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Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults (Review)

Gill D, Derry S, Wiffen PJ, Moore RA

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[Intervention Review]

Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults

Dipender Gill[1], Sheena Derry[2], Philip J Wiffen[3], R Andrew Moore[4]

[1]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [2]Oxford, UK. [3]Thame, UK. [4]Plymouth, UK

Contact address: Sheena Derry, sheena.derry@retired.ox.ac.uk.

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ABSTRACT

Background

Valproic acid and its sodium salt (sodium valproate) are antiepileptic drugs that are sometimes used to treat chronic neuropathic pain and fibromyalgia, although they are not licensed for this use.

Objectives

To evaluate the analgesic efficacy and adverse effects of valproic acid and sodium valproate in the management of chronic neuropathic pain and fibromyalgia.

Search methods

We identified randomised controlled trials (RCTs) of valproic acid and sodium valproate in acute, and chronic pain by searching MEDLINE, EMBASE and Cochrane CENTRAL to June 2011, together with reference lists of retrieved papers and reviews.

Selection criteria

RCTs that were double blind and of eight-weeks duration or longer, reporting on analgesic effects and adverse events with valproic acid and sodium valproate in the treatment of chronic neuropathic pain and fibromyalgia.

Data collection and analysis

Two review authors independently extracted results and scored for quality. We extracted efficacy and adverse event data, and examined issues of study quality.

Main results

We included three studies, two in diabetic neuropathy (42 participants treated with valproate, 42 with placebo), and one in post-herpetic neuralgia (23 treated with divalproex sodium, 22 with placebo). Study duration was eight or 12 weeks. No studies were found in fibromyalgia.

Only one study reported one of our primary outcomes (≥ 50% pain relief), while all three reported group means for pain reduction from baseline to endpoint. In all three studies; efficacy results were given only for participants who completed the study. One study in diabetic neuropathy and the study in post-herpetic neuralgia reported significant differences between active and placebo groups, but there were insufficient data for reliable pooled analysis.

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More adverse events were reported with active treatment than placebo, and included nausea, drowsiness and abnormal liver function tests. One participant taking sodium valproate withdrew due to serious derangement of liver enzymes.

Authors' conclusions

These three studies no more than hint that sodium valproate may reduce pain in diabetic neuropathy, and divalproex sodium in post-herpetic neuralgia, but the use of 'completer' analysis may overestimate efficacy, and there were too few data for pooled analysis of efficacy or harm, or to have confidence in the results of the individual studies. There is insufficient evidence to support the use of valproic acid or sodium valproate as a first-line treatment for neuropathic pain. There is more robust evidence of greater efficacy for a small number of other drugs.

PLAIN LANGUAGE SUMMARY

Valproic acid and sodium valproate for neuropathic pain and fibromyalgia

Neuropathic pain is caused by nerve damage, often accompanied by changes in the central nervous sytem, and fibromyalgia is a related complex pain syndrome. Many people with these conditions are disabled with moderate or severe pain for many years. Conventional analgesics are usually not effective treatment options. In light of the fact that there are similarities between the pathophysiologic and biochemical mechanisms observed in epilepsy and in neuropathic pain, it is not surprising that antiepileptic agents can be used to treat neuropathic pain. The aim of this review was to investigate the efficacy and adverse events associated with use of sodium valproate and valproic acid for the treatment of chronic neuropathic pain and fibromyalgia. We identified three relevant studies, two in diabetic neuropathy and a third in post-herpetic neuralgia. Two of the three studies report significantly greater reduction in pain for valproate than placebo, but studies were small (≤ 45 participants) and provided insufficient data for pooled analysis, and the methods of analysis used may have overestimated treatment effect. Adverse events such as nausea, sedation, drowsiness, vertigo, and abnormal liver function are more common with valproate than placebo, but these studies were unsuitable to allow for a comprehensive assessment of harm.

There is insufficient evidence to support the use of valproic acid or sodium valproate as a first-line treatment for neuropathic pain.

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BACKGROUND

An earlier review was published in *The Cochrane Library* as 'Anticonvulsant drugs for acute and chronic pain' (2000, issue 2). At the third update in 2003, 12 new included studies were identified, mainly of the newer antiepileptic gabapentin and lamotrigine. In total, the included studies provided data on six different medicines used in at least six identified neuropathic pain conditions. Issues of dose response and trial design added to the complexity. A decision was therefore taken to split that review into a number of smaller reviews each covering one medicine (chemical entity). This review looks at the evidence for valproic acid and sodium valproate. Reviews of gabapentin (Moore 2011), pregabalin (Moore 2009), carbamazepine (Wiffen 2011a), and lamotrigine (Wiffen 2011b) have also been completed.

Antiepileptic drugs currently used for neuropathic pain are: carbamazepine, clonazepam, gabapentin, lamotrigine, oxcarbazepine, phenytoin, topiramate, and valproate; license status may vary between regions.

Description of the condition

Neuropathic pain, unlike nociceptive pain such as gout and other forms of arthritis, is caused by nerve damage, often accompanied by changes in the central nervous system (CNS). The new (2011) definition of neuropathic pain is ''pain caused by a lesion or disease of the somatosensory system'" (Jensen 2011). Fibromyalgia is a complex pain syndrome, defined as widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points (Wolfe 1990), and frequently associated with other symptoms such as poor sleep, fatigue, and depression. More recently, a definition of fibromyalgia has been proposed based on symptom severity and the presence of widespread pain (Wolfe 2010). The cause or causes of fibromyalgia are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Many people with these conditions are significantly disabled with moderate or severe pain for many years. Conventional analgesics are usually not effective, although opioids may be in some individuals. Others may derive some benefit from a topical lidocaine patch or topical capsaicin. Treatment is more usually by unconventional analgesics such as antidepressants or antiepileptics.

