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[Intervention Review]

Pregabalin for neuropathic pain in adults

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ABSTRACT

Background

This review updates part of an earlier Cochrane Review titled "Pregabalin for acute and chronic pain in adults", and considers only neuropathic pain (pain from damage to nervous tissue). Antiepileptic drugs have long been used in pain management. Pregabalin is an antiepileptic drug used in management of chronic pain conditions.

Objectives

To assess the analgesic efficacy and adverse effects of pregabalin for chronic neuropathic pain in adults.

Search methods

We searched CENTRAL, MEDLINE, and Embase for randomised controlled trials from January 2009 to April 2018, online clinical trials registries, and reference lists.

Selection criteria

We included randomised, double-blind trials of two weeks' duration or longer, comparing pregabalin (any route of administration) with placebo or another active treatment for neuropathic pain, with participant-reported pain assessment.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality and biases. Primary outcomes were: at least 30% pain intensity reduction over baseline; much or very much improved on the Patient Global Impression of Change (PGIC) Scale (moderate benefit); at least 50% pain intensity reduction; or very much improved on PGIC (substantial benefit). We calculated risk ratio (RR) and number needed to treat for an additional beneficial (NNTB) or harmful outcome (NNTH). We assessed the quality of the evidence using GRADE.

Main results

We included 45 studies lasting 2 to 16 weeks, with 11,906 participants - 68% from 31 new studies. Oral pregabalin doses of 150 mg, 300 mg, and 600 mg daily were compared with placebo. Postherpetic neuralgia, painful diabetic neuropathy, and mixed neuropathic pain predominated (85% of participants). High risk of bias was due mainly to small study size (nine studies), but many studies had unclear risk of bias, mainly due to incomplete outcome data, size, and allocation concealment.

Postherpetic neuralgia: More participants had at least 30% pain intensity reduction with pregabalin 300 mg than with placebo (50% vs 25%; RR 2.1 (95% confidence interval (CI) 1.6 to 2.6); NNTB 3.9 (3.0 to 5.6); 3 studies, 589 participants, moderate-quality

evidence), and more had at least 50% pain intensity reduction (32% vs 13%; RR 2.5 (95% CI 1.9 to 3.4); NNTB 5.3 (3.9 to 8.1); 4 studies, 713 participants, moderate-quality evidence). More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo (62% vs 24%; RR 2.5 (95% CI 2.0 to 3.2); NNTB 2.7 (2.2 to 3.7); 3 studies, 537 participants, moderate-quality evidence), and more had at least 50% pain intensity reduction (41% vs 15%; RR 2.7 (95% CI 2.0 to 3.5); NNTB 3.9 (3.1 to 5.5); 4 studies, 732 participants, moderate-quality evidence). Somnolence and dizziness were more common with pregabalin than with placebo (moderate-quality evidence): somnolence 300 mg 16% versus 5.5%, 600 mg 25% versus 5.8%; dizziness 300 mg 29% versus 8.1%, 600 mg 35% versus 8.8%.

Painful diabetic neuropathy: More participants had at least 30% pain intensity reduction with pregabalin 300 mg than with placebo (47% vs 42%; RR 1.1 (95% CI 1.01 to 1.2); NNTB 22 (12 to 200); 8 studies, 2320 participants, moderate-quality evidence), more had at least 50% pain intensity reduction (31% vs 24%; RR 1.3 (95% CI 1.2 to 1.5); NNTB 22 (12 to 200); 11 studies, 2931 participants, moderate-quality evidence), and more had PGIC much or very much improved (51% vs 30%; RR 1.8 (95% CI 1.5 to 2.0); NNTB 4.9 (3.8 to 6.9); 5 studies, 1050 participants, moderate-quality evidence). More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo (63% vs 52%; RR 1.2 (95% CI 1.04 to 1.4); NNTB 9.6 (5.5 to 41); 2 studies, 611 participants, low-quality evidence), and more had at least 50% pain intensity reduction (41% vs 28%; RR 1.4 (95% CI 1.2 to 1.7); NNTB 7.8 (5.4 to 14); 5 studies, 1015 participants, low-quality evidence). Somnolence and dizziness were more common with pregabalin than with placebo (moderate-quality evidence): somnolence 300 mg 11% versus 3.1%, 600 mg 15% versus 4.5%; dizziness 300 mg 13% versus 3.8%, 600 mg 22% versus 4.4%.

