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Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews (Review)

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[Overview of Reviews]

Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews

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ABSTRACT

Background

Antiepileptic drugs have been used for treating different types of neuropathic pain, and sometimes fibromyalgia. Our understanding of quality standards in chronic pain trials has improved to include new sources of potential bias. Individual Cochrane reviews using these new standards have assessed individual antiepileptic drugs. An early review from this group, originally published in 1998, was titled 'Anticonvulsants for acute and chronic pain'. This overview now covers the neuropathic pain aspect of that original review, which was withdrawn in 2009.

Objectives

To provide an overview of the relative analgesic efficacy of antiepileptic drugs that have been compared with placebo in neuropathic pain and fibromyalgia, and to report on adverse events associated with their use.

Methods

We included reviews published in the*Cochrane Database of Systematic Reviews* up to August 2013 (Issue 7). We extracted information from each review on measures of efficacy and harm, and methodological details concerning the number of participants, the duration of studies, and the imputation methods used, in order to judge potential biases in available data.

We analysed efficacy data for each painful condition in three tiers, according to outcome and freedom from known sources of bias. The first tier met current best standards - at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) for dropouts, an intention-to-treat (ITT) analysis, in parallel group studies with at least 200 participants lasting eight weeks or more. The second tier used data from at least 200 participants where one or more of the above conditions were not met. The third tier of evidence related to data from fewer than 200 participants, or with several important methodological problems that limited interpretation.

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Main results

No studies reported top tier results.

For gabapentin and pregabalin only we found reasonably good second tier evidence for efficacy in painful diabetic neuropathy and postherpetic neuralgia. In addition, for pregabalin, we found evidence of efficacy in central neuropathic pain and fibromyalgia. Point estimates of numbers needed to treat for an additional beneficial effect (NNTs) were in the range of 4 to 10 for the important outcome of pain intensity reduction over baseline of 50% or more.

For other antiepileptic drugs there was no evidence (clonazepam, phenytoin), so little evidence that no sensible judgement could be made about efficacy (valproic acid), low quality evidence likely to be subject to a number of biases overestimating efficacy (carbamazepine), or reasonable quality evidence indicating little or no effect (lamotrigine, oxcarbazepine, topiramate). Lacosamide recorded such a trivial statistical superiority over placebo that it was unreliable to conclude that it had any efficacy where there was possible substantial bias.

Any benefits of treatment came with a high risk of adverse events and withdrawal because of adverse events, but serious adverse events were not significantly raised, except with oxcarbazepine.

Authors' conclusions

Clinical trial evidence supported the use of only gabapentin and pregabalin in some neuropathic pain conditions (painful diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain) and fibromyalgia. Only a minority of people achieved acceptably good pain relief with either drug, but it is known that quality of life and function improved markedly with the outcome of at least 50% pain intensity reduction. For other antiepileptic drugs there was no evidence, insufficient evidence, or evidence of a lack of effect; this included carbamazepine. Evidence from clinical practice and experience is that some patients can achieve good results with antiepileptics other than gabapentin or pregabalin.

There is no firm evidence to answer the important pragmatic questions about which patients should have which drug, and in which order the drugs should be used. There is a clinical effectiveness research agenda to provide evidence about strategies rather than interventions, to produce the overall best results in a population, in the shortest time, and at the lowest cost to healthcare providers.

PLAIN LANGUAGE SUMMARY

Antiepileptic drugs to treat neuropathic pain or fibromyalgia- an overview of Cochrane reviews

Neuropathic pain is pain coming from damaged nerves. It is different from pain messages carried along healthy nerves from damaged tissue (eg a fall, cut, or arthritic knee). Neuropathic pain is treated by different medicines than pain from damaged tissue. Medicines such as paracetamol or ibuprofen are probably not 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. Our understanding of fibromyalgia (a condition of persistent, widespread pain and tenderness, sleep problems, and fatigue) is lacking, but fibromyalgia can respond to the same medicines as neuropathic pain.

Antiepileptic drugs (previously called anticonvulsants) are used for treating epilepsy, but have also been used for treating neuropathic pain and fibromyalgia. Many of the drugs have been the subject of individual Cochrane reviews. In August 2013 we collected all these Cochrane reviews on antiepileptic drugs together to provide an overview. Individual antiepileptic drugs work in different ways, and there is no expectation that they are equally effective.

We found that only for gabapentin and pregabalin was there some evidence that they worked in long-term nerve pain with diabetes (painful diabetic neuropathy) and pain after shingles (postherpetic neuralgia). Pregabalin also had evidence of efficacy in central neuropathic pain (typically pain after stroke) and in fibromyalgia. The drugs work very well in some people with these painful conditions, with pain reduced by half. However, only between 1 in 10 and 1 in 4 people will get this level of benefit, depending on the pain condition and the drug. Most people will get no pain relief.

The antiepileptic drugs produced side effects in most people taking them, and for about 1 in 4 these could not be tolerated so they stopped taking the drug. Serious side effects were no more common with antiepileptic drugs than with a harmless placebo.

The evidence we found did not meet current best standards, and as a result it may overestimate benefit. The biggest concern is a lack of any evidence for most drugs in most types of neuropathic pain and fibromyalgia. For lacosamide and lamotrigine there is evidence

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of a lack of effect; for other antiepileptic drugs (including carbamazepine, clonazepam, phenytoin, valproate) there is no evidence of effect or insufficient evidence of effect.

BACKGROUND

Description of the condition

Neuropathic pain tends to be chronic and may be present for months or years. The 2011 International Association of the Study of Pain definition of neuropathic pain is "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011) based on an earlier consensus meeting (Treede 2008). Neuropathic pain may be caused by nerve damage, and is often followed by changes in the central nervous system (CNS) (Moisset 2007). It is complex, and neuropathic pain features can be found in patients with joint pain (Soni 2013). Moreover, neuropathic pain and fibromyalgia patients experience similar sensory phenomena (Koroschetz 2011).

Fibromyalgia is 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 is 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, are not well understood, but it has features in common with neuropathic pain, including changes in the CNS. Some peripheral nerve fibre changes seen in neuropathic pain also occur in fibromyalgia (Oaklander 2013; Üçeyler 2013). Many people with these conditions are significantly disabled with moderate or severe pain for many years.

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, 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). Estimates vary between studies, often because of small numbers of cases. The incidence of trigeminal neuralgia has been estimated at 4 in 100,000 per year (Katusic 1991; Rappaport 1994), while more recently, 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). A systematic review of chronic pain demonstrated that some neuropathic pain conditions, such as painful diabetic neuropathy, can be more common, with prevalence rates up to 400 per 100,000 person years (McQuay 2007). The prevalence of neuropathic pain was reported as being 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008) and as high as 8% in the UK (Torrance 2006), and about 7% in a systematic review of studies published since 2000 (Moore 2013a). The incidence of some forms of neuropathic pain, such as diabetic neuropathy and postherpetic neuralgia, is increasing (Hall 2013). Fibromyalgia is common, especially in women, with an all-age prevalence of 12%, and a female to male ratio of 6:1 (McNally 2006).