Data for the incidence of neuropathic pain is difficult to obtain. However, a systematic review of prevalence and incidence in the Oxford Region of the UK indicates prevalence rates per 100,000 of 34 for postherpetic neuralgia, 400 for diabetic neuropathy and trigeminal neuropathy, and 2000 for fibromyalgia (McQuay 2007). Different estimates in the UK indicate incidences per 100,000 person years observation of 40 (95% confidence interval (CI) 39 to 41) for post-herpetic neuralgia, 27 (26 to 27) for trigeminal neuralgia, 1 (1 to 2) for phantom limb pain, and 15 (15 to 16) for painful diabetic neuropathy, with rates decreasing in recent years for phantom limb pain and post-herpetic neuralgia and increasing for painful diabetic neuropathy (Hall 2006). The prevalence of neuropathic pain in Austria was reported as being 3.3% (Gustorff 2008).

Neuropathic pain and fibromyalgia are commonly difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. A multidisciplinary approach is currently advocated, with physical therapies, cognitive therapies, or a combination of the two now being combined with pharmacological interventions.

Description of the intervention

Valproic acid, a fatty acid, and its sodium salt, sodium valproate, became established as the most used antiepileptic and mood-stabilising drug worldwide from the 1970s onwards. They are most commonly used in the treatment of epilepsy and manic phases of bipolar disorder. They are not licensed for the treatment of neuropathic pain and fibromyalgia, but are sometimes used when first-line therapies have failed.

The two drugs have a 1:1 dose relationship. Valproic acid (trade names include Depakote and Convulex) is available in tablet form in doses of 150 mg to 500 mg; sodium valproate (trade names include Epilim and Episenta) is available in tablet or capsule form in doses of 100 mg to 500 mg, and also as granules, liquid and syrup.

Valproic acid and sodium valproate can cause birth defects, so are contraindicated in pregnancy. They are associated with a number of potentially serious adverse effects, including liver toxicity, blood or hepatic disorders, and pancreatitis, in addition to more common side effects such as weight gain, nausea, diarrhoea, and hair loss.

How the intervention might work

There are similarities between the pathophysiologic and biochemical mechanisms observed in epilepsy and in neuropathic pain. The pathophysiologic processes are similar and appear to result, in part, from activation of N-methyl-D-aspartate (NMDA) receptors, among other mechanisms. The susceptibility of primary afferents and transmission neurons to the effects of sodium channel blockers in neuropathic pain models has been well recognized and is similar to that in models of epilepsy. In the light of these mechanistic similarities, it is not surprising that antiepileptic agents can be used to treat neuropathic pain (Backonja 2002). Valproic acid is thought to inhibit an enzyme (GABA transaminase), and thereby increases levels of gamma amino butyric acid (GABA, a neurotransmitter) in the brain. It is also thought to block sodium and calcium channels. Although their mechanism of action in pain relief is not yet fully understood, increasing levels of GABA and stabilisation of cell membranes probably results in a reduction of pain signals being processed in the brain. A number of other putative mechanisms of action have been suggested based on the effects on signal transduction in neurons (Toth 2005).

Valproic acid is not licensed for the treatment of neuropathic pain or fibromyalgia, but is sometimes used when first-line therapies have failed.

Why it is important to do this review

Several antiepileptic drugs, such as pregabalin (Moore 2009), gabapentin (Moore 2011), and carbamazepine (Wiffen 2011a), have shown efficacy in treating some types of neuropathic pain, while others have not (Wiffen 2011b). The NICE guidelines (NICE 2010) do not recommend valproate for neuropathic pain whilst the very recent American Academy of Neurology (AAN 2011) guideline update regarding pharmacologic and nonpharmacologic treatment of painful diabetic neuropathy (PDN) does recommend that sodium valproate should be considered for the treatment of PDN. It is important to review all the evidence in neuropathic pain,

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by different conditions, to establish whether valproic acid or its sodium salt have clinical utility in this area.

There have been several recent changes in how efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria of what constitutes moderate or substantial benefit (Dworkin 2008); older trials may only report participants with "any improvement". Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be longer, up to 12 weeks, providing a more rigorous and valid assessment of efficacy in chronic conditions. New standards have evolved for assessing efficacy in neuropathic pain, and we are now applying stricter criteria for inclusion of trials and assessment of outcomes, and are more aware of problems that may affect our overall assessment. To summarise some of the recent insights that make a new review necessary, over and above including more trials:

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution (see Moore 2005 for acute pain). This is true in acute pain and arthritis (Moore 2010a) as well as in fibromyalgia; in all cases average results usually describe the experience of almost no-one in the trial. Data expressed as averages are potentially misleading, unless they can be proven to be suitable.
2. As a consequence, we have to depend on dichotomous results (the individual either has or does not have the outcome) usually from pain changes or patient global assessments. The IMMPACT group has helped with their definitions of minimal, moderate, and substantial improvement (Dworkin 2008). In arthritis, trials shorter than 12 weeks, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010a); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
3. The proportion with at least moderate benefit can be small, even with an effective medicine, falling from 60% with an effective medicine in arthritis, to 30% in fibromyalgia (Moore 2010a; Straube 2008; Sultan 2008). A Cochrane review of pregabalin in neuropathic pain and fibromyalgia demonstrated different response rates for different types of chronic pain (higher in diabetic neuropathy and postherpetic neuralgia and lower in central pain and fibromyalgia) (Moore 2009). This indicates that different neuropathic pain conditions should be treated separately from one another, and that pooling should not be done unless there are good grounds for doing so.
4. Finally, individual patient analyses indicate that patients who get good pain relief (moderate or better) have major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010b).