Mixed or unclassified post-traumatic neuropathic pain: More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo (48% vs 36%; RR 1.2 (1.1 to 1.4); NNTB 8.2 (5.7 to 15); 4 studies, 1367 participants, low-quality evidence), and more had at least 50% pain intensity reduction (34% vs 20%; RR 1.5 (1.2 to 1.9); NNTB 7.2 (5.4 to 11); 4 studies, 1367 participants, moderate-quality evidence). Somnolence (12% vs 3.9%) and dizziness (23% vs 6.2%) were more common with pregabalin.

Central neuropathic pain: More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo (44% vs 28%; RR 1.6 (1.3 to 2.0); NNTB 5.9 (4.1 to 11); 3 studies, 562 participants, low-quality evidence) and at least 50% pain intensity reduction (26% vs 15%; RR 1.7 (1.2 to 2.3); NNTB 9.8 (6.0 to 28); 3 studies, 562 participants, low-quality evidence). Somnolence (32% vs 11%) and dizziness (23% vs 8.6%) were more common with pregabalin.

Other neuropathic pain conditions: Studies show no evidence of benefit for 600 mg pregabalin in HIV neuropathy (2 studies, 674 participants, moderate-quality evidence) and limited evidence of benefit in neuropathic back pain or sciatica, neuropathic cancer pain, or polyneuropathy.

Serious adverse events, all conditions: Serious adverse events were no more common with placebo than with pregabalin 300 mg (3.1% vs 2.6%; RR 1.2 (95% CI 0.8 to 1.7); 17 studies, 4112 participants, high-quality evidence) or pregabalin 600 mg (3.4% vs 3.4%; RR 1.1 (95% CI 0.8 to 1.5); 16 studies, 3995 participants, high-quality evidence).

Authors' conclusions

Evidence shows efficacy of pregabalin in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy; evidence of efficacy in central neuropathic pain is inadequate. Some people will derive substantial benefit with pregabalin; more will have moderate benefit, but many will have no benefit or will discontinue treatment. There were no substantial changes since the 2009 review.

PLAIN LANGUAGE SUMMARY

Pregabalin for chronic neuropathic pain in adults

Bottom line

Moderate-quality evidence shows that oral pregabalin at doses of 300 mg or 600 mg daily has an important effect on pain in some people with moderate or severe neuropathic pain after shingles, or due to diabetes. Low-quality evidence suggests that oral pregabalin is effective after trauma due to stroke or spinal cord injury. Pregabalin appears not to be effective in neuropathic pain associated with HIV. Very limited evidence is available for neuropathic back pain, neuropathic cancer pain, and some other forms of neuropathic pain.

Background

Neuropathic pain comes from damage to the nervous system. It is different from pain messages that are carried along healthy nerves from damaged tissue (for example, from a fall or a cut, or from an arthritic knee). Neuropathic pain is often treated by different medicines (drugs) from those used for pain from damaged tissue, which we often think of as painkillers. Medicines that are sometimes used to treat depression or epilepsy can be effective in some people with neuropathic pain. One of these is pregabalin. Our definition of a good result was a high level of pain relief and ability to keep taking the medicine without side effects making people stop.

Study characteristics

In April 2018, for this update we searched for clinical trials that used pregabalin to treat neuropathic pain in adults. We found 31 new studies with 8045 participants. In total, we included 45 studies randomising 11,906 participants to treatment with pregabalin, placebo, or other drugs. Studies lasted 2 to 16 weeks. Most studies reported beneficial outcomes that people with neuropathic pain think are important. Results are available mainly for pain after shingles and pain resulting from nerve damage in diabetes.

Key results

For pain after shingles, 3 in 10 people had pain reduced by half or more with pregabalin 300 mg or 600 mg daily, and 2 in 10 with placebo. Pain was reduced by a third or more for 5 in 10 with pregabalin 300 mg or 600 mg daily, and 3 in 10 with placebo. For pain caused by diabetes, 3 or 4 in 10 people had pain reduced by half or more with pregabalin 300 mg or 600 mg daily, and 2 or 3 in 10 with placebo. Pain was reduced by a third or more for 5 or 6 in 10 people with pregabalin 300 mg or 600 mg daily, and 4 or 5 in 10 with placebo. Pregabalin also helped people with a mixed diagnosis (probably mainly pain after shingles and with diabetes) and people with pain after stroke. It did not work in people with HIV with neuropathic pain. There was no reliable evidence for any other type of neuropathic pain.

Side effects were more common with pregabalin (6 in 10) than with placebo (5 in 10). Dizziness and sleepiness occurred in about 1 to 3 in 10 people who took pregabalin. Serious side effects were uncommon and were not different between pregabalin and placebo. About 1 in 10 people taking pregabalin stopped taking it because of side effects.