Neuropathic pain and fibromyalgia are known to be difficult to treat effectively, with only a minority of individuals experiencing a clinically relevant benefit from any one intervention. 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 people with neuropathic pain may derive some benefit from a topical lidocaine patch or low concentration topical capsaicin, although evidence about benefits is uncertain (Derry 2012; Khaliq 2007). High concentration topical capsaicin may benefit some patients with postherpetic neuralgia, but it is contraindicated in diabetic neuropathy (Derry 2013). Treatment is more commonly by so-called unconventional analgesics, such as antidepressants like duloxetine and amitriptyline (Lunn 2009; Moore 2012a; Sultan 2008), or antiepileptics like gabapentin or pregabalin (Moore 2009; Moore 2011). The proportion of patients who achieve worthwhile pain relief (typically as at least 50% pain intensity reduction (Moore 2013b)) is small, typically 10 to 25% more than with placebo, with numbers needed to treat to benefit (NNTs) usually between 4 and 10.

Description of the interventions

Antiepileptic drugs (also known as anticonvulsants) have been used in pain management since the 1960s (Blom 1962), very soon after they were first used for their original indication. The clinical impression is that they are useful for some neuropathic pain symptoms. There is evidence from randomised trials about the effectiveness in neuropathic pain of a number of antiepileptics, including carbamazepine, pregabalin, phenytoin, gabapentin, and valproate. The use of antiepileptic drugs in chronic pain has tended to be confined to neuropathic pain, rather than nociceptive pain. Antiepileptics have long been recommended in combination with antidepressants, as in the treatment of postherpetic neuralgia (Monks 1994), despite any good evidence that combination pharmacotherapy is effective (Chaparro 2012). In the UK, carba-

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mazepine and phenytoin are licensed for the treatment of pain associated with trigeminal neuralgia, and gabapentin and pregabalin more generally for the treatment of neuropathic pain, though licensed indications vary in different parts of the world.
Antiepileptic drugs currently used for neuropathic pain are: carbamazepine, clonazepam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, and valproate; licensed status varies from country to country.

How the intervention might work

Different antiepileptic drugs will have different mechanisms of action, not all of which are likely to be well understood, especially in terms of how a particular drug produces pain relief in any particular individual with any particular chronic pain condition. Pain pathways are complicated, with multiple possible points for action of drugs (Dickenson 2007). Pain that manifests in different diseases may operate through common mechanisms, but the same symptom in two patients may be caused by different mechanisms. It is therefore impossible to predict the mechanisms responsible for an individual's pain based on the aetiology of the neuropathy or on the distribution or nature of symptoms (Woolf 1999).
Antiepileptics in general are thought to reduce the ability of the neuron to fire at high frequency (Chong 2000). The two standard explanations are enhanced gamma-aminobutyric acid (GABA) inhibition (valproate, clonazepam), or a stabilising effect on neuronal cell membranes, possibly by modulating ion channels. A third possibility is action via N-methyl-D-aspartate (NMDA) receptor sites (Dickenson 2007). For specific drugs:

- Gabapentin is thought to act by binding to calcium channels and modulating calcium influx. This mode of action confers antiepileptic, analgesic and sedative effects. Recent research indicates that gabapentin acts by blocking new synapse formation (Barres 2009). Clearcut explanations are not available.
- Pregabalin has a mechanism of action similar to gabapentin, binding to calcium channels and modulating calcium influx as well as influencing GABAergic neurotransmission. It is more potent than gabapentin and therefore used at lower doses. Again, clearcut explanations are not available.
- Lamotrigine is chemically unrelated to other antiepileptic agents. It is thought to exert its antiepileptic effect via sodium channels. There is some evidence that agents that block sodium channels are useful in the treatment of neuropathic pain (McCleane 2000). More recently it has been shown that neuronal alpha-4-beta2-nicotinic acetylcholine receptors may be a target for lamotrigine, and this may mediate its antiepileptic effects (Zheng 2010).
- Lacosamide is described as a functionalised amino acid molecule that selectively enhances the slow inactivation of voltage-gated sodium channels and interacts with the collapsin-response mediator protein-2 (Beydoun 2009; Errington 2008). Voltage-gated sodium channels play an important role in the excitability of nociceptors.
- Carbamazepine and its keto analogue oxcarbazepine are also thought to work by blocking voltage-gated sodium channels, making the cells less excitable.
- There is no consensus as to how phenytoin exerts any analgesic effects. It may involve voltage-gated sodium channel blockade.
- Valproate is thought to influence GABAergic neurotransmission. 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).
- Clonazepam has been suggested to work by antagonising hyperexcitability of neurotransmission through the enhancement of inhibitory GABAergic signalling pathways.
- Topiramate has been shown to block activity-dependent, voltage-gated sodium channels, enhance the action of GABA receptors, inhibit L-type voltage-gated calcium channels, presynaptically reduce glutamate release and post-synaptically block kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Chong 2003).

Risks of treatment

Antiepileptic drug use is not without risk: serious adverse effects have been reported, including deaths from haematological reactions (blood dyscrasias; Sweetman 2005) and life-threatening cutaneous problems (Chung 2010). The most common adverse effects are impaired mental and motor function, which may limit clinical use, particularly in older people (Grahame-Smith 1992; Rall 1992; Sweetman 2005). A distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of antiepileptic drugs during pregnancy (Holmes 2001).

Why it is important to do this overview

There has been a large increase in the amount of information available, and substantial changes in the way we appraise studies (AUREF 2012), which together necessitate a different approach to this topic.
Systematic reviews originally combined all antiepileptic drugs at any dose in any condition, and used any definition of pain improvement as an outcome, largely because of the paucity of available data from randomised trials at that time (McQuay 1995). A number of developments have changed this approach. First, for drugs such as gabapentin, pregabalin, and others, large modern studies have been performed to high standards, so the amount of

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evidence has increased. There have also been major developments in the understanding of the requirements for evidence to be trustworthy and reliable (Moore 2010b; Moore 2012b), all of which are now included in the authors' reference guide for the Pain, Palliative, and Supportive Care Review Group (AUREF 2012), as additional requirements above those of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Neuropathic pain and fibromyalgia can be seriously disabling and are difficult to treat, but we know that effective pain relief is associated with large improvements in associated symptoms such as depression, fatigue, sleep problems, quality of life, and work (Hoffman 2010; Moore 2010a). There is also growing information that early good response to therapy reflects good long term response in terms of pain and quality of life (Clauw 2013).

A number of reviews of individual antiepileptic drugs versus placebo in neuropathic pain conditions and fibromyalgia have been completed, using these new methodological criteria. An overview is required to facilitate indirect comparisons between individual antiepileptics, providing estimates of relative efficacy that can help to inform treatment choices. An overview using high methodological standards is useful for patients and their professional carers, as well as being a possible first step to performing mixed-treatment comparisons or network meta-analyses.

Antiepileptic drugs have very diverse mechanisms of action, and because a drug has efficacy in one neurological condition that does not necessarily translate to a different neurological condition. The convention has been that antiepileptic dugs are examined as a group, and data from different antiepileptics have been previously been combined. This overview review will examine efficacy and harm according to individual drug, and individual painful condition.

OBJECTIVES

To provide an overview of the relative analgesic efficacy of antiepileptic drugs compared with placebo in neuropathic pain and fibromyalgia, and to report on adverse events associated with their use.

METHODS

Criteria for considering reviews for inclusion

We included all Cochrane reviews of randomised, double blind trials (RCTs) of antiepileptic drugs for the treatment of neuropathic pain conditions or fibromyalgia pain.