This Cochrane review will therefore assess evidence in ways that make both statistical and clinical sense, and will use developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010c). Trials included and analysed will need to meet a minimum of reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc), and size (ideally a minimum of 500+ participants in a comparison in which numbers needed to treat (NNTs) are four or above (Moore 1998)). This does set high standards, and marks a departure from how reviews have been conducted previously.

OBJECTIVES

1. To assess the analgesic efficacy of valproic acid and sodium valproate for chronic neuropathic pain and fibromyalgia.
2. To assess the adverse events associated with the clinical use of valproic acid and sodium valproate for chronic neuropathic pain and fibromyalgia.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies if they were randomised controlled trials (RCTs) with double blind assessment of outcomes reported after eight weeks of treatment or longer. Full journal publication was required, with the exception of extended abstracts of otherwise unpublished clinical trials. We excluded short abstracts (usually meeting reports), studies that were non-randomised, studies of experimental pain, case reports, and clinical observations.

Types of participants

We included adult participants aged 18 years and above. Participants could have one or more of a wide range of chronic neuropathic pain conditions including:

- painful diabetic neuropathy;
- post-herpetic neuralgia;
- trigeminal neuralgia;
- phantom limb pain;
- postoperative or traumatic neuropathic pain;
- complex regional pain syndrome;
- cancer-related neuropathy;
- Guillain Barré;
- HIV-neuropathy;
- spinal cord injury;
- fibromyalgia.

We also included studies of participants with more than one type of neuropathic pain, with the intention to analyse results according to the primary condition.

Types of interventions

Valproic acid or sodium valproate in any dose, by any route, administered for the relief of neuropathic pain or fibromyalgia, and compared to placebo, no intervention or any other active comparator. We did not include studies using these drugs to treat pain resulting from the use of other drugs.

Types of outcome measures

Studies had to report pain assessment as either the primary or secondary outcome.

We anticipated that a variety of outcome measures would be used in the studies. We expected the majority of studies to use standard subjective scales for pain intensity or pain relief, or both. We paid particular attention to IMMPACT definitions for moderate and substantial benefit in chronic pain studies (Dworkin 2008). These are defined as at least 30% pain relief over baseline (moderate), at least 50% pain relief over baseline (substantial), much or very

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much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes are different from those set out in an earlier review of antidepressants for neuropathic pain (Saarto 2007), concentrating on dichotomous outcomes where pain responses are not normally distributed.

Primary outcomes

1. Patient-reported pain relief of 30% or greater.
2. Patient-reported pain relief of 50% or greater.
3. Patient-reported PGIC much or very much improved.
4. Patient-reported PGIC very much improved.

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Withdrawals due to lack of efficacy.
3. Participants experiencing any adverse event.
4. Participants experiencing any serious adverse event.
5. Withdrawals due to adverse events.
6. Specific adverse events, particularly somnolence and dizziness.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- Cochrane CENTRAL, (to 2 June 2011);
- MEDLINE (via Ovid), (to 2 June 2011);
- EMBASE (via Ovid) (to 2 June 2011).

See Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the CENTRAL search strategy.

There was no language restriction.

Searching other resources

We searched reference lists of retrieved articles and reviews, and online databases for any additional studies.

Data collection and analysis

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors read these studies independently and reached agreement by discussion. The studies were not anonymised in any way before assessment.

Data extraction and management

Two review authors extracted and agreed on data, using a standard form, before entry into Review Manager (RevMan) or any other analysis method was undertaken. Data extracted included information about the pain condition and number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event, or serious adverse event).

Assessment of risk of bias in included studies

We used the 'Risk of bias' tool available in RevMan 5.1 to report on sequence generation, allocation concealment, blinding, study size, and other risks such as reporting of dropouts.

Measures of treatment effect

We planned to use dichotomous data to calculate relative risk (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below). We planned to calculate numbers needed to treat to benefit (NNTs) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNT becomes the number needed to treat to harm (NNH), and is calculated in the same manner. We did not attempt to analyse continuous data (group mean results) because there appeared to be some errors in reporting of standard error/standard deviation, and it is possible that the underlying distribution was skewed, as is commonly the case for relief of pain.

Unit of analysis issues

We planned to split the control treatment arm between active treatment arms in a single study if the active treatment arms were not combined for analysis.

Dealing with missing data

Where possible, we used intention-to-treat (ITT) analysis. The ITT population consisted of participants who were randomised, took the assigned study medication, and provided at least one post-baseline assessment. Missing participants were assigned zero improvement.

Assessment of heterogeneity

We intended to deal with clinical heterogeneity by combining studies that examined similar conditions. Statistical heterogeneity would have been assessed visually (L'Abbé 1987) and with the use of the I^2 statistic. We planned to investigate heterogeneity if I^2 was greater than 50%.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility (Moore 2010a). The review did not depend on what authors of the original studies chose to report or not, though clearly this resulted in difficulties with studies failing to report any dichotomous results. Continuous data, which probably poorly reflect efficacy and utility, was extracted and used for illustrative purposes only.

We planned to investigate the potential influence of publication bias by examining the number of participants in trials with zero effect (RR of 1.0) needed for the point estimate of the NNT to increase beyond a clinically useful level (Moore 2008). In this case, we chose a clinically useful level as 10.

Data synthesis

We planned to undertake meta-analysis using a fixed-effect model. We would have used a random-effects model for meta-analysis if there was significant heterogeneity and it was considered appropriate to combine studies.