Pregabalin is helpful for some people with chronic neuropathic pain. It is not possible to know beforehand who will benefit and who will not. Current knowledge suggests that a short course of treatment (perhaps four weeks) is the best way of telling.

Quality of the evidence

We rated the quality of the evidence using four levels: very low, low, moderate, and high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. We judged that most evidence was of moderate quality, which means that even though research provides a good indication of the likely effect, effects may be substantially different. The main issues were small size for some studies and inadequate reporting of important methodological information. Results have not changed substantially since the 2009 review.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Pregabalin 300 mg compared with placebo for postherpetic neuralgia

Patient or population: adults with moderate or severe pain associated with postherpetic neuralgia
Settings: community
Intervention: oral pregabalin 300 mg, typically for 8 weeks or longer after initial titration
Comparison: oral placebo

Outcome	Probable outcome with pregabalin	Probable outcome with placebo	RR and NNTB or NNTH (95% CI)	No. of studies (participants)	Quality of the evidence (GRADE)	Comments
At least 30% pain intensity reduction	500 per 1000	250 per 1000	RR 2.1 (1.6 to 2.6) NNTB 3.9 (3.0 to 5.6)	3 (589)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
At least 50% pain intensity reduction	320 per 1000	130 per 1000	RR 2.5 (1.9 to 3.4) NNTB 5.3 (3.9 to 8.1)	4 (713)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
Patient Global Impression of Change - much or very much improved	320 per 1000	150 per 1000	RR 2.1 (1.5 to 2.9) NNTB 5.9 (4.2 to 9.8)	3 (568)	Low	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders, and once because of susceptibility to publication bias
Lack of efficacy withdrawal	30 per 1000	90 per 1000	RR 0.4 (0.2 to 0.7) NNTB 18 (11 to 47)	5 (933)	High	

Somnolence	160 per 1000	55 per 1000	RR 3.0 (1.9 to 4.5) NNTH 9.5 (7.0 to 15)	5 (933)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events
Dizziness	290 per 1000	81 per 1000	RR 3.6 (2.6 to 5.1) NNTH 4.8 (3.9 to 6.2	5 (933)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events
Adverse event withdrawal	140 per 1000	53 per 1000	RR 2.7 (1.8 to 4.2) NNTH 11 (7.8 to 19)	5 (933)	High	

CI: confidence interval; LOCF: last observation carried forward; NNTB: number needed to treat for an additional beneficial outcome compared with placebo; NNTH: number needed to treat for an additional harmful outcome compared with placebo; RR: risk ratio

Descriptors for levels of evidence (EPOC 2015).
High quality: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[a] is low.
Moderate quality: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[a] is moderate.
Low quality: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[a] is high.
Very low quality: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[a] is very high.
[a]Substantially different: a large enough difference that it might affect a decision

BACKGROUND

This is an update of a Cochrane Review titled "Pregabalin for acute and chronic pain in adults", published in 2009 (Moore 2009), and itself is an update on a series of previous systematic reviews examining antiepileptic drugs in painful conditions (McQuay 1995; Wiffen 2000; Wiffen 2005).

The review has now been split, and this update will consider only neuropathic pain because of the large amount of information now available on neuropathic pain, and because of a Cochrane policy to separate fibromyalgia into separate reviews. A separate updated review of pregabalin for fibromyalgia has been published (Derry 2016a). The information about acute pain is unchanged and probably out of date, mainly because the clinical question is now different. Rather than examining efficacy of pregabalin as an analgesic in established pain, the question now is whether perioperative use of pregabalin as part of a complex intervention with several components reduces the occurrence or intensity of postoperative pain, or even chronic pain after surgery. Many individual studies have examined pregabalin in this context, together with systematic reviews (Eipe 2015; Gurusamy 2014; Liébana-Hermoso 2018).

This latest update is based on a template for drugs to treat neuropathic pain and applies current standards for Cochrane Reviews, including assessment of the reliability of evidence based on GRADE and on criteria for what constitutes reliable evidence in chronic pain (Moore 2010a; Moore 2013a; Appendix 1).

Description of the condition

Neuropathic pain is a consequence of a pathological maladaptive response of the nervous system to 'damage' from a wide variety of potential causes (Colloca 2017). It is characterised by pain in the absence of a noxious stimulus, or exaggerated levels of pain evoked by minor or moderate nociceptive stimuli. Neuropathic pain may be spontaneous (continuous or paroxysmal) in its temporal characteristics or may be evoked by sensory stimuli (dynamic mechanical allodynia, where pain is evoked by light touch of the skin).

