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Zonisamide for neuropathic pain in adults (Review)

Moore RA, Wiffen PJ, Derry S, Lunn MPT

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TABLE OF CONTENTS

[Intervention Review]

Zonisamide for neuropathic pain in adults

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ABSTRACT

Background

Antiepileptic drugs have been used in pain management since the 1960s; some have shown efficacy in treating different neuropathic pain conditions. The efficacy of zonisamide for the relief of neuropathic pain has not previously been reviewed.

Objectives

To assess the analgesic efficacy and associated adverse events of zonisamide for chronic neuropathic pain in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO), MEDLINE, EMBASE, and two clinical trials databases (ClinicalTrials.gov. and the World Health Organisation Clinical Trials Registry Platform) to 1 August 2014, together with reference lists of retrieved papers and reviews.

Selection criteria

We included randomised, double-blind studies of at least two weeks' duration comparing zonisamide with placebo or another active treatment in chronic neuropathic pain. Participants were adults aged 18 and over. We included only full journal publication articles and clinical trial summaries.

Data collection and analysis

Two review authors independently extracted efficacy and adverse event data, and examined issues of study quality. We considered the evidence using three tiers. First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, 8 to 12 weeks duration, parallel design); second tier evidence derived from data that failed to meet one or more of these criteria and were considered at some risk of bias but with adequate numbers in the comparison; and third tier evidence derived from data involving small numbers of participants that were considered very likely to be biased or used outcomes of limited clinical utility, or both.

We planned to calculate risk ratio (RR) and numbers needed to treat (NNT) and harm (NNH) for one additional event using standard methods expected by The Cochrane Collaboration.

Main results

We included a single study treating 25 participants (13 zonisamide, 12 placebo) with painful diabetic neuropathy over 12 weeks. No first or second tier evidence was available for any outcome. The small size of the study and potential major bias due to a high proportion of early study withdrawals with zonisamide precluded any conclusions being drawn. There were two serious adverse events (one death) in zonisamide-treated participants, which were apparently not related to treatment.

Authors' conclusions

The review found a lack of evidence suggesting that zonisamide provides pain relief in any neuropathic pain condition. Effective medicines with much greater supportive evidence are available.

PLAIN LANGUAGE SUMMARY

Zonisamide for neuropathic pain in adults

Neuropathic pain can arise from damage to nerves and injury to the central nervous system. It is different from pain messages carried along healthy nerves from damaged tissue (a fall, or cut, or arthritic knee). Neuropathic pain is treated by different medicines than those used for pain from damaged tissue. Medicines like paracetamol or ibuprofen are not usually effective in neuropathic pain, while medicines that are sometimes used to treat depression or epilepsy can be very effective in some people with neuropathic pain.

Zonisamide is one of a type of medicine normally used to treat epilepsy. Some of these medicines are also useful for treating neuropathic pain. We looked for clinical trials that used zonisamide to treat neuropathic pain. We found a single study with 25 participants treated either with zonisamide or placebo. Study reporting may have led to major over-estimation of any treatment effects because most (8/13) participants treated with zonisamide withdrew before the end of 12 weeks of treatment for a variety of reasons, mostly adverse events (side effects).

There was too little information, which was of inadequate quality, to give any guidance as to whether zonisamide works as a pain medicine in any neuropathic pain condition. Other medicines have been shown to be effective in some types of neuropathic pain.

BACKGROUND

This review is based on a template for reviews of drugs used to relieve neuropathic pain. The aim is for all reviews to use the same methods, based on new criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Appendix 1). An overview review of antiepileptic drugs for treating neuropathic pain found no Cochrane review for zonisamide (Wiffen 2013).