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Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis for:

- dose of valproic acid or sodium valproate;
- different painful conditions.

Sensitivity analysis

None were planned, because the evidence base is known to be too small to allow reliable analysis; in particular, we would not have pooled results from neuropathic pain of different origins.

RESULTS

Description of studies

Results of the search

The searches yielded seven relevant studies. One further study was identified via www.clinicaltrials.gov: this study (NCT00221637), in patients with "peripheral neuropathic pain", recruited only 40 patients and was terminated in 2007 due to slow recruitment and treatments beyond expiry date. No results are available.

Included studies

Three studies fulfilled the inclusion criteria.

Agrawal 2009 and Kochar 2004 both considered the use of sodium valproate in the treatment of diabetic neuropathy using prospective, single-centre, randomised, double-blinded placebo-controlled trials of three months duration.

Kochar 2005 considered the use of divalproex sodium (valproic acid and sodium valproate in molar ratio 1:1) in the treatment of post-herpetic neuralgia also using a prospective, single-centre, randomised, double-blinded placebo-controlled trial, but of eight weeks duration.

We did not find any studies in which valproate or divalproex sodium were used in the treatment of fibromyalgia.

Excluded studies

Kochar 2002 considered the use of sodium valproate in treating diabetic neuropathy using a prospective, single-centre, randomised, double-blinded placebo-controlled trial, but we excluded it as it was only of four weeks duration.

Otto 2004 considered the use of valproic acid in the treatment of pain associated with polyneuropathy in general, with the study taking the form of a prospective, single-centre, cross-over study. As the duration of each phase of the cross-over study was only four weeks, we excluded this study.

Hardy 2001 was an open-label phase II study investigating the use of sodium valproate in cancer-related pain. This study was not a randomised, double-blinded, placebo-controlled trial, and was only of two weeks duration, and hence was excluded.

Drewes 1994 investigated the effect of sodium valproate in chronic central pain associated with spinal cord injury, through a prospective, double-blinded, placebo-controlled study. Each phase lasted for three weeks, and so we excluded the study.

No relevant studies were found in fibromyalgia, or in other types of neuropathic pain such as trigeminal neuralgia, phantom limb pain and HIV neuropathy.

Risk of bias in included studies

Allocation

Only Kochar 2005 adequately described the methods used to ensure that allocation of participants to treatment groups was concealed. Agrawal 2009 and Kochar 2004 did not describe this.

Blinding

Only Kochar 2004 adequately described the methods used to ensure that participants and interacting investigators were unable to differentiate between the treatment and control tablets. Agrawal 2009 and Kochar 2005 did not describe this.

Incomplete outcome data

A number of participants withdrew in all three studies. In Agrawal 2009, although all 20 participants in the treatment group completed the study, 1/21 participants in the control group withdrew. In Kochar 2005, 1/23 participants in the treatment group withdrew, and 4/22 participants in the control group withdrew. In Kochar 2004, 1/22 participants in the treatment group withdrew, and 3/23 participants in the control group withdrew.

All three studies performed efficacy analyses on only those participants who completed the study (completer analysis). Although the absolute numbers that were excluded from analyses was small, it is not possible to dismiss them because of the small group sizes and the fact that there was an imbalance between groups in withdrawals due to adverse events, and due to lack of efficacy and compliance. Missing participants can be added back in (analysed as non-responders) for dichotomous outcomes, but this is not possible when mean data are reported.

Selective reporting

All three studies (Agrawal 2009; Kochar 2005; Kochar 2004) reported the outcomes specified in the methods, although these were usually not our preferred (primary) outcomes.

Other potential sources of bias

Treatment group size was an issue. Individual groups included between 20 and 23 participants, and not all of these participants were included in the completer analyses. Studies with small group sizes tend to overestimate efficacy (Kjaergard 2001; Nuesch 2010).

See Figure 1 for a summary of the risk of bias in included studies.

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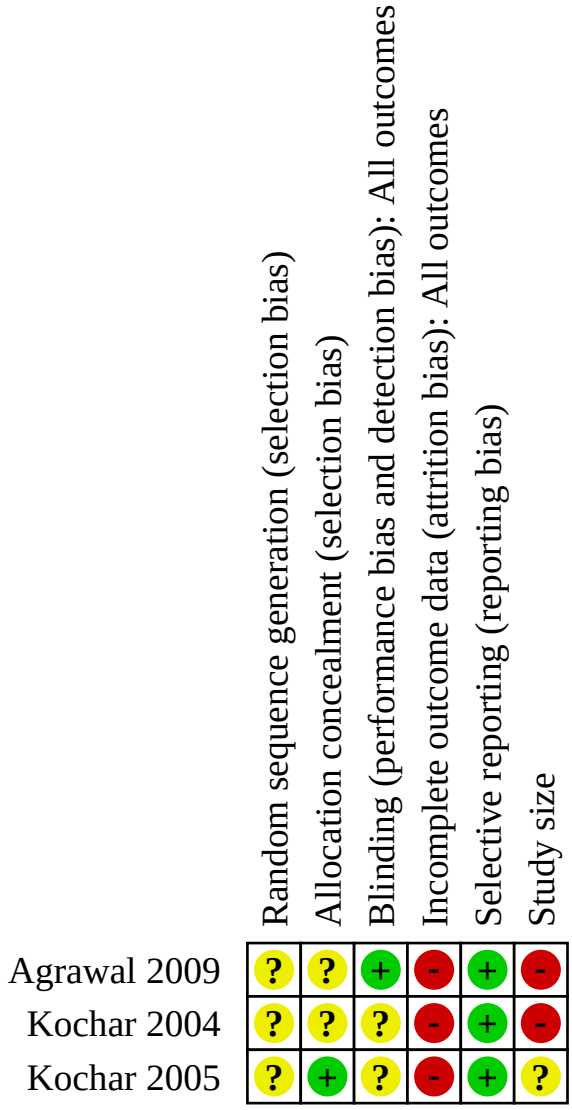
Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

Although the studies used several different scales to measure pain, the mean visual analogue score (VAS) was employed by all. In the absence of dichotomous data for pain intensity or pain relief, we have reported the mean VAS for consistency and to facilitate comparison. We did not carry out any pooled analysis because of small numbers in each treatment group, and because the underlying distribution was not shown to be Gaussian (normal).