Neuropathic pain is heterogeneous in etiology, pathophysiology, and clinical presentation. 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 upon at an earlier consensus meeting (Treede 2008). Neuropathic pain is associated with a variety of sensory loss (numbness) and sensory gain (allodynia) clinical phenomena, the exact patterns of which vary between people and diseases, perhaps reflecting different pain mechanisms operating within an individual person and, therefore, potentially predictive of response to treatment (Demant 2014; Helfert 2015; von Hehn 2012). A new approach of subgrouping people with peripheral neuropathic pain of different etiologies according to intrinsic sensory profiles has generated three profiles that may be related to pathophysiological mechanisms (Baron 2017).

Pre-clinical research hypothesises a bewildering array of possible pain mechanisms that may operate in people with neuropathic pain, which largely reflect pathophysiological responses in both the central and peripheral nervous systems, including neuronal interactions with immune cells (Baron 2012; Calvo 2012; von Hehn 2012). Overall, treatment gains in neuropathic pain, with even the most effective of available drugs, are modest (Finnerup 2015; Moore 2013b), and a robust classification of neuropathic pain is not yet available (Finnerup 2013).

Neuropathic pain is usually classified according to the cause of nerve injury. Causes are many, but common causes of neuropathic pain include diabetes (painful diabetic neuropathy (PDN)); shingles (postherpetic neuralgia (PHN)); amputation (stump and phantom limb pain); post surgery or trauma, stroke, or spinal cord injury; trigeminal neuralgia; and HIV infection. Sometimes the cause is unknown.

Many people with neuropathic pain conditions are significantly disabled by moderate or severe pain for many years. Chronic pain conditions constituted five of the 11 top-ranking conditions for years lived with disability in 2010 (Vos 2012), and they are responsible for considerable loss of quality of life and employment, along with increased healthcare costs (Moore 2014a). A US study found that healthcare costs were threefold higher for people with neuropathic pain than for matched controls (Berger 2004). A UK study and a German study showed a two- to threefold higher level of use of healthcare services by people with neuropathic pain than by those without (Berger 2009; Berger 2012). For PHN, for example, studies demonstrated large loss of quality of life and substantial costs (Scott 2006; van Hoek 2009).

Systematic reviews have reported the overall prevalence of neuropathic pain in the general population at between 7% and 10% (van Hecke 2014), and a systematic review of studies published since 2000 reported overall prevalence of 7% (Moore 2012a). Individual countries have reported prevalence rates of 3.3% in Austria (Gustorff 2008), 6.9% in France (Bouhassira 2008), and up to 8% in the UK (Torrance 2006). Some forms of neuropathic pain, such as PDN and post-surgical chronic pain (which is often neuropathic in origin), are increasing (Hall 2008). The prevalence of PHN is likely to fall if vaccination against the herpes virus becomes widespread.

Estimates of incidence for particular origins of neuropathic pain vary between individual studies, often because of small numbers of cases. In primary care in the UK, between 2002 and 2005, the incidences (per 100,000 person-years' observation) were 28 (95% confidence interval (CI) 27 to 30) for PHN, 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 PDN (Hall 2008). Other studies have estimated an incidence of 4 in 100,000 per year for trigeminal neuralgia (Katusic 1991; Rappaport 1994), and 12.6 per 100,000 person-years for trigeminal neuralgia and 3.9 per 100,000 person-years for PHN in a study of facial pain in the Netherlands (Koopman 2009). One systematic review of chronic

pain demonstrated that some neuropathic pain conditions, such as PDN, can be more common than other neuropathic pain conditions, with prevalence rates up to 400 per 100,000 person-years (McQuay 2007). It is also the case that pain not classified as neuropathic can have neuropathic features. In a recent community study of joint pain, features of neuropathic pain were common and were present in more than half of those reporting pain of at least moderate severity (Soni 2013).

Neuropathic pain is difficult to treat effectively, with only a minority of people experiencing a clinically relevant benefit from any one intervention (Kalso 2013; Moore 2013b). A multi-disciplinary approach combining pharmacological interventions with physical or cognitive (or both) interventions is now advocated. Evidence for more invasive interventional therapies such as neural blockade or intrathecal medication is very weak, or is non-existent (Dworkin 2013). Conventional analgesics such as paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) are not thought to be effective, but evidence to support or refute that view is lacking (Moore 2015a; Wiffen 2016). Some people may derive some benefit from a topical lidocaine patch or low-concentration topical capsaicin, although evidence about benefits is uncertain (Derry 2012; Derry 2014). High-concentration topical capsaicin may benefit some people with PHN (Derry 2017). Treatment is often by so-called 'unconventional analgesics' (pain modulators) such as antidepressants (duloxetine and amitriptyline; Lunn 2014; Moore 2014b; Moore 2015b; Sultan 2008), or antiepileptics (gabapentin or pregabalin; Moore 2009; Wiffen 2013; Wiffen 2017a). Evidence for efficacy of opioids is unconvincing (Derry 2016b; Gaskell 2016; Stannard 2016; Wiffen 2015).