Description of the condition

The 2011 International Association for the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) based on a definition agreed at an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, but is often followed by changes in the central nervous system (Moisset 2007). The origin of neuropathic pain is complex (Apkarian 2011; Baron 2010; Baron 2012; Tracey 2011; von Hehn 2012), and neuropathic pain features can be found in patients with joint pain (Soni 2013). Many people with neuropathic pain conditions are disabled with significant levels of pain for many years. Chronic painful conditions comprise 5 of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and are responsible for considerable loss of quality of life, employment, and increased health costs (Moore 2014a).

The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), as high as 8% in the UK (Torrance 2006), about 7% in a systematic review of studies published since 2000 (Moore 2014a), and 7% to 10% in a systematic review of epidemiological studies published between 1966 and 2012 (van Hecke 2014). The prevalence of some types of neuropathic pain, such as diabetic neuropathy and postsurgical chronic pain (which is often neuropathic in origin), is increasing (Hall 2008). Estimates vary between studies, often because of small numbers of cases. A systematic review of chronic

pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy (PDN), can be more common, with prevalence rates up to 400 per 100,000-person years (McQuay 2007) illustrating how common the condition was, as well as its chronicity.

In primary care in the UK, the incidences per 100,000-person years observation, have been reported as 28 (95% confidence interval (CI) 27 to 30) for postherpetic neuralgia, 27 (95% CI 26 to 29) for trigeminal neuralgia (facial pain), 0.8 (95% CI 0.6 to 1.1) for phantom limb pain, and 21 (95% CI 20 to 22) for painful diabetic neuropathy (Hall 2008). In other studies, the incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while a study of facial pain in The Netherlands found incidences per 100,000-person years of 12.6 for trigeminal neuralgia and 3.9 for postherpetic neuralgia (Koopman 2009).

Neuropathic pain is difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention (Moore 2013b). A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical, or cognitive interventions, or both. Conventional analgesics are usually not effective. Some patients may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, though evidence about benefits is uncertain (Derry 2012; Derry 2014). High concentration topical capsaicin may benefit some patients with postherpetic neuralgia (Derry 2013). Treatment is often by so-called unconventional analgesics, such as antidepressants like duloxetine and amitriptyline (Lunn 2014; Moore 2012a; Moore 2014b) or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2014c; Wiffen 2013).

The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction; Moore 2013a) is small, generally only 10% to 25% more than with placebo, with numbers needed to treat for an additional beneficial outcome (NNT) usually between 4 and 10 (Kalso 2013; Moore 2013b). Neuropathic pain is not particularly different from other chronic pain conditions in that only a small proportion of trial participants have a good response to treatment (Moore 2013b).

An overview of treatment guidelines points out some general similarities, but also differences in approach (O'Connor 2009). Many guidelines suggest the use of opioids when other treatments have failed. For example, the current National Institute for Health and Care Excellence (NICE) guidance for non-specialist use suggests offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia), with switching if first, second, or third drugs tried are not effective or not tolerated (NICE 2013). Tramadol is suggested as a rescue therapy, and morphine, for example, is not suggested as a useful therapy unless advised by a specialist.

Description of the intervention

Zonisamide is a sulphonamide antiepileptic drug created in the 1970s and found to have potent anticonvulsant activity. It is approved in the USA, UK, Japan, and Australia for treatment of various forms of epilepsy. Daily doses of oral zonisamide are usually in the range of 200 mg to 600 mg daily. Typical adverse events in zonisamide studies in epilepsy include somnolence, dizziness, and anorexia. A preliminary uncontrolled open-label study on only 27 patients with a variety of chronic pain conditions suggested that zonisamide might be effective (Hasegawa 2004), and there are indications from randomised trials that it might be useful in migraine prophylaxis (Mohammadianinejad 2011).

