Management of aggression, agitation and behavioural disturbances in dementia: valproate preparations

Evidence summary
Published: 10 March 2015
nice.org.uk/guidance/esuom41

Key points from the evidence

The content of this evidence summary was up-to-date in March 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Evidence from randomised controlled trials (RCTs) suggests that valproate preparations (including sodium valproate and valproate semisodium) are no more effective than placebo for treating agitation or behavioural disturbances in people with dementia. Adverse effects such as falls, sedation, gait disturbances, tremor, muscular weakness, thrombocytopenia, gastrointestinal disorders and urinary tract infections were more common in people taking valproate preparations than placebo.

Regulatory status: off-label. This topic was prioritised because there is uncertainty about the balance of risks and benefits of valproate preparations for this indication.
<table>
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<tr>
<th>Effectiveness</th>
<th>Safety</th>
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<tr>
<td>• No statistically significant difference between valproate preparations and placebo after 6 weeks' treatment for change from baseline on the Cohen Mansfield Agitation Inventory score in people with dementia (meta-analysis of 3 RCTs, n=216).</td>
<td>• Nausea and tremor are very common adverse effects (occurring in 10% or more people) of valproate preparations (Epilim summary of product characteristics).</td>
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<td>• No statistically significant difference between valproate semisodium and placebo after 24 months' treatment in time to development of clinically significant agitation or psychosis in people with Alzheimer's disease (1 RCT; n=313).</td>
<td>• Meta-analysis of 4 RCTs (n=394) showed about double the rate of any adverse at 6 weeks among participants taking valproate preparations compared with those taking placebo.</td>
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<th>Patient factors</th>
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<td>• Dropout rates in the largest RCT were high (around 61% in both groups). Dropout rates due to adverse effects were 16.3% in the valproate semisodium group and 7.5% in the placebo group (1 RCT; n=313).</td>
<td>• The dosages of sodium valproate or valproate semisodium used in the studies varied.</td>
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**Introduction and current guidance**

According to the NICE guideline on dementia and a best practice guide produced by the Alzheimer's Society and endorsed by the Department of Health, non-pharmacological interventions tailored to the individual person's preferences, skills and abilities are recommended first line. NICE advises that people with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a 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. Treatment with an antipsychotic drug may be offered after various conditions have been met. An acetylcholinesterase inhibitor or memantine may be offered in some circumstances.
Other drugs have been used off-label for non-cognitive symptoms of dementia; however, evidence to support their use is limited. The NICE full guideline on dementia concluded that there was insufficient evidence to support the use of anticonvulsant mood stabilisers, such as sodium valproate, valproate semisodium or carbamazepine, for the treatment of depression or anxiety in people with dementia. This evidence summary reviews the best available evidence for the use of valproate preparations for managing aggression, agitation and behavioural disturbances in dementia. It includes a Cochrane review which included the 3 studies on valproate preparations that were considered by NICE (Porsteinsson et al. 2001, Sival et al. 2002 and Tariot et al. 2001) and 2 additional studies. Another evidence summary considers carbamazepine for these indications.

Full text of introduction and current guidance.

Product overview

Sodium valproate is available in a variety of standard-release oral preparations which are licensed for the treatment of epilepsy. It is also available in a variety of prolonged and modified-release preparations; licensed indications for these vary according to the preparation (see individual summaries of product characteristics for details). Valproate semisodium (also known as divalproex sodium; Depakote) is licensed for the treatment of manic episodes in bipolar disorder when lithium is contraindicated or not tolerated.

None of the valproate preparations are licensed for the management of aggression, agitation and behavioural disturbances in dementia, therefore using any of them for this indication is off-label.

In January 2015, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued new information and strengthened warnings relating to the risk of abnormal pregnancy outcomes associated with valproate preparations.

Full text of product overview.

Evidence review

- This evidence summary is based on a Cochrane review (Lonergan et al. 2009) and 1 RCT which was published after the Cochrane review (Tariot et al. 2011). An observational study (Meinhold et al. 2005) is also discussed.