The proportion of people who achieve worthwhile pain relief (typically at least 50% pain intensity reduction) is small - generally only 10% to 25% more than with placebo (Moore 2013a; Moore 2013b; Moore 2013c), with the number needed to treat for an additional beneficial outcome (NNTB) 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).

Current National Institute for Health and Care Excellence (NICE) guidance for pharmacological management of neuropathic pain suggests offering a choice of amitriptyline (Moore 2012b), duloxetine (Lunn 2014), gabapentin (Wiffen 2017a), or pregabalin as initial treatment for neuropathic pain (with the exception of trigeminal neuralgia) (Moore 2009), with switching if the first, second, or third drug tried is not effective or is not tolerated (NICE 2013). This concurs with other recent guidance (Finnerup 2015).

Description of the intervention

Pregabalin is an alkylated analogue of γ-aminobutyric acid (GABA) and is structurally related to gabapentin. Marketing reports worldwide sales of pregabalin (as Lyrica®) in 2014 as USD5.4 billion, with 12th position in terms of gross sales and with an annual growth rate of about 12% (PharmaMarketing 2017). Almost 40 companies worldwide manufacture or sell pregabalin (Pharmacompass 2018). Primary care prescribing of pregabalin in England in 2017 amounted to 6.3 million prescriptions at a cost of £216 million for all conditions, including pain and epilepsy (PCA 2018).

Pregabalin is licensed for treatment of peripheral and central neuropathic pain in adults. European approval for marketing was granted in 2004, and US approval in 2005. Dosage is up to 600 mg daily, as two or three divided doses. It is usually given as oral tablets, but a solution (20 mg/mL) is also available. Treatment is started with 150 mg daily, increasing after three to seven days to 300 mg daily, and after a further seven days to 600 mg daily, depending on individual patient response and tolerability (EMC 2017). Pregabalin is excreted by the kidneys, and people with renal impairment require reduced doses. Gradual discontinuation over a period of one week is recommended.

Pregabalin is absorbed more rapidly and results in a higher blood concentration when taken in the fasted state, but taking it with food has no clinically important effect on the extent of absorption. With repeated doses, a steady state is reached within 24 to 48 hours. Pregabalin does not bind to plasma proteins and is not metabolised to any extent in the body.

Some reports have described misuse, abuse, and dependence with pregabalin and gabapentin, and have reviewed the consequences (Evoy 2017; Quintero 2017; Schjerning 2016). Abuse potential is a concern, especially for people with a history of substance abuse.

How the intervention might work

Pregabalin binds to the $\alpha 2\delta$ type 1 protein of the P/Q voltage-dependent calcium channel and reduces the central release of excitatory molecules (Patel 2016). In addition, GABA-mimetic properties have been shown in rats (de Guglielmo 2013).

Pregabalin has antiepileptic, analgesic, and anxiolytic effects; it is more potent than gabapentin and therefore is used at lower doses.

Why it is important to do this review

The earlier review was completed in 2009 (Moore 2009), when pregabalin had been licensed for neuropathic pain for only a few years and for limited conditions. Pregabalin is now one of the first-line recommended drugs for neuropathic pain (other than trigeminal neuralgia), and many more trials have been completed, some examining different conditions. It is therefore appropriate to update the review, to bring together the most up-to-date evidence. Standards used to assess evidence in chronic pain trials have evolved substantially in recent years, with particular attention now paid to trial duration, withdrawals, and statistical imputation follow-

ing withdrawal, all of which can substantially alter estimates of efficacy (Appendix 1). The most important change is the move from using mean pain scores, or mean change in pain scores, to the number of people who have a large decrease in pain (by at least 50%) and who continue in treatment, ideally in trials of 8 to 12 weeks' duration or longer. Pain intensity reduction of 50% or more correlates with improvements in co-morbid symptoms, function, and quality of life. These standards are set out in the *PaPaS Author and Referee Guidance for Pain Studies of the Cochrane Pain, Palliative and Supportive Care Group* (PaPaS 2012).