Diabetic neuropathy

Although Agrawal 2009 and Kochar 2004 both investigated the use of sodium valproate in the treatment of diabetic neuropathy, there were insufficient data for pooled analysis. Moreover, none of the studies fulfilled all of the criteria of reliable evidence (Moore 2010c).

Agrawal 2009 conducted a completer analysis of 20 participants taking 20 mg/kg/day (equivalent to 1400 mg/day for a 70 kg participant) of sodium valproate, compared with 20 participants taking placebo. Efficacy was reported as group means after three months, and although statistical significance was observed between zero and three months for the treatment arm when using the VAS (8.0 ± standard error of the mean (SEM) 0.2 at zero months; 6.2 ± 0.3 at three months; $P < 0.001$), there was no statistically significant difference observed ($P < 0.1$) in the treatment group compared with the placebo group (7.4 ± 0.3 at zero months, 6.9 ± 0.2 at three months; $P < 0.1$). Mean pain intensity in both groups

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after three months remained above 6/10, which is considered to be moderate to severe.

Kochar 2004 conducted a completer analysis of 21 participants taking 500 mg/day of sodium valproate, compared with 18 participants taking placebo. As with Agrawal 2009, efficacy was reported as group means after three months, but in this case, the difference in mean VAS scores after three months between the treatment group (6.0 ± SEM 2.0 at zero months; 3.0 ± 2.1 at three months) and the placebo group (5.7 ± 1.7 at zero months; 6.0 ± 1.8 at three months) was statistically significant (P < 0.001). Only in the active treatment group did pain intensity after three months fall to 3/10, which is considered to be mild.

Post-herpetic neuralgia

In Kochar 2005, 23 participants took 1000 mg/day of divalproex sodium (valproic acid and sodium valproate in molar ratio 1:1), and 22 participants took placebo. After eight weeks, 13 out of 22 completers (13 out of the 23 original participants; 57%) taking sodium valproate achieved at least 50% pain relief, while only two out of 18 completers (two out of the original 23 participants; 8.7%) taking placebo achieved this outcome. In terms of group means, the change in VAS score after eight weeks for the treatment group (70 ± SEM 9.2 at zero weeks; 31 ± 30 at eight weeks) and the placebo group (63 ± 9 at zero weeks; 55 ± 18 at eight weeks) was statistically significant (P < 0.0001). Only in the active treatment group did pain intensity after three months approach 30/100, which would be considered to be mild.

Although Kochar 2005 also provided data on the PGIC score (at last visit), results for this are given only as percentages. These percentages did not convert back (or approximate) to whole participant numbers again, for example resulting in less than half of one patient in one category. For this reason, we chose not to use these data.

Withdrawals

In Agrawal 2009, of the 87 patients that were screened, four were not included; three of these did not fulfil the inclusion criteria, and one withdrew consent. Thus 83 patients were allocated into four groups; the two groups relevant to this review are those treated with sodium valproate (n = 20) and those treated with placebo (n = 21). There were no withdrawals from the valproate group, although one patient withdrew from the placebo group due to persistence of pain (lack of efficacy).

Kochar 2005 screened and enrolled 48 patients, 24 each being allocated into the valproate and placebo group. One participant was excluded from the valproate group because of insufficient pain, and two from the placebo group; one due to insufficient pain, and the other due to withdrawal of consent. In terms of dropouts, one participant withdrew from the valproate group because of adverse events, and four from the placebo group; two because of non-compliance, and two due to persistence of pain.

In Kochar 2004, 48 participants were screened, and five were not included (four did not fulfil the inclusion criteria, and one withdrew consent). Thus, 43 participants were randomised, 22 into the valproate group, and 21 into the placebo group. One patient withdrew from the valproate group because of adverse events, and three withdrew from the placebo group due to lack of compliance.

To summarise, the greatest number of withdrawals was observed in the placebo groups, and this was associated with persistence of pain or non-compliance. The number of withdrawals from the valproate groups was fewer (with a maximum of one participant in any one study), and was associated with adverse events.

Adverse events

Adverse events with placebo were observed only in Agrawal 2009, where one patient reported nausea.

In Agrawal 2009, where 20 mg/kg/day (equivalent to 1400 mg/day in a 70 kg participant) of sodium valproate was administered for three months in 20 participants, there were two reports of 'nausea', one of 'sedation', and one of a 'change in liver enzymes'. It is not clear whether these adverse events all occurred in different participants, however, and none were withdrawn from treatment.

Sodium valproate was also administered for three months in Kochar 2004, although at the lower dose of 500 mg/day. Of the 22 participants, two developed 'nausea', and one 'minor drowsiness'; one participant developed a 'major side-effect in the form of deranged liver function tests' after one month, and was withdrawn from the study.

In Kochar 2005, participants in the valproate group took 1000 mg/day of divalproex sodium for eight weeks. Of the 24 participants, three "complained of nausea, dizziness, drowsiness, and mild change in appetite, which gradually subsided over a period of three to five days, and did not require stopping of the drug". There was one incidence of severe vertigo 10 days into treatment, as a result of which, the participant was withdrawn from the study.