- The Cochrane review included 5 RCTs which compared valproate semisodium or sodium valproate with placebo in people with dementia and agitation. Three of these studies were included in a meta-analysis of efficacy (n=216). There was no statistically significant difference
between valproate preparations and placebo for change from baseline in the Cohen Mansfield Agitation Inventory (CMAI) score after 6 weeks' treatment (mean difference −2.20; 95% confidence interval [CI] −6.38 to 1.99). The CMAI score examines 29 types of agitated behaviour, including pacing, verbal or physical aggression, screaming, and restlessness. The Cochrane review reported that the results from the other 2 studies could not be interpreted due to methodological problems. Overall, the Cochrane review concluded that valproate preparations are ineffective for treating agitation in people with dementia and are associated with an unacceptable rate of adverse events. Based on current evidence they could not recommend valproate treatment for the management of agitation in people with dementia.

- Tariot et al. (2011) was a double-blind RCT (n=313) which investigated whether treatment with valproate semisodium could delay or prevent the development of psychiatric signs and symptoms in people with moderate Alzheimer's disease but no agitation or psychosis. After 24 months' treatment, there was no statistically significant difference between the valproate semisodium group and the placebo group for time to development of clinically significant agitation or psychosis (as defined by Neuropsychiatric Inventory (NPI) scores and clinical assessment) [hazard ratio 0.96; p=0.88]. However, the study may not have had sufficient power to detect a difference between the 2 groups.

- A US observational study (Meinhold et al. 2005) aimed to assess the behavioural, mood and cognitive effects of valproate semisodium (as monotherapy or in combination with benzodiazepines or antipsychotics) in 450 nursing home residents with a history of behavioural problems associated with dementia. Behaviour and mood symptoms were measured using a minimum data set assessment. However, it is unclear if this is a valid and appropriate tool to measure behaviour and mood symptoms. Results after initiation of valproate treatment were inconsistent, with improvements reported for some measures of mood and behaviour but not others. The results of this observational study should be viewed with caution. Where improvements were reported, the differences appeared minimal and the clinical significance of the findings is unclear.

- In the Cochrane review (Lonergan et al. 2009) meta-analysis of 4 of the included studies (n=394) showed a statistically significant increase in any adverse effects at 6 weeks among participants taking valproate preparations compared with those taking placebo (odds ratio 1.99; 95% CI 1.29 to 3.08). One of the studies included in this meta-analysis was terminated early due to the high drop-out rate in the valproate group compared with the placebo group. Nineteen people (22%) in the valproate group and 3 people (4%) in the placebo group dropped out due to adverse effects (p=0.001). The meta-analysis also found statistically significant increases in adverse effects such as sedation, nausea, vomiting or diarrhoea, urinary tract infections and thrombocytopenia in participants taking valproate compared with placebo.
In the study by Tariot et al. (2011) there were statistically significant increases in sedation scores for participants receiving valproate semisodium compared with those receiving placebo (p=0.02). Some other adverse effects such as falls, gait disturbances, tremor, muscular weakness, depressed mood, diarrhoea and constipation occurred more frequently (in the range 17–39%) in the valproate group compared with the placebo group (in the range 8–32%).

Full text of evidence review.

**Context and estimated impact for the NHS**

The dosages of sodium valproate and valproate semisodium used in the studies varied. One of the studies used a low dose of sodium valproate (240 mg twice a day); whereas another study used a dose of sodium valproate titrated to 1500 mg per day. The studies which evaluated valproate semisodium used a dose titrated to around 800–1000 mg per day or 10–12 mg/kg bodyweight per day. Cost will depend on the preparation used and the dose.

Full text of context and estimated impact for the NHS.

**Information for the public**

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people or their carers’ with behavioural disturbances associated with dementia who are thinking about trying valproate preparations.

**About this evidence summary**

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.
Full evidence summary

Introduction and current guidance

Dementia can be caused by many brain disorders, most of which progress gradually over several years. The symptoms of dementia occur in 3 groups:

- cognitive dysfunction, resulting in problems with memory, language, attention, thinking, orientation, calculation, and problem-solving
- non-cognitive symptoms and behaviour that challenges such as changes in personality, emotional control, social behaviour, depression, agitation, hallucinations and delusions
- difficulties with activities of daily living, such as driving, shopping, eating, and dressing (NICE clinical knowledge summary on dementia).

Agitation has been reported in up to 70% of people with dementia. No formal definition of agitation has been published, although a widely accepted definition is: ‘inappropriate verbal, vocal or motor activity that is not explained by needs or confusion per se’ (Lonergan et al. 2009). The NICE/SCIE clinical guideline on dementia published in November 2006 gives recommendations on the care of people with all types of dementia. This includes managing behavioural and psychological symptoms.