This Cochrane Review assesses the evidence using methods that make both statistical and clinical sense, and uses developing criteria for what constitutes reliable evidence in chronic pain (Moore 2010a). Trials included and analysed meet a minimum of standards for reporting quality (blinding, randomisation), validity (duration, dose and timing, diagnosis, outcomes, etc.), and size (ideally at least 500 participants for a comparison in which the NNTB is 4 or above; Moore 1998). This approach sets high standards for demonstration of efficacy and marks a departure from the way reviews were conducted previously.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of pregabalin for chronic neuropathic pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) with double-blind (participant and observers) assessment of participant-reported outcomes following two weeks of treatment or longer. Studies had to include a minimum of 25 participants per treatment arm (Dechartres 2013; Moore 1998; Roberts 2015; Thorlund 2011; Wiffen 2017b), participants had to have at least moderate pain intensity at baseline for there to be sensitivity (pain relief cannot be measured in the absence of pain), and pain assessments had to be made by participants themselves, as professionals consistently tend to underestimate pain (Seers 2018).

We required full journal publication, with the exception of online summaries of clinical trial results otherwise unpublished, along with abstracts providing sufficient data for analysis. We did not include short abstracts (usually meeting reports with inadequate or no reporting of data). We excluded studies of experimental pain, case reports, and clinical observations.

Types of participants

We included adult participants aged 18 years and older, with one or more chronic neuropathic pain conditions including (but not limited to):

- cancer-related neuropathy;
- central neuropathic pain;
- complex regional pain syndrome (CRPS) Type II;
- HIV neuropathy (HIV-associated painful sensory neuropathy);
- painful diabetic neuropathy;
- phantom limb pain;
- postherpetic neuralgia;
- postoperative or traumatic neuropathic pain;
- spinal cord injury; or
- trigeminal neuralgia.

When we included studies with more than one type of neuropathic pain, we analysed results according to the primary condition, if identifiable.

Types of interventions

We included studies that delivered pregabalin in any dose, by any route, for relief of neuropathic pain, in comparison with placebo or any other active comparator. We did not include studies comparing pregabalin with a test drug that has not been marketed if there was no placebo comparator.

Types of outcome measures

We anticipated that studies would use a variety of outcome measures; most studies used standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both. We were 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 were 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 Scale (PGIC; moderate); and
- very much improved on PGIC (substantial).

These outcomes concentrate on dichotomous outcomes (more or less pain relief), as pain responses do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50% pain intensity reduction, and ideally no worse than mild pain (Moore 2013c; O'Brien 2010).

Primary outcomes

- Participant-reported pain intensity reduction of 30% or greater

- Participant-reported pain intensity reduction of 50% or greater
- Patient-reported global impression of clinical change (PGIC) much or very much improved
- Patient-reported global impression of clinical change (PGIC) very much improved

Secondary outcomes

- Withdrawals due to lack of efficacy, to adverse events, and for any cause
- Participants experiencing any adverse event
- Participants experiencing any serious adverse event (Serious adverse events typically include any untoward medical occurrences or effects that at any dose result in death, are life-threatening, require hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, are congenital anomalies or birth defects, are 'important medical events' that may jeopardise the patient, or may require an intervention to prevent one of the above characteristics or consequences)
- Specific adverse events, particularly somnolence and dizziness

Search methods for identification of studies

Electronic searches

For this update, we searched the following databases, without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Register of Studies Online (CRSO), on 30 April 2018.
- MEDLINE via Ovid, 1 January 2009 to 30 April 2018.
- Embase via Ovid, 1 January 2009 to 30 April 2018.

See Appendix 2 for the CENTRAL search strategy, Appendix 3 for the MEDLINE search strategy, and Appendix 4 for the Embase search strategy.

Searching other resources

We reviewed the bibliographies of any identified RCTs and review articles, and we searched clinical trial databases (ClinicalTrials.gov (ClinicalTrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/)) and the Pfizer Clinical Study Report Synopses (pfizer.com/science/research_clinical_trials/trial_results) to identify additional published or unpublished data. We did not contact investigators or study sponsors.