Serious adverse events

Only one serious adverse event was reported in the 66 participants taking active treatment and 64 treated with placebo (abnormal liver function tests with sodium valproate in Kochar 2004).

DISCUSSION

Summary of main results

This review found few relevant studies; we included three and excluded another four. Of the included studies, Agrawal 2009 and Kochar 2004 included participants with diabetic neuropathy, and Kochar 2005 participants with post-herpetic neuralgia.

The main limiting factor in the included studies was the small sample sizes. Statistically greater improvements in pain scores with active treatment compared with placebo were reported only in the study looking at post-herpetic neuralgia (Kochar 2005) and one of the studies looking at diabetic neuropathy (Kochar 2004). The lack of consistency in results may be attributable to the small sample sizes, which make the results susceptible both to the random play of chance and systematic bias, and to slightly different patient populations. In diabetic neuropathy, Agrawal 2009 included patients with type I diabetes, whereas Kochar 2004 did not. Although the presentation of diabetic neuropathy may be similar in both type I and II diabetes, the underlying disease process may differ, and affect the response to treatment.

The few included studies do suggest some support for the use of sodium valproate and divalproex sodium in the treatment of diabetic neuropathy and post-herpetic neuralgia. This must

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be interpreted with caution given the many limiting factors we describe, particularly the very limited numbers of participants and the limitations of the studies.

In terms of adverse events, incidences of nausea, drowsiness, sedation, changes in liver enzymes and vertigo were reported, with only one considered serious (raised liver enzymes). However, with the limited sample sizes, estimates of the frequency of these and their relation to treatment dosage are not possible.

The authors believe that there will be no need for an update of this review, unless the place of valproate in therapy changes.

Overall completeness and applicability of evidence

Two studies investigated diabetic neuropathy (Agrawal 2009 and Kochar 2004) and one post-herpetic neuralgia (Kochar 2005). Although studies investigating treatment of cancer-related neuropathy (Hardy 2001), chronic central pain (Drewes 1994) and polyneuropathy in general (Otto 2004) were identified, together with one other example of a study investigating treatment of diabetic neuropathy (Kochar 2002), these failed to meet the inclusion criteria employed in the current review. In one case (Hardy 2001), this was because the study was a phase II open-label trial, but in the other cases, this was due to inadequate duration of study. Including the two studies of four-weeks' duration would not have changed the findings of this review as they also were small. Kochar 2002 showed significantly greater improvement in mean pain score with sodium valproate than placebo in PDN (completer analysis, n = 52); Otto 2004 (combining both periods of cross-over) showed no significant difference in median total pain between groups in polyneuropathy (completer analysis, n = 31). No studies were found in fibromyalgia or other categories of neuropathic pain.

Potential harm from valproic acid and its derivatives cannot be determined from the studies in this review. Harm has been best studied when they are used to treat epilepsy, and these risks are almost certainly present for chronic pain patients. Valproic acid is known to be associated with a number of rare, but serious adverse events, including haemorrhagic pancreatitis, coagulopathies, bone marrow suppression, valproic acid-induced hepatotoxicity and encephalopathy (Gerstner 2008), and is teratogenic (Kluger 2008).

Quality of the evidence

Only three studies (Agrawal 2009; Kochar 2004; Kochar 2005) satisfied the inclusion criteria for this systematic review. The sample sizes in all of these were limited, and only Kochar 2005 provided dichotomous data on the number of participants achieving at least 50% pain relief, which we consider to be a preferred measure of efficacy. The continuous measures of pain employed in all three studies included VAS, short form McGill Pain Questionnaire, and Present Pain Intensity, with Agrawal 2009 and Kochar 2005 also using an 11-point Likert Scale. Although Kochar 2005 also offered data from the PGIC score, this was given in the form of percentages that did not translate back to whole person equivalents, and hence were not assessed in this review.

The 'Risk of bias' assessment showed that all three studies were at high risk due to small sample size and use of completer analysis, with further unknown risks from inadequate reporting of methods used for sequence generation (3/3 studies), allocation concealment (2/3), and blinding (2/3). The possibility of publication bias from unpublished negative results cannot be excluded, with potential large effects on any overall assessment given the paucity of any positive results.

Potential biases in the review process

We believe the search methodology used here to be unbiased, and the selection criteria relevant to the nature of chronic neuropathic pain and fibromyalgia.

Agreements and disagreements with other studies or reviews

Although there have been a number of systematic reviews investigating options in the treatment of chronic neuropathic pain and fibromyalgia, none have focused specifically on the use of sodium valproate or valproic acid. Wong 2007 reviewed antiepileptic drugs for painful diabetic neuropathy, including one study of sodium valproate that we excluded because of the short duration (Kochar 2002), and one that we included, but which gave no dichotomous efficacy data (Kochar 2004). Previous systematic reviews of antiepileptic drugs for treating chronic pain have found very limited evidence on valproic acid or its salt. One systematic review (McQuay 1995), included a single study of valproate in migraine prophylaxis. No more studies were reported in a second review (Collins 2000), while another (Wiffen 2005) included one study, which we excluded from this review because of the short duration. Finnerup 2005 again included some studies we excluded because of their short duration, but came to very similar conclusions.

In 2006, EFNS guidelines claimed that because of conflicting results, further trials of valproic acid in neuropathic pain were needed before its level of recommendation was settled (Attal 2006). Guidelines from the Canadian Pain Society report valproic acid as a possible fourth-line therapy (Moulin 2007), and recommendations from the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain place valproic acid amongst third-line therapies for patients who cannot tolerate or who do not respond adequately to first- and second-line medications (Dworkin 2010).