How the intervention might work

Zonisamide probably has a range of different modes of action. These include reducing sodium-dependent high firing action potentials in nerves, and inhibiting some calcium currents that may prevent the spread of seizure discharges between cells. Zonisamide also alters dopamine, 5-hydroxytryptamine (5-HT), and acetylcholine metabolism, and weakly inhibits carbonic anhydrase, as well as having effects on gamma amino butyric acid (GABA)-mediated neuronal inhibition and glutamate release (Brodie 2012). Any or all of these effects could possibly have relevance to treatment of neuropathic pain, either peripherally or centrally. Animal studies (Bektas 2014; Sakaue 2004; Tanabe 2008), human studies in central neuropathic pain (Takahashi 2004), and peripheral neuropathic pain exist with positive outcomes (Atli 2005; Krusz 2003).

Why it is important to do this review

Zonisamide is not commonly prescribed for neuropathic pain and it is not licensed for the treatment of neuropathic pain in the UK or USA, but the potential for benefit from this drug needs to be investigated. This review is one of a series of reviews covering the role of antiepileptics in neuropathic pain, and this review will be included in an update of an overview review (Wiffen 2013).

The standards used to assess evidence in chronic pain trials have changed substantially, with particular attention being paid to trial duration, withdrawals, and statistical imputation following withdrawal, all of which can substantially alter estimates of efficacy. The most important change is the move from using average pain scores, or average change in pain scores, to the number of patients who have a large decrease in pain (by at least 50%); this level of pain relief has been shown to correlate with improvements in comorbid symptoms, function, and quality of life. These standards are set out in the Cochrane Pain, Palliative and Supportive Care Group's Author and Referee Guidance for pain studies (AUREF 2012).

This Cochrane review will 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 2010a; Moore 2012b). Studies 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 at least 400 participants in a comparison in which the NNT is four or above (Moore 1998)). This sets high standards and marks a departure from how reviews have been done previously.

OBJECTIVES

To assess the analgesic efficacy and associated adverse events of zonisamide for chronic neuropathic pain in adults.

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 participant outcomes following two weeks of treatment or longer, although the emphasis of the review was on studies of eight weeks or longer. We required full journal publication, with the exception of online clinical trial results or summaries of otherwise unpublished clinical trials and abstracts with sufficient data for analysis. We did not include short abstracts (usually meeting reports). We excluded studies that were non-randomised, studies of experimental pain, case reports and clinical observations.

Types of participants

Studies included adults aged 18 years and above. Participants could have one or more of a wide range of chronic neuropathic pain conditions, but we specifically searched for and included:

- painful diabetic neuropathy;
- postherpetic neuralgia;
- trigeminal neuralgia;
- phantom limb pain;
- postoperative or traumatic neuropathic pain;
- complex regional pain syndrome (CRPS), Type I and Type II;
- cancer-related neuropathy;
- human immunodeficiency virus (HIV) neuropathy;
- spinal cord injury; and
- poststroke pain.

If studies included participants with more than one type of neuropathic pain, we planned to analyse results according to the primary condition.

Types of interventions

Zonisamide at any dose, by any route, administered for the relief of neuropathic pain and compared to placebo or any active comparator.

Types of outcome measures

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity, or pain relief, or both. We are particularly interested in Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (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 much improved on Patient Global Impression of Change (PGIC) (moderate), and very much improved on PGIC (substantial). These outcomes are different from those used in most earlier reviews, concentrating as they do on dichotomous outcomes where pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50%, and with pain not worse than mild (Moore 2013a; O'Brien 2010).

We intended to include a 'Summary of findings' table as set out in the author guide (AUREF 2012), although the limited amount of data meant that this was not possible. The 'Summary of findings' table would have included outcomes of at least 50% and at least 30% pain intensity reduction, PGIC, adverse event withdrawals, serious adverse events, and death.

Primary outcomes

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

Secondary outcomes

1. Any pain-related outcome indicating some improvement.
2. Participants experiencing any adverse event.
3. Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an

'important medical event' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics/consequences.

4. Specific adverse events, particularly somnolence and dizziness.
5. Withdrawals due to adverse events.
6. Withdrawals due to lack of efficacy.