Search methods for identification of reviews

Reviews were known to the authors and published in *The Cochrane Database of Systematic Reviews;* there was no additional searching.

Data collection and analysis

Three review authors independently selected reviews for inclusion, assessed methodological quality, and extracted data. Disagreements were resolved by discussion.

Selection of reviews

Included reviews assessed RCTs evaluating the effects of an antiepileptic drug given for relief of moderate to severe neuropathic pain or fibromyalgia pain, compared to placebo, and included:

- details of inclusion and exclusion criteria;
- details of databases searched and relevant search strategies;
- patient-reported pain relief; and
- summary results for at least one desired outcome.

Data extraction and management

We extracted data from the included reviews using a standard data extraction form, using original study reports only if specific data were missing.

We collected information on the following:

- number of included studies and participants;
- drug, dose, and any dose-escalation strategy that might be relevant;
- painful condition (eg painful diabetic neuropathy, postherpetic neuralgia, human immunodeficiency virus (HIV)-neuropathy, fibromyalgia).

We extracted information on risk ratio (relative risk, RR) and numbers needed to treat to benefit (NNT), to prevent an event (NNTp), and to harm (NNH), or calculated these for the following.

Primary outcomes:

1. patient reported pain relief of 30% or greater;
2. patient reported pain relief of 50% or greater;
3. Patient Global Impression of Change (PGIC) much or very much improved;
4. PGIC very much improved.

Secondary outcomes:

1. withdrawals due to adverse events;
2. withdrawals due to lack of efficacy;
3. participants experiencing any adverse event;
4. participants experiencing any serious adverse event;
5. specific adverse events, such as somnolence and dizziness, as reported.

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Assessment of methodological quality of included reviews

Quality of included reviews

We assessed each included review to see if it satisfied the criteria specified in the 'Assessment of multiple systematic reviews' (AMSTAR) measurement tool (Shea 2007) for rigorous methodological quality.

Each review was required to:

1. provide an *a priori* design;
2. carry out duplicate study selection and data extraction;
3. carry out a comprehensive literature search;
4. include published and unpublished studies irrespective of language of publication;
5. provide a list of studies (included and excluded);
6. assess and document the scientific quality of the included studies;
7. use the scientific quality of the included studies appropriately in formulating conclusions;
8. use appropriate methods to combine the findings of studies; and
9. state conflicts of interest.

For each review we assessed the likelihood of publication bias by calculating the number of participants in studies with zero effect (relative benefit of one) that would be needed to give an NNT too high to be clinically relevant (Moore 2008). In this case we considered an NNT of $\geq$ 10 for the outcome of patient reported pain relief of 30% or greater to be the cut-off for clinical relevance. We used this method because statistical tests for presence of publication bias have been shown to be unhelpful (Thornton 2000).

Quality of evidence in included reviews

Prespecified inclusion criteria state that all included reviews must use only primary studies that are both randomised and double-blind, so minimising the risk of bias from these items. All must also include only patients with at least moderate pain intensity at baseline (visual analogue scale > 30/100, categorical rating scale > 1/3, and numerical rating scale > 3/10), providing a sensitive assay of analgesic efficacy.

We analysed 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 for dropouts, report an intention-to-treat (ITT) analysis, last eight or more weeks, have a parallel-group design, and have at least 200 participants (preferably at least 400) in the comparison (Moore 2010b; Moore 2012b). These top-tier results are reported first.
- The second tier used data from at least 200 participants but where one or more of the above conditions was not met (eg reporting at least 30% pain intensity reduction, using LOCF or a completer analysis, or lasting four to eight weeks).
- A third tier of evidence related to data from fewer than 200 participants, or where there are 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, data synthesis was not reasonable, and may be misleading, but an indication of beneficial effects might be possible.

Data synthesis

We used information on the selected efficacy outcomes to draw up comparisons of analgesic efficacy, using indirect comparison of different drugs from almost identical clinical trial conditions, with placebo as a common comparator (Glenny 2005; Song 2003). It was known that direct comparison studies were almost completely absent, and for the most part too small to be of value, but we have noted them where they impart useful observations.

If the selected efficacy outcomes were not provided in an individual review, wherever possible we calculated them from the data provided. No further data synthesis was planned or carried out.

RESULTS

Description of included reviews

We found and included 10 Cochrane reviews reporting on the use of antiepileptic drugs for treating neuropathic pain or fibromyalgia; these were carbamazepine (Wiffen 2011a), clonazepam (Corrigan 2012), gabapentin (Moore 2011), lacosamide (Hearn 2012), lamotrigine (Wiffen 2011b), oxcarbazepine Zhou 2013), phenytoin (Birse 2012), pregabalin (Moore 2009), topiramate (Wiffen 2013), and valproic acid (Gill 2011). We did not find a review for levetiracetam. No reviews were excluded.

The numbers of studies and participants in each individual review are shown in Summary of results A; 91 studies with 17,955 participants provided evidence relating efficacy or harm of treatment in at least one of the painful conditions considered in this overview. Carbamazepine was the exception in that only 19% of participants were in studies lasting over six weeks; most were in studies shorter than four weeks. For the other antiepileptic drugs with data, most or all participants were in studies lasting longer than six weeks, mostly in studies of 10 to 12 weeks or longer.

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Summary of results A: Details of included reviews

Drug	Included studies	Participants	Duration of studies (weeks)
Pregabalin	19	7003	88% of participants in studies over 6 weeks
Gabapentin	29	3571	70% of participants in studies over 6 weeks
Lacosamide	6	2022	10 to 18
Topiramate	4	1864	12
Lamotrigine	11	1511	96% of participants in studies over 6 weeks
Carbamazepine	15	1076	19% of participants in studies over 6 weeks
Oxcarbazepine	4	779	16 to 18
Valproic acid	3	129	8 to 13
Clonazepam	0	0	No included studies
Phenytoin	0	0	No included studies
Levetiracetam			No review

Methodological quality of included reviews

All the studies included in the reviews were randomised and double blind, and included participants with at least moderate pain. Each included review fulfilled all requirements of the AMSTAR measurement tool (Shea 2007).

Effect of interventions

The effects of interventions has three sections: efficacy, study withdrawals, and adverse events. We dealt with these in different ways:

- for efficacy, individual pain conditions were considered separately, and within each condition results are presented here by outcome, by drug, and by dose or dose range used.
- for study withdrawal and adverse events, all pain conditions were combined.

No information was available for clonazepam and phenytoin, and so little for valproic acid that no meaningful interpretation was possible. These three drugs were not considered further in this overview.

In this results section, we concentrated on drugs and doses for which data were available. For many conditions and outcomes, no data were available on many drugs. To avoid repetition of 'no data' statements, it can be assumed that where no results are shown for a drug or dose, no data were available.

Some reviews reported results for what was described as mixed neuropathic pain. What constituted mixed neuropathic pain varied considerably, and because the utility of those results was uncertain, no data were presented for mixed neuropathic pain.

Efficacy outcomes

First tier evidence

No unequivocally unbiased first tier evidence meeting current best standards was available. The most common faults were the use of LOCF or other imputation method for dropouts, short studies lasting four weeks or less, small size, and the use of outcomes of limited value to patients or clinical practice.

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Second tier evidence

Evidence was rated as second tier predominantly because LOCF imputation had been used. In some cases, notably for carbamazepine, short duration trials of four weeks or less may also have contributed residual biases.