The NICE/SCIE guideline on dementia recommends that people with dementia who develop non-cognitive symptoms that cause them significant distress or who develop behaviour that challenges should be offered an assessment at an early opportunity to establish likely factors that may generate, aggravate or improve such behaviour. Individually tailored care plans that help carers and staff address the behaviour that challenges should be developed, recorded in the notes and reviewed regularly.

According to NICE and a best practice guide produced by the Alzheimer’s Society and endorsed by the Department of Health, non-pharmacological interventions tailored to the individual person’s preferences, skills and abilities are recommended first line. NICE advises that people with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a 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. Treatment with an antipsychotic drug may be offered after various conditions have been met; due to the potential risk of increased cerebrovascular adverse events and increased mortality. An acetylcholinesterase inhibitor or memantine may be offered in some circumstances but evidence to support their use for this indication is generally limited. Other drugs that have been used off-label for non-cognitive
symptoms of dementia include antidepressants, anticonvulsants and benzodiazepines, adrenergic beta-blockers and hypnotics. However, evidence to support their use is lacking.

The NICE full guideline on dementia concluded that there was insufficient evidence to support the use of anticonvulsant mood stabilisers, such as sodium valproate, valproate semisodium or carbamazepine, for the treatment of depression or anxiety in people with dementia. This evidence summary reviews the best available evidence for the use of valproate preparations for managing aggression, agitation and behavioural disturbances in dementia. It includes a Cochrane review which included the 3 studies on valproate preparations that were considered by NICE (Porsteinsson et al. 2001, Sival et al. 2002 and Tariot et al. 2001) and 2 additional studies. Another evidence summary considers carbamazepine for these indications.

Non-cognitive symptoms and behaviour that challenges are included in the NICE quality standard on dementia. A NICE pathway brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams. In September 2010, the Department of Health published an implementation plan for Living well with dementia: a national dementia strategy.

Product overview

Drug action

Sodium valproate is an anticonvulsant. The most likely mode of action is potentiation of the inhibitory action of gamma amino-butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA (summaries of product characteristics for example: Epilim).

Some valproate preparations contain sodium valproate and valproic acid for example Epilim Chrono controlled release tablets and Epilim Chronosphere modified release granules. Valproate semisodium (also known as divalproex sodium; Depakote) is described in the summary of product characteristics as a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.

Regulatory status

Sodium valproate is available in a variety of standard-release oral preparations which are licensed for the treatment of generalised, partial or other epilepsy. Sodium valproate is also available in a variety of prolonged and modified-release formulations, some of which contain both sodium valproate and valproic acid. Some sodium valproate preparations are also licensed for the
treatment of manic episodes in bipolar disorder when lithium is contraindicated or not tolerated (see individual summaries of product characteristics for details).

Valproate semisodium (Depakote 250 mg tablets and Depakote 500 mg tablets) is licensed for the treatment of manic episodes in bipolar disorder when lithium is contraindicated or not tolerated.

None of the valproate preparations are licensed for the management of aggression, agitation and behavioural disturbances in dementia, therefore using any of them for this indication is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using valproate preparations outside their authorised indications.

In January 2015, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued new information and strengthened warnings relating to the risk of abnormal pregnancy outcomes associated with valproate preparations.

**Cost**

According to the Drug Tariff (January 2015):

- 100 sodium valproate 200 mg gastro-resistant tablets cost £4.46
- 100 sodium valproate 500 mg gastro-resistant tablets cost £8.52
- 300 ml sodium valproate 200 mg/5 ml oral sugar free solution costs £5.05
- 90 valproate semisodium 250 mg gastro-resistant tablets (Depakote) cost £14.60
- 90 valproate semisodium 500 mg gastro-resistant tablets (Depakote) cost £29.15

Details on the costs of other valproate preparations are included in the context and estimated impact for the NHS section.

**Evidence review**

This evidence summary is based on a Cochrane review (Lonergan et al. 2009) and 1 randomised controlled trial (Tariot et al. 2011) which was published after the Cochrane review. An observational study (Meinhold et al. 2005) is also discussed.
Clinical effectiveness

Lonergan et al. 2009

A Cochrane review, which evaluated valproate preparations for people with dementia and agitation, included 5 RCTs that compared sodium valproate or valproate semisodium with placebo. The trials were:

- A double-blind crossover RCT (n=14; 6 weeks treatment with each treatment option with a 2 week washout period between; mean age 86 years) which compared sodium valproate (dose titrated to a maximum of 1500 mg per day; mean 1135 mg per day) with placebo in people with Alzheimer’s disease (Hermann et al. 2007).