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) (via CRSO) to 1 August 2014.
- MEDLINE (via Ovid) 1946 to 1 August 2014.
- EMBASE (via Ovid) 1976 to 1 August 2014.

The search strategies for CENTRAL, MEDLINE, and EMBASE are given in Appendix 2, Appendix 3, and Appendix 4.

Searching other resources

We reviewed the bibliographies of all randomised trials identified and review articles, and searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and WHO ICTTRP (http://apps.who.int/trialsearch/) to identify additional published or unpublished data. We did not contact investigators or study sponsors.

Data collection and analysis

The intention was to perform separate analyses according to particular neuropathic pain conditions. Analyses combining different neuropathic pain conditions, if done, would be for exploratory purposes only. In the event there were insufficient data for any pooled analyses.

Selection of studies

We determined eligibility by first reading the title and 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; decisions were made by two review authors. Two review authors then read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We have included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Data extraction and management

Two review authors independently extracted data using a standard form and checked for agreement before entry into Review Manager (RevMan 2014) or any other analysis tool. We included information about the pain condition and number of participants treated, drug and dosing regimen, study design (for example, parallel-group or cross-over, placebo or active control, titration schedule), 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 Oxford Quality Score as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996).

Two authors independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study:

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process - for example, random number table; computer random number generator); or unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); or unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (for example, open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, for example, identical tablets; matched in appearance and smell); or unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with

incomplete data as: low risk (< 10% of participants did not complete the study, or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); or high risk of bias (used 'completer' analysis).

5. Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We planned to use dichotomous data to calculate risk ratio (RR) with 95% confidence intervals (CI) using a fixed-effect model unless significant statistical heterogeneity was found (see below), and to calculate 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. Continuous data would not be used. In the event, there were insufficient data and we were able only to present results descriptively.

Unit of analysis issues

For cross-over studies, we planned to use first period data only, where possible.

Dealing with missing data

We planned to use intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication, and provided at least one post-baseline assessment. Where possible we assigned zero improvement to missing participants.

Assessment of heterogeneity

We planned to deal with clinical heterogeneity by combining studies that examined similar conditions, and to assess statistical heterogeneity visually (L'Abbé 1987), and with the use of the I^2 statistic, but no pooling of data was possible.

Assessment of reporting biases

The aim of this review was to use dichotomous data of known utility and of value to patients (Moore 2010b; Moore 2013a). The review did not depend on what authors of the original studies chose to report or not, though clearly difficulties arose in studies failing to report any dichotomous results. We extracted and used continuous data, which probably poorly reflect efficacy and utility, only where useful for illustrative purposes.

We planned to assess publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNT of 10 or higher) (Moore 2008). We were unable to do this because of a lack of data.

Data synthesis

We planned to use a fixed-effect model for meta-analysis unless there was significant clinical heterogeneity and it was still considered appropriate to combine studies, in which case we would have used a random-effects model. There were insufficient data for any pooled analysis.

We assessed data for each painful condition in three tiers, according to outcome and freedom from known sources of bias.

- The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation method other than baseline observation carried forward (BOCF) for dropouts, reported an intention-to-treat (ITT) analysis, lasted eight or more weeks, had a parallel-group design, and had at least 200 participants (preferably at least 400) in the comparison (Moore 2010a; Moore 2012b). These top-tier results would be reported first.
- The second tier used data from at least 200 participants, but where one or more of the above conditions was not met (for example, reported at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasted four to eight weeks).
- The third tier of evidence related to data from fewer than 200 participants, or where there were expected to be significant problems because, for example, of very short duration studies of less than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation concealment, attrition, or incomplete outcome data. For this third tier of evidence, no data synthesis is reasonable, and may be misleading, but an indication of beneficial effects might be possible.

Subgroup analysis and investigation of heterogeneity

We planned all analyses to be according to individual painful conditions, because placebo response rates with the same outcome can vary between conditions, as can the drug-specific effects (Moore 2009).