Painful diabetic neuropathy

Results of efficacy analyses for different outcomes are shown in Summary of results B. The numbers of participants available for any one analysis were typically between about 400 and 800.

There was no evidence of benefit for lamotrigine or topiramate. For lacosamide statistical benefit was seen at 400 mg daily, but not 600 mg daily, and the lower CI was close to 1. For oxcarbazepine 600 to 1800 mg daily, two of the three included studies, with 75% of participants, were not significantly different from placebo; no pooled analysis was available.

Gabapentin, lacosamide, and pregabalin showed evidence of efficacy at least for one dose or dosing regimen. For both carbamazepine and gabapentin, benefit was seen only when combining a wide range of dosing regimens used, and no evidence was available for a particular daily dose.

The point estimates of NNTs were in the range of 5 to 11 for different outcomes.

Summary of results B: Painful diabetic neuropathy - efficacy analyses for different outcomes

Drug	Dose (mg/day)	Number of		Percent achieving outcome with		RR (95% CI)	NNT (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: at least 50% pain intensity reduction							
Gabapentin	600 to 3600	4	829	40	23	1.8 (1.4 to 2.2)	5.8 (4.3 to 9.0)
Lacosamide	400	2	412	35	25	1.4 (1.01 to 1.9)	10 (5.2 to 120)
	600	2	407	28	25	1.1 (0.8 to 1.6)	*Not calculated*
Lamotrigine	200 to 400	3	773	26	24	1.1 (0.8 to 1.4)	*Not calculated*
Pregabalin	300	3	645	38	29	1.3 (1.1 to 1.6)	11 (6.1 to 54)
	600	4	1005	46	30	1.5 (1.3 to 1.8)	6.3 (4.6 to 10)
Outcome: at least 30% pain intensity reduction							
Pregabalin	300	1	304	58	52	1.1 (0.9 to 1.4)	*Not calculated*
	600	2	641	62	48	1.3 (1.1 to 1.5)	6.8 (4.4 to 15)
Outcome: Patient Global Impression of Change -excellent							
Gabapentin	600 to 3600	2	408	24	14	1.9 (1.3 to 3.0)	9.6 (5.5 to 35)
Outcome: Patient Global Impression of Change - very good or excellent							
Gabapentin	600 to 3600	3	466	43	31	1.5 (1.1 to 1.9)	8.1 (4.7 to 28)
Lacosamide	400	4	715	33	24	1.5 (1.2 to 1.9)	12 (6.6 to 52)

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(*Continued*)

	600	2	407	24	17	1.4 (0.9 to 2.1)	*Not calculated*
Pregabalin	300	1	195	42	33	1.3 (0.9 to 1.8)	*Not calculated*
	600	3	702	54	36	1.5 (1.3 to 1.8)	5.4 (3.9 to 9.2)

CI: confidence interval; NNT: number needed to treat to benefit; RR: risk ratio
Note: NNT was not calculated when the RR showed no significant difference between treatments

Postherpetic neuralgia

Results of efficacy analyses for different outcomes are shown in Summary of results C. The numbers of participants available for the analyses were more than 1000 only for gabapentin for a PGIC outcome of very good or excellent at the end of the study.
Gabapentin and pregabalin showed evidence of efficacy at least for one dose or dosing regimen. The point estimates of NNTs mostly were in the range of 4 to 11 for different outcomes, but were as low as 2.7 and 4.0 for pregabalin 600 mg for at least 30% and 50% pain intensity reduction respectively.

Summary of results C: Postherpetic neuralgia - efficacy analyses for different outcomes

Drug	Dose (mg/day)	Number of		Percent achieving outcome with		RR (95% CI)	NNT (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: at least 50% pain intensity reduction							
Gabapentin	1800 to 3600	3	892	33	20	1.7 (1.3 to 2.2)	7.5 (5.2 to 14)
Pregabalin	300	3	535	30	11	2.7 (1.9 to 4.0)	5.3 (3.9 to 8.1)
	600	3	551	39	14	2.8 (2.0 to 3.9)	4.0 (3.1 to 5.5)
Outcome: at least 30% pain intensity reduction							
Pregabalin	300	1	191	41	17	2.4 (1.4 to 3.9)	4.2 (2.8 to 8.9)
	600	2	356	58	21	2.8 (2.0 to 3.8)	2.7 (2.2 to 3.7)
Outcome: Patient Global Impression of Change - excellent							

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(*Continued*)

Gabapentin	1800 to 3600	2	563	15	6	2.7 (1.5 to 4.8)	11 (7.0 to 22)
Outcome: Patient Global Impression of Change - very good or excellent							
Gabapentin	1800 to 3600	4	1121	38	20	1.9 (1.5 to 2.3)	5.5 (4.3 to 7.7)
CI: confidence interval; NNT: number needed to treat to benefit; RR: risk ratio							

Central neuropathic pain

Results of efficacy analyses for different outcomes are shown in Summary of results D. For central neuropathic pain, the only data available were for pregabalin 600 mg daily. Although from limited numbers of studies and participants, the results demonstrated reasonable efficacy, with point estimates for NNT of 3.5 and 5.6 for at least 30% and 50% pain intensity reduction, respectively.

Summary of results D: Central neuropathic pain - efficacy analyses for different outcomes

Drug	Dose (mg/day)	Number of		Percent achieving outcome with		RR (95% CI)	NNT (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: at least 50% pain intensity reduction							
Pregabalin	600	2	176	25	7	3.6 (1.5 to 8.4)	5.6 (3.5 to 14)
Outcome: at least 30% pain intensity reduction							
Pregabalin	600	1	136	42	13	3.1 (1.6 to 6.1)	3.5 (2.3 to 7.0)
CI: confidence interval; NNT: number needed to treat to benefit; RR: risk ratio							

Trigeminal neuralgia

No second tier results were available for trigeminal neuralgia.

HIV-related neuropathic pain

No second tier results were available for HIV-related neuropathic pain.

Fibromyalgia

Results of efficacy analyses for different outcomes are shown in Summary of results E. The numbers of participants available for the analyses were large for pregabalin at doses of 300, 450, and 600 mg daily.

Pregabalin 450 mg daily had lower (better) NNTs than either 300 mg or 600 mg daily.

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Summary of results E: Fibromyalgia - efficacy analyses for different outcomes

Drug	Dose (mg/day)	Number of		Percent achieving outcome with		RR (95% CI)	NNT (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: at least 50% pain intensity reduction							
Pregabalin	300	4	1374	21	14	1.5 (0.2 to 2.9)	14 (9.0 to 33)
	450	4	1376	25	14	1.7 (1.4 to 2.1)	9.8 (7.0 to 16)
	600	3	1122	24	15	1.6 (1.3 to 2.1)	11 (7.1 to 21)
Outcome: at least 30% pain intensity reduction							
Pregabalin	300	4	1374	39	28	1.4 (1.2 to 1.6)	9.2 (6.3 to 17)
	450	4	1376	43	28	1.5 (1.3 to 1.8)	6.6 (5.0 to 9.8)
	600	3	1122	39	28	1.4 (1.2 to 1.6)	9.1 (6.1 to 18)
Outcome: Patient Global Impression of Change - excellent							
Pregabalin	300	4	1352	17	11	1.7 (1.2 to 2.9)	16 (9.9 to 37)
	450	4	1354	19	11	1.8 (1.4 to 2.4)	11 (7.9 to 20)
	600	3	1095	12	7	1.7 (1.1 to 2.4)	21 (12 to 83)
Outcome: Patient Global Impression of Change - very good or excellent							
Pregabalin	300	4	1374	36	28	1.5 (1.2 to 1.9)	11 (7.3 to 26)
	450	4	1376	42	28	1.5 (1.3 to 1.8)	6.8 (5.1 to 10)
	600	3	1122	41	28	1.5 (1.2 to 1.7)	7.7 (5.4 to 13)

CI: confidence interval; NNT: number needed to treat to benefit; RR: risk ratio

Third tier evidence

Carbamazepine

Results for carbamazepine were judged third tier because studies were typically small, of short duration (typically four weeks or less), were unclear about how they dealt with study withdrawal, typically reported any level of benefit, and had a wide range of doses.