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that sodium valproate and divalproex sodium may be effective in the treatment of chronic pain associated with diabetic neuropathy and post-herpetic neuralgia, respectively. However, based on the quantity and limitations of the available evidence, the use of these medications should be reserved for cases where other proven treatment options (e.g. Moore 2009, Moore 2011, Lunn 2009) have failed, are not available, or are not tolerated.

Implications for research

This review highlights the limited availability of high standard, randomised, double-blinded placebo-controlled trials investigating the use of sodium valproate and valproic acid in the treatment of chronic neuropathic pain and fibromyalgia. Evidenced-based decisions require further study, but since these drugs are associated with known serious adverse effects, and alternative therapies are available, it is unlikely that any large trials will be conducted. In these circumstances a registry of their use in this context would be desirable.

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CHARACTERISTICS OF STUDIES

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

Agrawal 2009

Study characteristics	
Methods	Prospective single-centre randomised, double-blinded, placebo-controlled trial; excluded participants previously treated with glyceryl trinitrate, or male patients on concurrent sildenafil therapy Study duration 3 months
Participants	N = 83 (80 completed); Type I and II diabetics with symptoms of diabetic neuropathy and daily neuropathic pain ≥ moderate for > 3 months; mean age ~59 years; duration of diabetes ~8 years
Interventions	Sodium valproate 20 mg/kg/day, n = 20 Glyceryl trinitrate 0.4 mg, n = 20 Sodium valproate + glyceryl trinitrate, n = 22 Placebo, n = 21 no rescue medication allowed
Outcomes	Group mean pain intensity (SF-MPQ, VAS, PPI, PLS) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4
Risk of bias	

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Agrawal 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"placebo tablets used were similar in colour, size and texture"
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes in Methods were reported in some way, although not necessarily as our preferred outcome
Study size	High risk	Treatment groups < 50 participants

Kochar 2004

Study characteristics	
Methods	Prospective single-centre, randomised, placebo-controlled trial Study duration 3 months
Participants	N = 43 (39 completed); Type II diabetes mellitus ≥ 6 months; good glycaemic control; painful diabetic neuropathy with daily neuropathic pain ≥ moderate for > 3 months; HbA1c < 11; PI > 4/10; mean duration of diabetes ~9 years; M:F 21:18; mean age ~55 years; baseline pain ~6/10
Interventions	Sodium valproate 500 mg/day, n = 22 Placebo, n = 21
Outcomes	Group mean pain intensity (MPQ, VAS and PPI) Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

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Kochar 2004 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	'the patients received either 500mg (one tablet) of sodium valproate once a day, or similar type of placebo one tablet once a day.'
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis
Selective reporting (reporting bias)	Low risk	All relevant outcomes in Methods were reported in some way, although not necessarily as our preferred outcome.
Study size	High risk	Treatment groups < 50 participants

Kochar 2005

Study characteristics	
Methods	Prospective single-centre, randomised, double-blinded, placebo-controlled trial; not enriched Study duration 8 weeks
Participants	N = 48 (45 completed); post-herpetic neuralgia; M:F 22:18; mean age ~57 years; duration of post-herpetic neuralgia ~8 months; baseline pain ~66/100
Interventions	Divalproex sodium 1000 mg/day, n = 23 Placebo, n = 22
Outcomes	Group mean pain intensity (SF-MPQ, VAS, Likert, PPI) PGIC - 4 categories, scale not reported, percentages used which could not be converted to participant numbers Specific adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	'Allocation of numbers and decoding was done by the statistician.'; 'Decoding was done at the end of the study by the statistician, and the patients who received drug and placebo were placed in groups A and B, respectively.'
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	Completer analysis

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Kochar 2005 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All relevant outcomes in Methods were reported in some way, although not necessarily as our preferred outcome.
Study size	Unclear risk	Treatment groups < 50 participants

DB - double blind; PLS - Likert scale; PGIC - patient global impression of change; PI - pain intensity: PPI - present pain intensity; R - randomised; SF-MPQ - short form McGill pain questionnaire; VAS - visual analogue scale; W - withdrawal

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

Study	Reason for exclusion
Drewes 1994	Cross-over study, with each phase only lasting 3 weeks
Hardy 2001	Phase II study, with no placebo control
Kochar 2002	Trial duration only 4 weeks
Otto 2004	Cross-over study, with each phase lasting only 4 weeks

APPENDICES

Appendix 1. Search strategy for MEDLINE (via OVID)

1. exp PAIN/
2. exp PERIPHERAL NERVOUS SYSTEM DISEASES/
3. exp SOMATOSENSORY DISORDERS/
4. FIBROMYALGIA/ or exp MYOFASCIAL PAIN SYNDROMES/ or POLYMYALGIA RHEUMATICA/
5. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
6. (fibromyalgi* or fibrosti* or FM or FMS).mp.
7. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Valproic acid/ or (valproic acid or valproate or sodium valproate).mp.
10. (Convulex or Depakote or Depakene or Depacon or Depakine or Epilim or Episenta or Stavzor).mp.
11. 9 or 10
12. 8 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. or/13-20
22. exp animals/ not humans.sh.
23. 21 not 22

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24.23 and 12

Appendix 2. Search strategy for EMBASE (via OVID)