Sensitivity analysis

We planned no sensitivity analysis because the evidence base is known to be too small to allow reliable analysis.

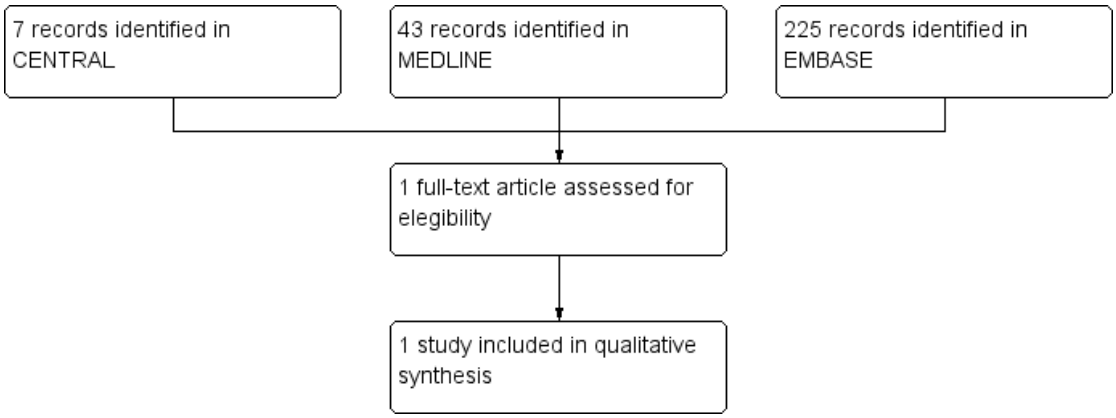
RESULTS

Description of studies

Results of the search

We identified seven potentially relevant records in CENTRAL, 43 in MEDLINE, and 225 in EMBASE.
After examining titles and abstracts of these studies, only one was found to be eligible for inclusion in the review (Atli 2005) (Figure 1). Searches on clinical trial databases revealed no ongoing or completed but unpublished studies.

Figure 1. Study flow diagram.



Included studies

We included a single study of 25 participants in painful diabetic neuropathy. It was a 12-week, parallel-group comparison of zonisamide, titrated over six weeks to a target dose of 300 mg to 600 mg daily (13 participants) with placebo (12 participants). All participants had experienced their pain for at least three months, and the intensity at study entry was moderate or severe (average score 6/10 on NRS). The mean age was 59 years, with about 40% men. Of 17 patients entering the screening phase who were not randomised, the most common reasons for exclusion were insufficient pain, elevated glycosylated haemoglobin, or no reason given by the patient. Details are provided in Characteristics of included studies table. The study was funded by a grant from Elan Pharmaceuticals.

Excluded studies

No study was excluded after obtaining a copy to read in detail.

Risk of bias in included studies

Potential biases are reported in the 'Risk of bias' section of the Characteristics of included studies table. The greatest risks of bias came from small study size and the use of LOCF imputation when 8 of 13 patients treated with zonisamide withdrew before the end of the study (mostly because of adverse events), compared with a single withdrawal with placebo.

Allocation

No information was provided on the method of randomisation or its concealment.

Blinding

The trial was described as double-blind, and therapies were double-encapsulated to ensure identical appearance.

Incomplete outcome data

Eight of 13 patients treated with zonisamide withdrew before the end of the study (mostly because of adverse events), compared with a single withdrawal with placebo.

Other potential sources of bias

LOCF imputation was used, and the study was very small, with only 25 participants randomised and 16 completing the study.

Effects of interventions

The evidence could not be considered first or second tier because of the small size and use of LOCF imputation.

Third tier evidence

Participant-reported pain relief of 50% or greater

There were 3/11 responders with $\geq$ 50% pain intensity reduction in the final week of the study with zonisamide, and none with placebo. It is not clear whether or not this result was obtained using LOCF imputation.