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For painful diabetic neuropathy, carbamazepine 600 to 3600 mg daily (4 studies, 829 participants) reported 40% achieving any pain benefit compared to 23% with placebo; the RR was 1.8 (95% CI 1.4 to 2.2), and NNT 5.8 (95% CI 4.3 to 9.0). Ony two studies with 98 participants provided results for carbamazepine compared to placebo in trigeminal neuralgia, with an RR of 6.0 (95% CI 2.8 to 13), and an NNT of 1.7 (95% CI 1.3 to 2.2).

Gabapentin

Results for gabapentin in fibromyalgia were judged third tier because there was only one small study with 150 participants. At least 30% pain intensity reduction with gabapentin at doses up to 2400 mg daily was achieved by 49%, compared with 31% with placebo. The risk ratio was 1.6 (95% CI 1.1 to 2.4) and NNT 5.4 (95% CI 2.9 to 31).

Lacosamide

Results for lacosamide in fibromyalgia were judged third tier because there was only a single small study with 179 participants. A PGIC of very good or excellent with lacosamide 400 mg daily was achieved by 37% of participants, compared with 27% with placebo. The risk ratio was 1.4 (95% CI 0.9 to 2.2).

Withdrawals

Withdrawal rates for all causes, and because of lack of efficacy or adverse events, are shown in Summary of results F.

All-cause withdrawal rates were not available in all reviews. Rates were higher with lacosamide and oxcarbazepine than placebo. The all-cause withdrawal rate for gabapentin was similar to placebo.

Withdrawals due to adverse events were much higher with antiepileptic drug than placebo except for carbamazepine, where studies were short, and for the low dose of 150 mg daily of pregabalin. Where data from different doses of the same antiepileptic were available, there was a clear elevation in withdrawal rates with higher doses, as with pregabalin (Figure 1). NNH values fell (were worse) as doses increased, and adverse event withdrawal rates with an antiepileptic were frequently 10% or more higher than with placebo, reflecting these low NNH values.

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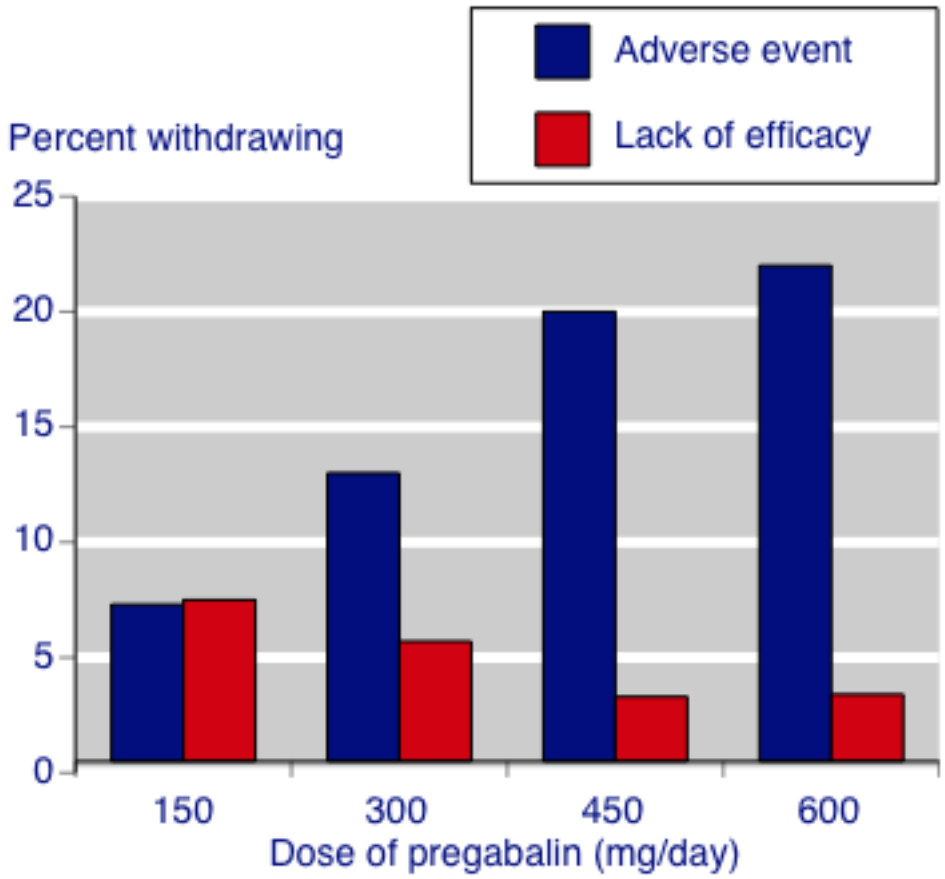
Figure 1. Withdrawals due to adverse events or lack of efficacy according to daily dose of pregabalin



Withdrawals due to lack of efficacy presented the opposite picture. Withdrawal rates were lower with an antiepileptic than placebo, again with a dose response for pregabalin (Figure 1). Numbers needed to prevent one lack of efficacy withdrawal were high, typically 15 or above.

Summary of results F: Withdrawal rates across all conditions

Drug	Dose (mg/day)	Number of		Percent withdrawing with		RR (95% CI)	NNH (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: all-cause withdrawal							
Gabapentin	≥1200	17	3063	20	19	1.1 (0.9 to 1.2)	*Not calculated*

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(*Continued*)

Lacosamide	400	5	874	34	28	1.3 (1.03 to 1.6)	16 (7.9 to 350)
	600	3	594	55	26	2.1 (1.7 to 2.7)	3.4 (2.7 to 4.7)
Oxcarbazepine	600 to 1800	3	634	26	6.8	3.8 (2.3 to 6.2)	5.3 (4.1 to 7.4)
Outcome: withdrawal due to adverse events							
Carbamazepine	100 to 2400	9	573	4	0	*Not calculated*	*Not calculated*
Gabapentin	≥1200	17	3022	12	8.0	1.4 (1.1 to 1.7)	32 (19 to 100)
Lacosamide	400	5	874	18	9.1	2.0 (1.4 to 2.9)	11 (7.5 to 22)
	600	3	594	35	9.1	3.8 (2.5 to 5.8)	3.9 (3.2 to 5.1)
Oxcarbazepine	1200 to 1800	2	524	25	3.3	4.1 (2.2 to 7.6)	5.2 (4.0 to 7.5)
Pregabalin	150	5	964	7.1	6.2	1.2 (0.7 to 1.8)	*Not calculated*
	300	8	1874	13	7.4	1.8 (1.4 to 2.4)	17 (11 to 31)
	450	4	1377	20	10	1.8 (1.5 to 2.5)	11 (7.6 to 18)
	600	10	2231	22	7.6	3.1 (2.5 to 3.7)	6.8 (5.7 to 8.5)
Topiramate	400	3	1038	27	8.1	3.4 (2.4 to 4.7)	5.4 (4.3 to 7.1)
Outcome: withdrawal due to lack of efficacy							**NNTp (95% CI)**
Lacosamide	400	5	874	3.6	5.9	0.6 (0.3 to 1.2)	*Not calculated*
	600	3	594	4.4	3	1.4 (0.6 to 3.3)	*Not calculated*
Pregabalin	150	5	964	7.5	12	0.6 (0.4 to 0.9)	22 (12 to 120)
	300	7	1596	5.7	12	0.5 (0.3 to 0.7)	15 (11 to 27)
	450	4	1377	3.3	10	0.3 (0.2 to 0.5)	15 (11 to 26)
	600	10	2052	3.4	15	0.2 (0.15 to 0.3)	8.7 (7.1 to 11)
Topiramate	400	3	1038	12	18	0.7 (0.5 to 0.93)	17 (9.6 to 60)

