OR divalproex*) AND Topic=(random* OR trial OR placebo OR "double blind*" OR "blinded" OR "single blind*" OR "control group*") Timespan=Latest 5 years.	July 2010: 51 October 2016: 19 December 2017: 21
LILACS (BIREME) [Most recent search: 7 December 2017]	vaproate OR valpric$ OR divalproex$ [Words] and demenc$ OR dement$ OR alzheimer$ OR lewy [Words]	July 2010: 3 October 2016: 0 December 2017: 0
ALOIS (www.medicine.ox.ac.uk/alois) [Most recent search: 7 December 2017]	Keyword search: Valproate OR valproic OR divalproex	July 2010: 13 October 2016: 0 December 2017: 0
CENTRAL (the Cochrane Library) [Most recent search: 7 December 2017]	#1 MeSH descriptor Dementia explode all trees #2 MeSH descriptor Delirium, this term only #3 MeSH descriptor Wernicke Encephalopathy, this term only #4 MeSH descriptor Delirium, Dementia, Amnestic, Cognitive Disorders, this term only #5 dement* #6 alzheimer* #7 "lewy* bod*" #8 deliri* #9 "chronic cerebrovascular" #10 "organic brain disease" or "organic	July 2010: 2 October 2016: 0 December 2017: 15

(*Continued*)

	brain syndrome" #11 "normal pressure hydrocephalus" and "shunt*" #12 "benign senescent forgetfulness" #13 "cerebr* deteriorat*" #14 "cerebral* insufficient*" #15 "pick* disease" #16 creutzfeldt or jcd or cjd #17 huntington* #18 binswanger* #19 korsako* #20 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR # 11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19) #21 MeSH descriptor Valproic Acid, this term only #22 valproic #23 valproate #24 divalproex* #25 (#21 OR #22 OR #23 OR #24) #26 (#20 AND #25), from 2008 to 2010	
ClinicalTrials.gov [Most recent search: 7 December 2017]	Interventional Studies | dementia OR alzhiemer OR alzheimers OR alzheimer's OR agitation | valproate OR valproic OR divalproex	July 2010: 7 October 2016: 0 December 2017: 1
ICTRP (The WHO portal) [Most recent search: 7 December 2017]	Interventional Studies | dementia OR alzhiemer OR alzheimers OR alzheimer's OR agitation | valproate OR valproic OR divalproex AND date rec: 01/01/2008 ? 30/07/2010	July 2010: 4 October 2016: 0 December 2017: 1
Total		February 2008: 109 July 2010: 304 October 2016: 78 December 2017: 148 TOTAL: 639
Total after first assess and deduplication		February 2008: 11 July 2010: 12 October 2016: 4 December 2017: 14 TOTAL: 41

WHAT'S NEW

Last assessed as up-to-date: 7 December 2017.

Date	Event	Description
7 December 2017	New search has been performed	A top-up search was performed for this review on 7 December 2017
7 December 2017	New citation required but conclusions have not changed	No new studies added. Conclusions unchanged. Review revised in line with MECIR standards. New authors added

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 2, 2004

Date	Event	Description
4 November 2016	New search has been performed	An updated search was performed for this review on 04 November 2016. No new studies were identified for either inclusion or exclusion within the review
2 October 2014	New search has been performed	An update search was performed for this review on 30 July 2010. No new studies were identified for either inclusion or exclusion within the review An update search was performed for this review on 02 October 2015. No new studies were identified for either inclusion or exclusion within the review
31 October 2008	New search has been performed	February 2008: A new update search for the review was run. Some possible new studies for inclusion or exclusion were retrieved
31 October 2008	New citation required but conclusions have not changed	October 2008: Two new controlled studies were reviewed (Tariot, 2005; Herrman, 2007).These studies were incorporated into a meta analysis that examined the effect of valproate preparations on agitation as measured by the Cohen-Mansfield Agitation Index score and by the Brief Psychiatric Rating Scale. In addition, meta analysis was uses to examine the frequency of adverse events in valproate patients compared with placebo treated patients Both studies confirmed the Cochrane report of 2004 (Lonergan, 2004) that valproate preparations showed no effect on agitation as compared with placebo con-