PGIC much or very much improved and PGIC very much improved

This outcome was not measured.

Adverse events

Participants experiencing any adverse event

With zonisamide, 11/12 patients experienced at least one adverse event; with placebo it was 10/12.

Serious adverse events

One participant taking zonisamide withdrew from the study because of a serious adverse event (drug rash without systemic complications) from which the participant recovered completely soon after discontinuation of zonisamide.

Deaths

One patient taking zonisamide died from a myocardial infarction that was judged to be entirely unrelated to the study drug.

Withdrawals

All cause withdrawals were 8/13 for zonisamide and 1/12 with placebo.

DISCUSSION

Summary of main results

One small study tested zonisamide in painful diabetic neuropathy. There were insufficient data on which to make any judgement.

Overall completeness and applicability of evidence

The amount and quality of the available evidence is so small as to preclude any applicability in a clinical setting.

Quality of the evidence

The study was small, and with major methodological issues. It cannot be regarded as reliable.

Potential biases in the review process

We carried out a broad search for studies and think it is unlikely that significant amounts of data remain unknown to us.

Agreements and disagreements with other studies or reviews

We are not aware of any other reviews of zonisamide for relief of neuropathic pain.

AUTHORS' CONCLUSIONS

Implications for practice

This review found no evidence to suggest that zonisamide provides pain relief in any neuropathic pain condition. The single available study was small and potentially subject to major bias. There are

more effective medicines available for the more common neuropathic pain conditions (Lunn 2014; Kalso 2013; Moore 2013b; Wiffen 2013).

Implications for research

Reasonable levels of evidence exist for the benefit of other antiepileptic and antidepressant drugs in the treatment of chronic neuropathic pain (for example, 14 studies of pregabalin in 3680 participants (Moore 2009); 9 studies of duloxetine in 2776 participants (Lunn 2014)).

For zonisamide, the single study we have is so small and so open to bias and error as to be uninterpretable. While this does not appear to justify continued research with zonisamide, neither can it rule out any possible beneficial effects.

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This review was developed in collaboration with the Neuromuscular Diseases Review Group, and followed the agreed template for 'drug x for neuropathic pain'. The editorial process was primarily managed by PaPaS.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Atli 2005

Methods	Randomised, double-blind, placebo-controlled, parallel-group study Duration: 1- to 2-week screening phase before randomisation, a 12-week double-blind phase (6 weeks of titration and 6 weeks of fixed dose), and a 2-week follow-up phase subsequent to drug discontinuation
Participants	Adults 18 to 80 years with type I or type II DM. Primary inclusion criteria were a ≥ 3-month history of PDN and pain severity ≥ 40 mm on a 0 to 100 VAS, and/or ≥ 4 on a Likert scale 25 randomised to treatment: 13 zonisamide and 12 placebo. 40% male Baseline mean VAS 60/100; mean Likert 6.5/10 Mean age 59 years
Interventions	Zonisamide = 13 Placebo = 12 Zonisamide titrated in the first 6 weeks by 100 mg every 7 days, to a maximum dosage of 600 mg/day, or until the patient reached maximum relief of pain or started having significant adverse effects. When intolerable side effects occurred, the dose was reduced to the last tolerated dose. The minimum target dosage of zonisamide was 300 mg/day
Outcomes	The primary measure of efficacy was the difference between the baseline pain score (the screening phase) and the mean of the weekly pain scores for the maintenance phase, with LOCF imputation for the ITT population for analysis of efficacy. (Missing weekly mean scores from the 6-week maintenance phase were imputed with the last recorded weekly mean score after the start of treatment.) Post hoc analysis was also performed using a ≥ 50% reduction in pain score as the cutoff for response Adverse events Withdrawals
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on method
Allocation concealment (selection bias)	Unclear risk	No information on method
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo capsule contained a small amount of lactulose, and the zonisamide capsule was double-encapsulated so as to