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(*Continued*)

CI: confidence interval; NNT: number needed to treat to benefit; NNTp = number needed to treat to prevent; RR: risk ratio
Note: NNH or NNTp was not calculated when the RR showed no significant difference between treatments

Adverse events

Results for participants experiencing at least one adverse event or a serious adverse event are shown in Summary of results G.
Most (around 80%) participants experienced an adverse event with an antiepileptic, as did about 70% of participants receiving placebo. NNH values typically had a point estimate of about 7. Carbamazepine was atypical, probably because studies were short compared with somewhat longer studies with gabapentin, and studies of 12 weeks or longer with lacosamide, pregabalin, and topiramate.
Serious adverse events occurred at a much lower rate (typically 8% or lower), and were significantly higher with antiepileptic than placebo only for oxcarbazepine.

Summary of results G: Any adverse event and serious adverse events across all conditions

Drug	Dose (mg/day)	Number of		Percent with AE with		RR (95% CI)	NNH (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: participants experiencing any adverse event							
Carbamazepine	100 to 2400	4	346	66	27	2.4 (1.9 to 3.1)	2.6 (2.1 to 3.5)
Gabapentin	≥1200 mg	11	2356	66	51	1.3 (1.2 to 1.4)	6.6 (5.3 to 9.0)
Lacosamide	400	5	874	72	68	1.1 (0.99 to 1.2)	*Not calculated*
	600	3	594	79	73	1.1 (1.01 to 1.2)	*Not calculated*
Pregabalin	300	8	2190	82	67	1.2 (1.17 to 1.3)	6.6 (5.4 to 8.7)
	600	9	2540	83	67	1.3 (1.25 to 1.4)	6.1 (5.1 to 7.7)
Topiramate	25 to 400	2	398	82	71	1.2 (1.04 to 1.3)	8.6 (4.9 to 35)
Outcome: participants experiencing a serious adverse event							
Gabapentin	≥1200 mg	14	2702	4.0	3.2	1.3 (0.9 to 2.0)	*Not calculated*
Lacosamide	400	5	1304	6.6	6.3	1.0 (0.7 to 1.6)	*Not calculated*
	600	3	594	8.0	6.0	1.4 (0.7 to 2.6)	*Not calculated*
Oxcarbazepine	600 to 1800	3	634	8.0	2.5	3.7 (1.5 to 9.2)	17 (11 to 42)

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(*Continued*)

Pregabalin	300	8	1566	3.6	2.9	1.2 (0.7 to 2.1)	*Not calculated*
	600	9	2101	3.7	3.2	1.2 (0.7 to 1.8)	*Not calculated*
Topiramate	25 to 400	2	1586	6.6	7.5	0.9 (0.6 to 1.3)	*Not calculated*

CI: confidence interval; NNH: number needed to treat to harm; RR: risk ratio
Note: NNH was not calculated when the RR showed no significant difference between treatments

Particular adverse events

Results for particular adverse events are documented in Summary of results H for those reviews that presented data. For the most part particular adverse events reported were associated with the CNS, namely dizziness, somnolence, gait or balance disturbance, and tremor. Where these events were reported according to dose (lacosamide, pregabalin), there was a clear dose-response, with higher event rates and lower NNH values for higher doses. Rash may be a problem with lamotrigine, though the lower CI was close to unity.

There were no data on particular adverse events for carbamazepine, clonazepam, oxcarbazepine, phenytoin, or valproic acid, and limited information for topiramate.

Summary of results H: Particular adverse events across all conditions

Drug	Dose (mg/day)	Number of		Percent with AE with		RR (95% CI)	NNH (95% CI)
		Studies	Participants	Drug	Placebo		
Outcome: dizziness							
Gabapentin	≥1200	16	3150	21	7	3.2 (2.5 to 4.2)	7.0 (6.1 to 8.4)
Lacosamide	200	2	392	7	5	1.5 (0.7 to 3.5)	*Not calculated*
	400	5	876	15	6	2.7 (1.7 to 4.2)	11 (7.7 to 20)
	600	3	595	25	4	6.1 (3.2 to 12)	4.8 (3.8 to 6.3)
Pregabalin	150	6	854	13	8	1.6 (1.02 to 2.5)	19 (10 to 90)
	300	12	2910	29	9	3.4 (2.8 to 4.1)	4.9 (4.3 to 5.6)
	450	4	1376	43	10	4.1 (3.2 to 5.2)	3.1 (2.8 to 3.6)
	600	15	3382	34	8	4.7 (3.9 to 5.6)	3.8 (3.5 to 4.3)
Outcome: somnolence							
Gabapentin	≥1200	16	2800	16	5	3.2 (2.5 to 4.2)	9.2 (7.7 to 12)

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(*Continued*)

Pregabalin	150	6	854	12	7	2.1 (1.3 to 3.5)	18 (11 to 60)
	300	11	2239	20	5	4.0 (3.0 to 5.4)	6.9 (5.8 to 8.4)
	450	4	1376	21	5	4.2 (2.9 to 6.0)	6.4 (5.2 to 8.1)
	600	11	1370	21	7	4.2 (2.8 to 6.2)	6.7 (5.4 to 8.8)
Outcome: peripheral oedema							
Gabapentin	≥1200	9	2042	8.2	2.9	3.4 (2.1 to 5.3)	19 (14 to 29)
Outcome: gait disturbance or ataxia							
Gabapentin	≥1200	5	544	8.8	1.1	4.5 (1.9 to 11)	13 (9 to 24)
Outcome: balance disturbance							
Lacosamide	400	3	533	3.8	0	29 (0.7 to 1100)	*Not calculated*
	600	2	388	8.3	0	62 (0.7 to 5300)	*Not calculated*
Outcome: rash							
Lamotrigine	200 to 400	12	1745	9.5	5.6	1.4 (1.01 to 2.0)	26 (16 to 72)
Outcome: tremor							
Lacosamide	400	4	652	10	5	2.0 (1.1 to 3.7)	22 (12 to 160)
	600	2	388	13	0	19 (2.6 to 140)	8.1 (5.9 to 150)

AE: adverse event; CI: confidence interval; NNH: number needed to treat to harm; RR: risk ratio
Note: NNH was not calculated when the RR showed no significant difference between treatments

Deaths

Death was infrequently reported.