- A double-blind parallel group RCT (n=56; 6 weeks; mean age 85 years) which compared valproate semisodium (titrated to a mean dose of 826 mg per day) with placebo in people with Alzheimer’s disease, vascular dementia or other types of dementia (Porsteinsson et al. 2001).

- A double-blind crossover RCT (n=42; 3 weeks treatment with each option with a 1 week washout period between; mean age 80 years) which compared sodium valproate 240 mg twice daily with placebo in people with Alzheimer's disease, vascular dementia or other types of dementia (Sival et al. 2002).

- A double-blind parallel group RCT (n=172; 6 weeks; mean age 83 years) which compared valproate semisodium (titrated to a median dose of 1000 mg per day) with placebo in people with Alzheimer’s disease or vascular dementia. This study was stopped early because of a high dropout rate in the active treatment group compared with placebo (Tariot et al. 2001).

- A double-blind parallel group RCT (n=153; 6 weeks; mean age 84 years) which compared valproate semisodium (titrated to a mean dose of 800 mg per day) with placebo in people with a diagnosis of probable or possible Alzheimer’s disease (Tariot et al. 2005).

Hermann et al. (2007) was conducted in Canada, Tariot et al. (2001), Tariot et al. (2005) and Porsteinsson et al. (2001) were conducted in the USA and Sivial et al. (2002) was conducted in the Netherlands.

The Cochrane review reported that the results from 2 of the 5 studies (Tariot et al. 2001 and Sival et al. 2002) could not be interpreted because of methodological problems with these studies. The review concluded that these 2 studies do not support the use of valproate preparations to treat agitation in people with dementia (see evidence strengths and limitations).
Meta-analysis of the 3 other RCTs (n=216: Porsteinsson et al. 2001, Tariot et al. 2005 and Hermann et al. 2007) showed no statistically significant difference between participants treated with valproate preparations compared with those treated with placebo for change from baseline at 6 weeks in the Cohen Mansfield Agitation Inventory (CMAI) score (mean difference −2.20; 95% confidence interval [CI] −6.38 to 1.99). The CMAI score examines 29 types of agitated behaviour, including pacing, verbal or physical aggression, screaming, and restlessness. The frequency of these behaviours is measured on a 7-point scale from 1 (never occurs) to 7 (occurs several times an hour).

Meta-analysis of 2 of the RCTs (n=202: Porsteinsson et al. 2001 and Tariot et al. 2005) also showed no statistically significant difference between participants treated with valproate preparations compared with those treated with placebo for change from baseline at 6 weeks in the Brief Psychiatric rating scale (mean difference 0.23; 95% CI −2.14 to 2.60). The Brief Psychiatric Rating Scale measures 18 symptoms of physical and verbal aggression, hallucinatory behaviour, and abnormal thought content. These symptoms are each measured on a scale of 1 to 7, with 7 being the most severe.

Overall, the Cochrane review concluded that the evidence reviewed does not support the use of valproate preparations to treat agitation in people with dementia.

Tariot et al. 2011

This double-blind, placebo-controlled RCT conducted in the USA investigated whether treatment with valproate semisodium could delay or prevent the development of agitation or psychosis in people with Alzheimer's disease.

Participants over the age of 54 years (n=313, mean age 76 years) with moderate Alzheimer's disease (a mini-mental state examination [MMSE] score of 12 to 20 on a scale of 0 to 30) and absence of agitation or psychosis (defined by a score of less than 1 on the Neuropsychiatric Inventory (NPI) items, which assesses delusion, hallucinations and agitation or aggression) were recruited to the study. The NPI assesses 12 neuropsychiatric features of Alzheimer's disease. Frequency assessments range from 1 to 4 and severity assessments range from 1 to 3. The score is the product of frequency and severity assessment.

Participants were randomised to valproate semisodium (titrated to a dose of 10−12 mg/kg bodyweight per day) or placebo for 24 months followed by a 2-month period of single-blind treatment with placebo. It is unclear if allocation was concealed. Throughout the study period, participants could take a concomitant cholinesterase inhibitor (93% at baseline) or memantine...
(65% at baseline) at a stable dose. Other psychotropic medication (except non-tricyclic antidepressants or short-acting benzodiazepines up-to 3 times a week) was not permitted.