(*Continued*)

		trols. Further meta analysis also demonstrated among valproate patients increased adverse events, especially falls, infection, gastrointestinal disorders, and decreased platelet counts compared with placebo treated patients At this time valproate preparations cannot be recommended for the control of agitation in demented patients)
12 August 2005	New search has been performed	Minor update: 12 August 2005. In a new controlled study of the effect of divalproex sodium on agitation in demented patients, reported in abstract form, Tariot and associates (Tariot 2004) were unable to demonstrate any significant difference in agitation among treated patients (target dose of divalproex, 750 mg per day), compared with placebo controls. This study will be reviewed in greater detail when the published article becomes available
11 February 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

SB: drafting of updated review; selection of recent trials; extraction of data; interpretation of data analyses; updated review 2018.

UN: drafting of updated review; selection of recent trials; extraction of data; interpretation of data analyses; updated review 2018.

JL: drafting of review versions; selection of trials; extraction of data; interpretation of data analyses; original review 2004, updated review 2009, and updated review 2018.

AC: drafting of updated review; correspondence; selection of recent trials; extraction of data; interpretation of data analyses; updated review 2018.

E Lonergan (previous review author): drafting of review versions; correspondence; selection of trials; extraction of data; entry of data; interpretation of data analyses original review 2004 and updated review 2009.

Ann Ludvik: consumer editor.

This review was peer reviewed anonymously in April 2004.

DECLARATIONS OF INTEREST

SB: none known.

UN: none known.

JL: none known.

AC: none known.

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Internal sources

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Employing institution for S Baillon

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Employing institute of A Clifton

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- NIHR, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In many of the studies that the searches identified, the reporting of baseline clinical evaluation was not always specific or detailed. We took a pragmatic approach to avoid risking the loss of relevant evidence and included studies despite this information not being explicitly reported.

If an included study was discontinued due to a high level of dropout and adverse effects experienced by the treatment group, we decided that this presented a high risk of attrition bias and so excluded data from the pooled analysis from the outcome measures.

One of the aims stated in the protocol was to examine the effect of valproate preparations on carer burden. All of the included studies were carried out in long-term care settings and not in the community; consequently, none of the studies attempted to assess carer burden, and so analysis of such effects was not possible.

The original protocol proposed analysis treatment efficacy by type of dementia, degree of dementia, age, and sex if number of participants was sufficient. The low number of included studies meant that the number of participants were not sufficient for such subgroup analysis.

The original protocol stated participants receiving more than one psychopharmacological agent at the time of the study would be excluded from the report. In this 2018 updated review, we excluded participants receiving chronic therapy with other psychoactive medications from the review except for those studies where treatment with an additional psychotropic medication was permitted in the study protocol. Participants receiving treatment for dementia with cholinesterase inhibitors or memantine or receiving long-term unchanged antidepressant treatment were not excluded from the review. Often clear information regarding concomitant medication was not reported.

The original protocol proposed analysis of effect of treatment on one or more specific aspects of agitation. The low number of included studies meant that the number of participants were not sufficient for such analysis.

The original protocol proposed analysis of effect of treatment of different forms of valproic acid (e.g. divalproex versus sodium valproate). The number of included studies was too low to enable such analysis. It was also proposed to determine if the response to treatment was influenced by the dose or duration of treatment. Four of the five included studies involved the same duration of treatment preventing assessment of the impact of duration of treatment, and all studies varied in terms of the medication and dose used. The number of studies included was too low to enable any analysis of these aspects of the treatment.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimanic Agents [adverse effects; *therapeutic use]; Dementia [*complications]; Psychomotor Agitation [*drug therapy; etiology]; Randomized Controlled Trials as Topic; Treatment Outcome; Valproic Acid [adverse effects; *therapeutic use]

MeSH check words

Aged; Humans