- There were five deaths, with no causation or attribution to treatment, in carbamazepine studies.
- There were three deaths with gabapentin and five with placebo.
- There was one death in lacosamide studies.
- There were no deaths in topiramate studies.

DISCUSSION

Summary of main results

The main conclusion of this overview review of antiepileptic drugs is that only for gabapentin and pregabalin is there reasonably good evidence for efficacy in painful diabetic neuropathy and postherpetic neuralgia. In addition, for pregabalin, there is evidence of efficacy in central neuropathic pain and fibromyalgia. These effects were modest, however, with point estimates of NNTs in the range of 4 to 14 for the important outcome of 50% or more pain

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intensity reduction over baseline.

For other antiepileptic drugs there was no evidence (clonazepam, phenytoin), so little evidence that no sensible judgement could be made about efficacy (valproic acid), evidence that was of low quality and therefore likely to be subject to a number of biases overestimating efficacy (carbamazepine), or reasonable quality evidence indicating little or no effect (lamotrigine, oxcarbazepine, topiramate). Lacosamide recorded a statistical superiority over placebo, but the lower CI was very close to including 1, and with the possibility of residual biases in second tier evidence, and only limited numbers of participants in two studies, we considered it unreliable to conclude that lacosamide had efficacy.

Any benefits of treatment came with a high risk of adverse events and withdrawal because of adverse events, but serious adverse events were not significantly increased compared with placebo, except for oxcarbazepine. CNS adverse events were relatively common, and increased in incidence with higher doses. A dose response for lacosamide and pregabalin could be discerned, with lower (worse) NNH values at higher doses; for other drugs there was insufficient information to judge a dose response.

Overall completeness and applicability of evidence

The evidence was incomplete in several ways. We found no review for levetiracetam, an antiepileptic drug for which some randomised studies have been reported. For several antiepileptic drugs, reviews found either no studies, or small numbers of studies and participants, or studies with considerable limitations in the quality of evidence.

The evidence was also incomplete in that while neuropathic pain conditions of painful diabetic neuropathy and postherpetic neuralgia had been investigated, many other neuropathic pain conditions (trigeminal neuralgia, HIV-related neuropathy) had not. Fibromyalgia and central neuropathic pain were investigated in some studies, mainly using pregabalin. The reasons for this are obvious, as many neuropathic pain conditions are relatively uncommon, diagnoses are sometimes difficult, and studies recruiting sufficient numbers of participants in a reasonable timescale are likely to be logistically challenging.

Most results came from more modern, larger, high quality studies with diagnostic and inclusion criteria that met modern scientific needs and expectations, and that would make results applicable to populations with these pain conditions presenting in primary care. While some studies employed enrichment techniques, these have been shown not to influence efficacy estimates (Straube 2008). Many specialist pain clinics see patients with much more complex conditions, with long standing chronic pain and multiple morbidities, and it is not clear that results available would necessarily apply in those circumstances, or whether or how efficacy is dictated by clinical setting.

We are aware that erectile dysfunction has been a cause for concern for younger men treated with antiepileptic drugs for epilepsy (Smalldone 2004), and anorgasmia has been reported with gabapentin (Perloff 2011). Adverse event reporting of erectile dysfunction or anorgasmia in these trials was sparse or not present, and the effects of gabapentin on sexual function may not be well represented.

Quality of the evidence

Two issues reduced the quality of the evidence.

The first issue was that studies were small and of short duration. For amitriptyline in neuropathic pain and fibromyalgia, smaller studies (often of only a few weeks' duration) produced much lower (better) NNTs than larger (often longer) studies (Moore 2012a). This potentially very large bias towards better efficacy in smaller studies is also seen in musculoskeletal pain, particularly osteoarthritis (Nüesch 2010), and is likely to apply to antiepileptics for neuropathic pain.

The second issue for the reviews and the studies in them was the use of LOCF imputation, which has been shown to have a major bias impact in chronic pain studies when adverse event withdrawal rates are higher for active drug than with placebo (Moore 2012b). An estimate of the magnitude of this bias can be judged for pregabalin in fibromyalgia, where an individual patient data responder analysis (where withdrawal was considered non response - baseline observation carried forward (BOCF); Straube 2010) used data from the same four studies as the Cochrane review (Moore 2009), which used the LOCF analyses in the published papers. The difference can be seen in Summary of results I, which compares NNTs for the same doses, using the outcome of at least 50% pain intensity reduction over baseline at 12 to 14 weeks. Clearly LOCF imputation is without any large effect here.

Summary of results I: Effect of imputation method on efficacy estimates of pregabalin in fibromyalgia

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Pregabalin dose (mg)	LOCF NNT (95% CI)	BOCF NNT (95% CI)
300	9.2 (6.3 to 17)	14 (8.8 to 30)
450	6.6 (5.0 to 9.8)	12 (7.9 to 22)
600	9.1 (6.1 to 18)	8.8 (6.2 to 15)

BOCF: baseline observation carried forward; CI: confidence interval; LOCF: last observation carried forward; NNH: number needed to treat to harm

A pooled analysis of 11 pregabalin studies in painful diabetic neuropathy or postherpetic neuralgia with analysis by age also reports responder rates according to BOCF or LOCF imputation (Semel 2010). It showed that while responder rates for placebo were essentially the same with either imputation method, they were lower for pregabalin using BOCF. The magnitude of the difference varied by age and dose, but was between about 4% and 8% for 300 mg and 7% and 20% for 600 mg. Where the absolute gain for pregabalin over placebo was of the order of 10% to 20%, this implied a substantial overestimation of treatment effect with LOCF imputation in these conditions.

Adverse event withdrawal rates for pregabalin were more than 10% above placebo for pregabalin at 450 mg and 600 mg doses, and approached 10% with 300 mg, and would be predictive of a significant LOCF bias (Moore 2012b). Similar or larger excesses were seen for lacosamide, oxcarbazepine, and topiramate (Summary of results F), and for these drugs also LOCF might be expected to produce significant bias. Gabapentin, by contrast, only produced a 4% excess for active over placebo for doses of 1200 mg daily or above, and it may be that an LOCF overestimation of treatment effect is less apparent.

There is a clear need for analysis of data using a responder analysis, where responder includes both a pain intensity reduction of 50% or more over about 12 weeks - known to be an outcome patients want and to be associated with improved quality of life (Moore 2013a; Moore 2013b) - but where withdrawal is regarded as non-response. Such an outcome has direct implications for clinical practice.

Potential biases in the overview process

We know of no biases in the review process, other than a future requirement to search for individual patient data systematic reviews and meta-analyses, which are likely to be published outside Cochrane reviews, as with pregabalin or duloxetine (Straube 2010; Moore 2013e). The reviews included in the overview are all relatively recent. The oldest is 2009, but most are from 2011 onwards, with recent updates in some cases. This makes it unlikely that there is a substantial body of evidence from recent randomised trials that would substantially change these results. We know of none.

A potential criticism would be that the overview only considered only Cochrane reviews. This is consistent with the Cochrane Handbook's advice. The strength of this approach, in this case, is that all the individual Cochrane reviews have applied high standards of evidence, and have used contemporary information about bias particular to chronic pain trials. Few non-Cochrane reviews have been performed with similar stringency. As a consequence the overview provides a consistent approach to allow broad inferences to be drawn between different interventions in particular conditions, and to some extent between conditions.