1. VALPROIC ACID/ or VALPROATE SEMISODIUM/
2. (valproic acid or valproate).mp.
3. (Convulex or Depakote or Depakene or Depacon or Depakine or Epilim or Episenta or Stavzor).mp.
4. 1 or 2 or 3
5. exp CHRONIC PAIN/
6. exp PERIPHERAL NEUROPATHY/
7. exp SOMATOSENSORY DISORDER/
8. RHEUMATIC POLYMYALGIA/
9. exp MYOFASCIAL PAIN/
10. FIBROMYALGIA/
11. ((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp.
12. (fibromyalgi* or fibrosti* or FM or FMS).mp.
13. ((neur* or nerv*) adj6 (compress* or damag*)).mp.
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. random*.ti,ab.
16. factorial*.ti,ab.
17. (crossover* or cross over* or cross-over*).ti,ab.
18. placebo*.ti,ab.
19. (doubl* adj blind*).ti,ab.
20. assign*.ti,ab.
21. allocat*.ti,ab.
22. RANDOMIZED CONTROLLED TRIAL.sh.
23. DOUBLE-BLIND PROCEDURE.sh.
24. CROSSOVER PROCEDURE.sh.
25. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 4 and 14 and 25

Appendix 3. Search strategy for CENTRAL

1. MeSH descriptor Pain explode all trees
2. MeSH descriptor Peripheral Nervous System Diseases explode all trees
3. MeSH descriptor Somatosensory Disorders explode all trees
4. MeSH descriptor Fibromyalgia, this term only
5. MeSH descriptor Myofascial Pain Syndromes explode all trees
6. MeSH descriptor Polymyalgia Rheumatica explode all trees
7. ((pain* or discomfort*) and (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)):ti,ab,kw
8. (fibromyalgi* or fibrosti* or FM or FMS):ti,ab,kw
9. ((neur* or nerv*) and (compress* or damag*)):ti,ab,kw
10. (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9)
11. MeSH descriptor Valproic Acid, this term only
12. (valproic acid or valproate or sodium valproate):ti,ab,kw
13. (Convulex or Depakote or Depakene or Depacon or Depakine or Epilim or Episenta or Stavzor):ti,ab,kw
14. (12 OR 13)
15. 15 (10 AND 14) [33]

Appendix 4. Results in individual studies

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Study ID	Condition, treatment, dose and duration	Comparator Numbers in trial	Withdrawals	Efficacy	Adverse events (general)	Adverse events (specific)
Agrawal 2009	Diabetic neuropathy, sodium valproate, 20 mg/kg/day, 3 months	Placebo N = 41	Valproate = 0 Placebo = 1 (persistence of pain)	Mean ± SE VAS: Valproate: 8.0 ± 0.2 at 0 months, 6.2 ± 0.3 at 3 months, P < 0.001 Placebo: 7.4 ± 0.3 at 0 months, 6.9 ± 0.2 at 3 months, P < 0.1 Valproate vs placebo at end point: P < 0.1	No data	Sodium valproate: 2 nausea, 1 sedation, 1 liver enzyme changes Placebo: 1 nausea
Kochar 2005	Post-herpetic neuralgia, divalproex sodium, 1000 mg/day, 3 months	Placebo N = 45	Valproate = 1 (vertigo) Placebo = 4 (2 non-compliance, 2 persistence of pain)	At least 50% pain relief (ITT): Valproate: 13/23 Placebo: 2/22 Mean ± SE VAS: Valproate: 70 ± 9.2 at 0 months, 31 ± 30 at 3 months Placebo: 63 ± 9.2 at 0 months, 55 ± 18 at 3 months Valproate vs mean placebo at end point: P <0.0001	Divalproex sodium: 23 participants, 4 experiencing adverse effects Placebo: 0	Divalproex sodium: 3 'nausea, dizziness, drowsiness, and mild changes in appetite', 1 severe vertigo Placebo: 0
Kochar 2004	Diabetic neuropathy, sodium valproate, 500 mg/day, 8 weeks	Placebo N = 43	Treatment = 1 (abnormal LFTs) Placebo = 3 (all non-compliance)	Mean ± SE VAS: Valproate: 6.0 ± 2.0 at 0 months, 3.0 ± 2.1 at 3 months Placebo: 5.7 ± 1.7 at 0 months, 6.0 ± 1.8 at 3 months Valproate vs placebo at end point: P < 0.001	No data	Sodium valproate: 2 nausea, 1 sedation, 1 liver enzyme changes Placebo: 0

ITT - intention to treat; LFT - liver function tests; SE - standard error; VAS - visual analogue scale

WHAT'S NEW

Date	Event	Description
8 June 2020	Review declared as stable	See Published notes.

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HISTORY

Protocol first published: Issue 7, 2011
Review first published: Issue 10, 2011

Date	Event	Description
29 May 2019	Amended	Contact details updated.
18 July 2013	Review declared as stable	This review will be assessed for further updating in 2020 as it is unlikely that new evidence will be published.
27 June 2012	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

RAM and SD wrote the protocol. DG and SD carried out literature searches, identified studies for inclusion, and extracted data. DG entered data into RevMan, and SD checked it. All authors were involved in analysis of data and writing the full review.

DECLARATIONS OF INTEREST

SD and RAM have received research support from charities, government and industry sources at various times. RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. DG and PW have no interests to declare. There was no financial support or input to this review from any pharmaceutical company.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Trust, UK

External sources

- No sources of support supplied

NOTES

At June 2020, we are not aware of any potentially relevant studies likely to change the conclusions. This is not an active area of research and we do not expect any studies to be published that will affect our conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Diabetic Neuropathies [*drug therapy]; Fibromyalgia [*drug therapy]; Neuralgia, Postherpetic [*drug therapy]; Randomized Controlled Trials as Topic; Valproic Acid [adverse effects] [*therapeutic use]

MeSH check words

Adult; Humans

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