The primary outcome was time to development of clinically significant agitation or psychosis (defined as a score of at least 3 on 1 or more NPI items assessing delusions, hallucinations and agitation or aggression persisting for 2 weeks and clinical assessment that the new agitation or psychosis was clinically significant).

There was no statistically significant difference between the valproate semisodium group and the placebo group for time to development of clinically significant agitation or psychosis (hazard ratio 0.96; 95% CI's not reported; p=0.88). Twenty-five participants in the valproate semisodium sodium group and 29 participants in the placebo group developed clinically significant agitation or psychosis before the end of the study. However, fewer participants developed agitation or psychosis than was expected and a large proportion of participants (approximately 61% across the study) dropped out. This may have reduced the power of the study to show a difference between the 2 groups.

The study reported that there was no significant difference between the groups in any secondary outcomes including change from baseline in total NPI score or CMAI score, or the rate of nursing home placement. No p values were reported.

At 24 months there were no significant differences between the valproate semisodium group and the placebo group for mean MMSE score, Alzheimer's disease assessment scale – cognitive subscale score and the Alzheimer's disease co-operative study clinical global impression of change score. No p values were reported.

Meinhold et al. 2005

This US retrospective observational study of a long-term care database aimed to assess the behavioural, mood and cognitive effects of valproate semisodium in a population of nursing home residents with a history of behavioural problems associated with dementia. Behaviour and mood symptoms were measured using a minimum data set assessment. This is an assessment tool that is required by US insurance companies to be completed for nursing home residents on at least a quarterly basis. It is unclear if this is a valid and appropriate tool to measure behaviour and mood symptoms.

A total of 6009 people were screened and 3302 people (average age 83 years) had received 1 of the target medications (valproate semisodium, a benzodiazepine or an antipsychotic drug) for
behavioural problems and had a sufficient number of assessments over a 1-year observation period. Of these 450 people had received valproate semisodium and were included in the study. Approximately 70% were taking a dose of less than 825 mg per day and the rest were taking a higher dose.

The effect of valproate semisodium was assessed as monotherapy, in combination with benzodiazepines and in combination with antipsychotics. Minimum data set data was analysed before and after the initiation of valproate semisodium.

The paper did not report how many participants were included in the analysis of valproate semisodium monotherapy. Over approximately 150 days prior to initiation of valproate semisodium, it was reported that there was an increase in the frequency of behavioural symptoms as measured by mean minimum data set scores. After starting valproate semisodium, this trend was reportedly reversed (p≤0.05). However, the limited data in the paper makes it difficult to interpret this finding, and the clinical significance of this result is unclear (see evidence strengths and limitations).

In the 47 participants who received valproate semisodium in combination with benzodiazepines, there was no statistically significant in change in behavioural alterability [not defined] (p=0.089) and sleep cycle issues (p=0.077) after valproate semisodium was started. Statistically significant reductions in frequency of behavioural symptoms and expressions of verbal distress were reported (p≤0.05).

In the 173 participants who received valproate semisodium in combination with antipsychotics, there was no statistically significant change in behavioural frequency (p=0.087), cognitive skills of daily decision making (p=0.09) or loss of interest (p=0.21) after valproate semisodium was started. Statistically significant improvements were reported for some outcomes such as behavioural alterability, verbal expressions of distress and sleep cycle issues (p≤0.05). However, as for monotherapy, these findings are difficult to interpret and the clinical significance of these reductions is unclear.

Meinhold et al. 2005 was an observational study with a number of limitations (see evidence strengths and limitations) and the results should be viewed with caution.

Safety and tolerability

Lonergan et al. 2009
In the Cochrane review meta-analysis of 4 of the included 5 RCTs (n=394) showed a statistically significant increase in any adverse effects by 6 weeks among participants taking valproate preparations compared with those taking placebo (odds ratio 1.99; 95% CI 1.29 to 3.08). Meta-analysis of 3 RCTs (n=241) showed a statistically significant increase in sedation among participants taking valproate preparations compared with those taking placebo (odds ratio 2.48; 95% CI 1.37 to 4.47). Meta-analysis of 2 RCTs (n=208) showed a statistically significant increase in nausea, vomiting or diarrhoea among participants taking valproate preparations compared with those taking placebo (odds ratio 7.09; 95% CI 1.73 to 29.02). Meta-analysis of 2 RCTs (n=227) showed a statistically significant increase in urinary tract infection among participants taking valproate preparations compared with those taking placebo (odds ratio 3.02; 95% CI 1.04 to 8.80). Meta-analysis of 2 RCTs (n=186) showed a statistically significant increase in thrombocytopenia among participants taking valproate preparations compared with those taking placebo (odds ratio 7.91; 95% CI 1.92 to 32.57). Evaluation of the individual studies was also reported to show adverse effects such as falls, gastrointestinal disorders, and infections were more frequent in people taking valproate preparations than those taking placebo. Tariot et al. 2001 which used a dose of valproate semisodium titrated to a target dose of 20–30 mg/kg bodyweight per day was terminated early due to the high dropout rate in the valproate group compared to the placebo group. Nineteen people (22%) in the valproate group and 3 people (4%) in the placebo group dropped out due to adverse effects (p=0.001).