Agreements and disagreements with other studies or reviews

Previous Cochrane reviews have investigated antiepileptic drugs for neuropathic pain, originally in 2000 (Wiffen 2000), updated in 2005 (Wiffen 2005) and 2010 (Wiffen 2010). These were themselves updates of a previous systematic review (McQuay 1995). There have been two major changes over the past few decades. One is the increased number of studies and participants from 20 studies and 736 participants in 2000 to 91 studies and 17,955 participants in this overview review. The other change is in our understanding of biases in clinical trials and their reporting, leading to the uncovering and avoidance of previously unsuspected biases (Moore 2010b; Moore 2012b). These changes mean that we now analyse according to drug, dose and condition, and estimates of efficacy are more conservative.

While a number of other reviews and guidelines have sought to estimate efficacy and harm of antiepileptic drugs in neuropathic pain and fibromyalgia (Attal 2010; Bohlega 2010; Chetty 2012; Dworkin 2007; Finnerup 2005; Moulin 2007; NICE 2013; Phillips 2010; Sommer 2012) we are unaware of any that have

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applied the new higher standards to the evidence. While the guidelines are generally similar in the advice they give, there are subtle and sometimes important differences (O'Connor 2009). Gabapentin and pregabalin are favoured among antiepileptics, because for these two drugs there is substantial evidence of efficacy, as shown in this overview review. The review of guidelines is important as it provides a pain target for treatment of average pain reduced to numerical rating scale of 3/10 or less, or no worse than mild pain (Moore 2013b). The finding that only a proportion of participants have good levels of pain relief with antiepileptics in neuropathic pain or fibromyalgia is similar to that for other drug classes in these and other chronic and acute painful conditions (Moore 2013c).

Adverse event rates with pregabalin reported here are in agreement with those found in a wider systematic review of pregabalin across all conditions, predominantly epilepsy (Zaccara 2011).

It has also become clear that guidelines are seldom followed in neuropathic pain. Examples from the USA (Dworkin 2012) and England (Hall 2013) show that few patients with neuropathic pain receive first line treatments recommended by guidelines at initial presentation, and that use of treatments that are not recommended, or for which there is no evidence, is common. Worse is that a significant proportion of patients (1 in 7 in the USA, 1 in 5 in England) receive no treatment at all.

AUTHORS' CONCLUSIONS

Implications for practice

Among antiepileptic drugs, clinical trial evidence supports only the use of gabapentin and pregabalin in some neuropathic pain conditions (painful diabetic neuropathy, postherpetic neuralgia, and central neuropathic pain) and fibromyalgia. Only a minority of patients will achieve acceptably good pain relief with either drug, but the evidence we have is that quality of life and function improve markedly with the outcome of at least 50% pain intensity reduction (Moore 2013a; Moore 2013b). For lacosamide and lamotrigine there is evidence of a lack of effect; for other antiepileptic drugs, including carbamazepine, there is no evidence of effect or insufficient evidence of effect.

Numbers needed to treat (NNTs) for gabapentin and pregabalin at doses typically used in painful diabetic neuropathy were above 6. This estimate was based on second tier evidence with the potential to overestimate efficacy. For pregabalin in fibromyalgia a large overestimation of treatment effects using last observation carried forward (LOCF) imputation is known, and this imputation method was also used in painful diabetic neuropathy trials with gabapentin and pregabalin. The best evidence for antidepressants is from duloxetine (Lunn 2009) with an NNT of 6, supported by almost identical NNT estimates from newer analyses using top tier evidence and baseline observation carried forward (BOCF) (Moore 2013e). This might be sufficient to convince some practitioners that duloxetine is a better first line choice in painful diabetic neuropathy.

Implications for research

The knowledge that some antiepileptic (and antidepressant) drugs can give good pain relief raises some important questions, namely in which patients, and in which order, the drugs should be used. There is no firm evidence to support these important pragmatic questions. A wider examination of analgesic efficacy of drugs indicates that analgesic failure is common, should be expected, and alternative strategies pursued in the face of analgesic failure (Moore 2013c). This needs to be supported by pragmatic research to provide evidence about strategies rather than interventions, to produce the overall best results in a population, in the shortest time, and at lowest cost to healthcare providers. A clinical effectiveness for such a study has been proposed (Moore 2010c).

There is, in addition, an important research agenda regarding the reasons why some patients respond to a particular drug, while others do not. This knowledge could be used to improve treatment performance if it could be easily applied. While this is unlikely to be an easy research agenda, it is nonetheless one that needs attention, possibly by examining genetic associations or deep phenotyping of responder versus non-responder characteristics, or both.

A final research agenda relates to clinical trial design. Classical randomised controlled trials lack sensitivity to demonstrate efficacy when response rates are low and may be of limited use in these circumstances (Moore 2013d). Evidence from clinical practice and experience indicates that a few patients can achieve good results with antiepileptics other than gabapentin or pregabalin, despite classical trial designs failing to demonstrate those antiepileptics having any greater efficacy than placebo. What is needed are new trial designs that are able to detect low but important rates of response reliably. Enriched enrolment randomised withdrawal designs have the theoretical ability to do this, but they are few in number and heterogeneous in design and quality (McQuay 2008; Moore 2013d). Adaptive designs may also have some use in these circumstances.

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* *Indicates the major publication for the study*

WHAT'S NEW

Date	Event	Description
28 May 2019	Amended	Contact details updated.
15 December 2016	Review declared as stable	See Published notes.

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HISTORY

Protocol first published: Issue 6, 2013

Review first published: Issue 11, 2013

Date	Event	Description
20 December 2013	Amended	Results for pregabalin in fibromyalgia for the outcomes of 50% and 30% pain intensity reduction were transposed in November 2013 published version. These are now corrected

CONTRIBUTIONS OF AUTHORS

All authors were involved in writing the full review. PW, SD, and RAM wrote the protocol. PW and SD searched for reviews to include. PW, SD, and RAM prepared data tables of selected outcomes.

DECLARATIONS OF INTEREST

SD, RAM, AR, and PW have received research support from charities, government, and industry sources at various times. RAM, DA, EK, and PW have consulted for various pharmaceutical companies. RAM, DA, KH, EK and PC have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. AR has provided consultancy advice through Imperial College Consultants for a number of companies engaged in neuropathic pain drug development. He receives research funding from Pfizer and Astellas and owns share options in Spinifex Pharmaceuticals. ML has no interests to declare.

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Internal sources

- Oxford Pain Relief Trust, UK.

General institutional support

External sources

- No sources of support supplied

NOTES

At December 2016, this overview has been stabilised following discussion with the authors and editors. We are not aware of any additional information that would change the conclusions of this overview. We are planning a separate overview on 'Drugs for neuropathic pain - an overview of Cochrane reviews' which will serve to partially update and replace this overview. Another overview on drugs for fibromyalgia is also planned.

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INDEX TERMS

Medical Subject Headings (MeSH)

Amines [therapeutic use]; Anticonvulsants [*therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Fibromyalgia [*drug therapy]; Gabapentin; Intention to Treat Analysis; Neuralgia [*drug therapy]; Pain Measurement; Patient Dropouts; Pregabalin; Review Literature as Topic; gamma-Aminobutyric Acid [analogs & derivatives; therapeutic use]

MeSH check words

Humans

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