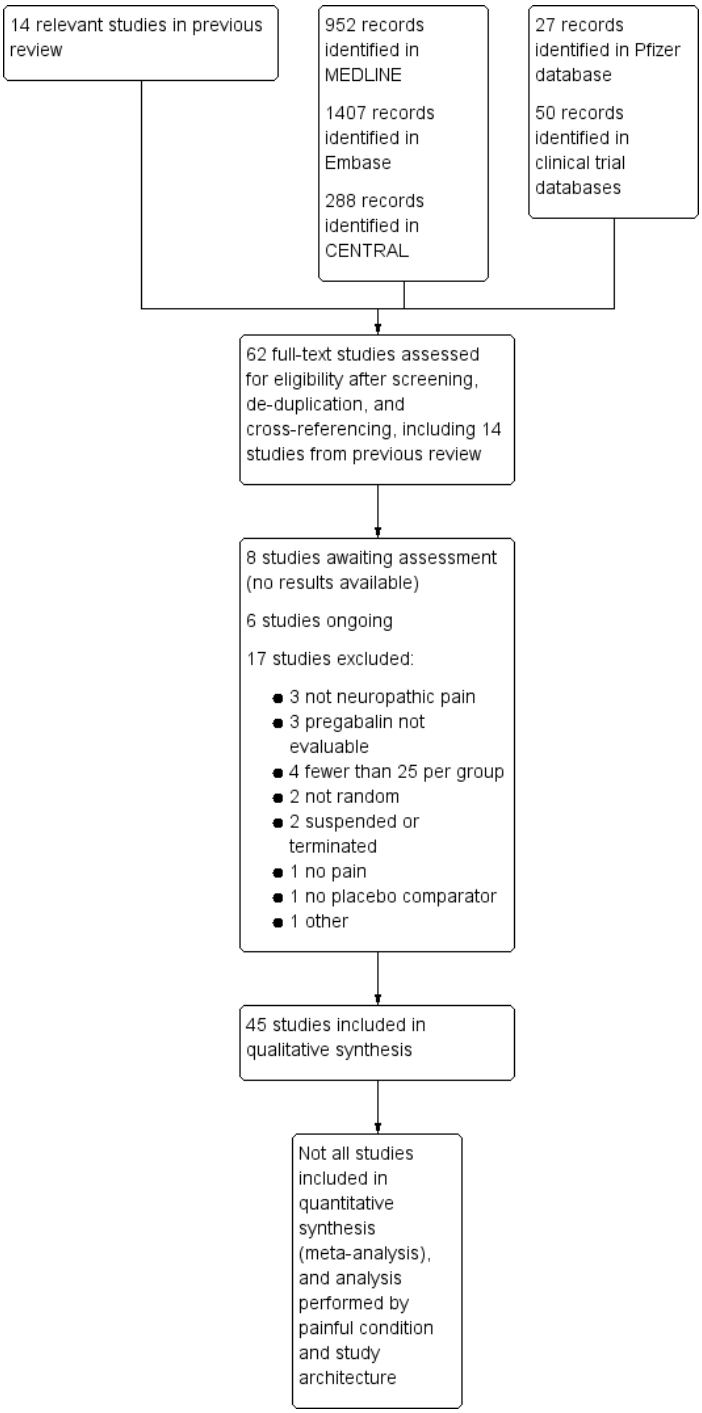
Data collection and analysis

We performed separate efficacy analyses according to particular neuropathic pain conditions, and we combined different neuropathic pain conditions in analyses for adverse events and withdrawals only.

Selection of studies

We determined eligibility by reading the abstract of each study identified by the search. We eliminated studies that clearly did not satisfy the inclusion criteria, and we obtained full copies of the remaining studies. Two review authors made the decisions. Two review authors (RAM, SD) then read these studies independently and reached agreement by discussion. We did not anonymise the studies in any way before assessment. We have provided a PRISMA flow chart to illustrate the flow of studies (Moher 1999) (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Three review authors (RAM, PW, SD) extracted data independently, using a standard data extraction form, and agreed on data before entry into Review Manager 5.3 (RevMan) (RevMan 2014). We included information about the pain condition and the number of participants treated, the drug and dosing regimen, study design, study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse events, particular adverse events, or serious adverse events).

Assessment of risk of bias in included studies

We used the Oxford Quality Score definitions of randomisation and blinding as the basis for inclusion (Jadad 1996), limiting inclusion to studies that were clearly randomised and double-blind as a minimum.

Two review authors (SD, PW) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8; Higgins 2011), and adapted from those used by Cochrane Pregnancy and Childbirth, with disagreements resolved by discussion. We assessed the following for each study.