Tariot et al. 2011

In Tariot et al. (2011), discontinuations due to adverse events occurred in 25/153 (16.3%) participants in the valproate semisodium group compared with 12/160 (7.5%) in the placebo group. About 94% of people in both groups experienced at least 1 adverse event.

Adverse events that occurred more frequently in the valproate semisodium group than in the placebo group included depressed mood (22% compared with 14%); asthenia (31% compared with 22%); falls (39% compared with 32%); gait disturbances (33% compared with 19%); muscular weakness (19% compared with 9%); somnolence (42% compared with 29%); tremor (29% compared with 13%); diarrhoea (25% compared with 12%); constipation (17% compared with 8%) and arthralgia (14% compared with 8%). There were statistically significant increases in sedation scores for people receiving valproate compared with those receiving placebo (p=0.02). No further statistical analysis was presented.
Summary of product characteristics

Sodium valproate and valproate semisodium have a variety of potential adverse effects. According to the summary of product characteristics (SPC) for Epilim, nausea and tremor are very common adverse events (occurring in 10% or more of people). Common adverse effects (occurring in between 1% and 10% of people) include liver injury, gastralgia, diarrhea, extrapyramidal disorders, memory impairment, somnolence, confusion, headache, nystagmus, hyponatraemia, anaemia, thrombocytopenia, deafness and hypersensitivity reactions.

Severe liver damage, including hepatic failure sometimes resulting in death, has been very rarely reported. The SPC recommends that liver function should be measured before treatment and then periodically monitored during the first 6 months of treatment, especially in those who seem most at risk, and those with a prior history of liver disease. Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are also recommended before starting treatment or before surgery, and in case of spontaneous bruising or bleeding.

Similar adverse effects are listed in the summaries of product characteristics for valproate semisodium (Depakote 250 mg tablets and Depakote 500 mg tablets).

The SPCs state that sodium valproate and valproate semisodium are contraindicated in people with active liver disease and people with a personal or family history of severe hepatic dysfunction, especially if it was drug-related and people with porphyria.

Evidence strengths and limitations

The Cochrane review (Lonergan et al. 2009) identified 5 RCTs that compared sodium valproate or valproate semisodium with placebo. Two of these RCTs (Tariot et al. 2001 and Sival et al. 2002) could not be interpreted due to methodological problems. Tariot et al. (2001) was terminated early due to the high drop-out rate in the valproate group compared with the placebo group (59% compared with 29%; 22% of the valproate group dropped out due to adverse effects). Sival et al. (2002) was a crossover design and was not included because no results from the first phase of the study were available raising questions over the analyses. The other 3 studies included in the meta-analysis on efficacy also had limitations, such as: allocation concealment was unclear which may have led to bias; treatment dose and preparation varied between the studies; and the number of participants included in the meta-analysis was small (n=216). The Cochrane review concluded that valproate preparations are ineffective for treating agitation in people with dementia and are associated with an unacceptable rate of adverse events. They recommended that more research on the use of valproate preparations for agitation in people with dementia was needed. Based on
currently available evidence they could not recommend valproate treatment for the management of agitation in people with dementia.

Tariot et al. 2011, which was published after the Cochrane review, aimed to assess whether treatment with valproate semisodium could delay or prevent the development of psychiatric signs and symptoms in people with Alzheimer's disease. No statistically significant difference was found between valproate semisodium and placebo for time to development of clinically significant agitation or psychosis. However, the study may have been underpowered to detect a difference between the 2 groups because fewer than expected people developed agitation or psychosis by the end of the study and a large proportion of participants stopped treatment early (around 61% in each group). Due to the selection criteria used it is possible that the study population may not have been representative of people with dementia likely to develop agitation or psychosis within the specified time period.