Atli 2005 (*Continued*)

		appear identical to the placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The placebo capsule contained a small amount of lactulose, and the zonisamide capsule was double-encapsulated so as to appear identical to the placebo" Patient-reported outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	"Five of the 13 patients randomized to zonisamide and 11 of the 12 patients randomized to placebo completed the study". LOCF imputation
Size	High risk	25 participants in total

DB: double blind; DM: diabetes mellitus; ITT: intention-to-treat; LOCF: last-observation-carried-forward; PDN: painful diabetic neuropathy; R: randomised; VAS: visual analogue scale; W: withdrawals

APPENDICES

Appendix 1. Methodological considerations for chronic pain

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, and longer trials provide 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, the following are some of the recent insights that must be considered in this new review.

1. Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011a; Moore 2011b), back pain (Moore 2010b; Moore 2010e), arthritis (Moore 2010c), as well as in fibromyalgia (Straube 2010), and generally in chronic pain (Moore 2014b); 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 Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (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 2010c); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.

3. The proportion of patients 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 2009; Moore 2010c; Moore 2014b; Straube 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 reasons for doing so.

4. Individual patient analyses and other evidence 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 2010d; Moore 2014a).

5. Imputation methods like last observation carried forward (LOCF), used when participants withdraw from clinical trials, can overstate drug efficacy especially when adverse event withdrawals with drug are greater than those with placebo (Moore 2012b).

Appendix 2. Search strategy for CENTRAL (via CRSO)

1. (zonisamid* or Exceglan or Excegram or Excegran or Zonegran):TI,AB,KY
2. MESH DESCRIPTOR pain EXPLODE ALL TREES
3. (pain* or analges*):TI,AB,KY
4. 2 or 3
5. 1 and 4 (7)

Appendix 3. Search strategy for MEDLINE via OVID

1. (zonisamid* or Exceglan or Excegram or Excegran or Zonegran).mp.
2. exp Pain/
3. (pain* or analges*).mp.
4. 2 or 3
5. 1 and 4
6. randomized controlled trial.pt.
7. randomized.ab.
8. placebo.ab.
9. drug therapy.fs.
10. randomly.ab.
11. trial.ab.
12. groups.ab.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 5 and 13 (43)

Appendix 4. Search strategy for EMBASE

1. (zonisamid* or Exceglan or Excegram or Excegran or Zonegran).mp.
2. exp Pain/
3. (pain* or analges*).mp.
4. 2 or 3
5. 1 and 4
6. crossover-procedure/
7. double-blind procedure/
8. randomized controlled trial/
9. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*).tw.
10. 6 or 7 or 8 or 9
11. 5 and 10 (225)

WHAT'S NEW

Date	Event	Description
28 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected

HISTORY

Protocol first published: Issue 7, 2014

Review first published: Issue 1, 2015

Date	Event	Description
7 January 2016	Review declared as stable	Stable until 2025. See Published notes.

CONTRIBUTIONS OF AUTHORS

Protocol: RAM and SD wrote the protocol, based on a PaPaS Group template for antiepileptic drugs for neuropathic pain. All authors approved it.

Review: RAM and SD searched for studies, selected studies for inclusion, and carried out data extraction. PW and ML acted as arbitrators. All authors were involved in writing the review.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product. ML has no conflicts relating to this review or any similar product. PW has no conflicts relating to this review or any similar product. RAM has no conflicts relating to this review or any similar product. For transparency we have received research support from charities, government, and industry sources at various times, but none relate to this review. We are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain.

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NOTES

A restricted search in December 2015 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in ten years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially to necessitate revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics [*therapeutic use]; Anticonvulsants [therapeutic use]; Diabetic Neuropathies [*drug therapy]; Isoxazoles [*therapeutic use]; Neuralgia [*drug therapy]; Zonisamide

MeSH check words

Adult; Female; Humans; Male; Middle Aged