Meinhold et al. 2005 was an observational study which used data from a US care database. Observational studies are prone to confounding and bias and the results of this study should be interpreted with caution. In this study behaviour and mood symptoms were measured using a minimum data set assessment. It is unclear if this is a valid and appropriate tool to measure behaviour and mood in people with dementia. In addition, the minimum clinically important differences for the observation sets used are not reported. Results after initiation of valproate treatment were inconsistent, with improvements reported for some measures of mood and behaviour but not others. Where improvements were reported, differences generally appeared minimal and their clinical significance is unclear. This was an observational study and no control group was available to compare adverse effects for instance.

The dose of sodium valproate and valproate semisodium used in the studies varied, and several of the studies allowed dose titration. All the RCTs were placebo-controlled and it is not known how valproate preparations compare with other drugs that have been used (mainly off-label) to manage aggression, agitation and behavioural disturbances in people with dementia; for example, carbamazepine.

**Context and estimated impact for the NHS**

**Cost effectiveness**

The dose of sodium valproate and valproate semisodium used in the studies varied. One of the studies used a low dose of sodium valproate (240 mg twice a day); whereas another study used a dose of sodium valproate titrated to 1500 mg per day. The studies which evaluated valproate
semisodium used a dose titrated to around 800–1000 mg per day or 10–12 mg/kg bodyweight per day.

The below table presents the cost of a variety of different valproate preparations.

**Table 1 Costs of valproate preparations**

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<thead>
<tr>
<th>Valproate preparations</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Sodium valproate gastro-resistant tablets</td>
<td>100 x 200 mg=£4.46&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>100 x 500 mg=£8.52&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium valproate 200 mg/5 ml oral sugar free solution</td>
<td>£5.05 for 300 ml&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sodium valproate 100 mg crushable tablets (Epilim)</td>
<td>£5.60 for 100&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Valproate semisodium gastro-resistant tablets (Depakote)</td>
<td>90 x 250 mg=£14.60 for 90&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>90 x 500 mg=£29.15 for 90&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Epilim Chrono controlled release tablets (sodium valproate and valproic acid)</td>
<td>100 x 200 mg=£11.65&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>100 x 300 mg=£17.47&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>100 x 500 mg=£29.10&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Epilim Chronosphere modified release granules (sodium valproate and valproic acid)</td>
<td>Available as 50 mg, 100 mg, 250 mg, 500 mg, 750 mg and 1 gram strengths. For all strengths 30 sachets=£30.00&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Episenta prolonged-release capsules (sodium valproate)</td>
<td>100 x 150 mg=£7.00&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>100 x 300 mg=£13.00&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Episenta prolonged-release granules (sodium valproate)</td>
<td>100 x 500 mg sachets=£21.00&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>100 x 1 gram sachets=£41.00&lt;sup&gt;b&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Prices taken from Drug Tariff (January 2015)

<sup>b</sup> Prices taken from MIMS (January 2015)
Current drug usage

No estimate of the current use of off-label valproate preparations for the management of aggression, agitation and behavioural disturbances in dementia in UK clinical practice was identified.

Information for the public

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people or their carers' with behavioural disturbances associated with dementia who are thinking about trying valproate preparations.

Relevance to NICE guidance programmes

This use of valproate preparations is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

In 2006, NICE published a guideline on dementia: supporting people with dementia and their carers in health and social care (NICE guideline CG42), which has been incorporated into a NICE pathway.

NICE technology appraisal guidance is available on donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (NICE technology appraisal 217).

NICE guidance related to the licensed indications for valproate preparations has also been published:

- The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (NICE guideline CG137)

- Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care (NICE guideline CG185).

References


**Development of this evidence summary**

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

**Expert advisers**

Professor Clive Ballard, Professor of Age Related Diseases, King’s College London
Declarations of interest

Clive Ballard has no specific conflicts of interest related to sodium valproate. He has received research grants and honoraria from Lundbeck Limited related to the use of memantine for the treatment of agitation in people with dementia and from Acadia Pharmaceuticals for the treatment of psychosis in people with Parkinson's disease and people with Alzheimer's disease. He has also received honoraria from Bristol Myers Squibb, Otusaka, Eli Lilly and Orion pharmaceutical companies for an advisory role related to the management of neuropsychiatric symptoms in people with dementia.

Nigel Barnes declared no relevant interests.

About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines’ summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

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