- **Random sequence generation (checking for possible selection bias).** We assessed the method used to generate the allocation sequence as having low risk of bias (any truly random process: random number table or computer random-number generator) or unclear risk of bias (when the method used to generate the sequence was not clearly stated). We excluded studies at high risk of bias that used a non-random process (odd or even date of birth; hospital or clinic record number).
- **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 having low risk of bias (telephone or central randomisation; consecutively numbered, sealed, opaque envelopes) or unclear risk of bias (when the method was not clearly stated). We excluded studies that did not conceal allocation and were therefore at high risk of bias (open list).
- **Blinding of participants and personnel (checking for possible performance bias), and blinding of outcome assessment (checking for possible detection bias).** We assessed the methods used to blind study personnel and participants (all outcomes were self-assessed) from knowledge of which intervention a participant received. We assessed the methods as having 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 this was achieved). We excluded studies at high risk of bias that were not double-blind.
- **Incomplete outcome data (checking for possible attrition bias due to the quantity, nature, and handling of incomplete outcome data).** We assessed the methods used to deal with incomplete data as having low risk of bias (fewer than 10% of participants did not complete the study or used 'baseline observation carried forward' (BOCF) analysis, or both), unclear risk of bias (used 'last observation carried forward' (LOCF) analysis), or high risk of bias (used 'completer' analysis).
- **Size of study (checking for possible biases confounded by small size)** (Dechartres 2013; Dechartres 2014; Moore 1998; Nüesch 2010; Thorlund 2011). We assessed studies as being at low risk of bias (200 or more participants per treatment arm), unclear risk of bias (50 to 199 participants per treatment arm), or high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We planned to use dichotomous data to calculate risk difference (RD) or risk ratio (RR) with 95% confidence intervals (CIs) using a fixed-effect model, and to calculate the number needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of absolute risk reduction (McQuay 1998). For unwanted effects, the number needed to treat becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner.

We planned to use the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with pregabalin than with control (placebo or active control), we used the term 'number needed to treat to prevent one event (NNTp)'.
- When significantly more adverse outcomes occurred with pregabalin than with control (placebo or active control), we used the term 'number needed to treat for an additional harmful outcome or to cause one event (NNTH)'.

We did not plan to use continuous data for the primary outcome because this is inappropriate when there is an underlying skewed distribution, as is usually the case with analgesic response.

Unit of analysis issues

The unit of analysis was the individual participant. For cross-over studies, we planned to use first period data when possible, but otherwise to use available data and to consider any potential bias that this study design presented.

Dealing with missing data

We used intention-to-treat (ITT) analysis when 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. We assigned zero improvement (baseline observation carried forward (BOCF)) to missing participants wherever possible.

We paid particular attention to methods used for imputation of missing data due to withdrawals for adverse events and lack of efficacy.

Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually (L'Abbé 1987), and by using the I^2 statistic (Higgins 2003). When the I^2 value was greater than 50%, we considered possible reasons for this.

Assessment of reporting biases

The aim of this review was to use dichotomous outcomes of known utility and of value to people with neuropathic pain (Hoffman 2010; Moore 2010a; Moore 2010b; Moore 2010c; Moore 2014a). The review did not depend on what the authors of original studies chose to report or not, and studies that did not report dichotomous results for an outcome did not contribute to pooled analyses for that outcome. We extracted and used continuous data, which probably reflect efficacy and utility poorly, for illustrative purposes only.

We assessed publication bias using a method designed to detect the quantity of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNTB of 10 or higher in this condition; Moore 2008). We considered that fewer than 400 participants in unpublished null effect studies could give rise to doubts about the impact of efficacy results.

We looked for effects of possible enrichment, either complete or partial, on enrolment of participants into these studies. 'Enrichment' typically means including participants known to respond to a therapy, and excluding those known not to respond or to suffer unacceptable adverse effects, although for gabapentin, no significant effects have been shown from partial enrichment (Straube 2008). We would not pool enriched enrolment randomised withdrawal (EERW) studies, known to produce higher estimates of efficacy, but would consider them in a separate analysis (McQuay 2008; Moore 2015c). That analysis would consider issues of quality and bias specific to EERW designs (Moore 2015c).

Data synthesis

We used dichotomous data of known utility (Moore 2010a; Moore 2013a). The review would not depend on what additional information authors of the original studies chose to report or not.

We planned to undertake a quantitative synthesis and to present data in forest plots if data were sufficient. In the event of substantial clinical heterogeneity, we would switch off the totals in the forest plots.

- We would undertake a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that is clinically meaningful.
- We would undertake a meta-analysis only when we obtained data from at least two studies and 200 participants for analysis (Moore 1998).
- We planned to use RevMan for meta-analysis and Excel for NNTB and NNTH (RevMan 2014).

We examined differences in NNTB or NNTH values between the 2009 original review and this 2018 update, using the z-test (Tramèr 1997).

Quality of the evidence

We used the GRADE system to assess the quality of evidence related to the key outcomes listed in Types of outcome measures, as appropriate (Appendix 5). Two review authors (RAM, SD) independently rated the quality of the evidence for each outcome.

We paid particular attention to inconsistency when point estimates varied widely across studies, or when confidence intervals (CIs) of studies showed minimal or no overlap (Guyatt 2011); and to potential for publication bias based on the quantity of unpublished data required to make the result clinically irrelevant (Moore 2008).

There may be circumstances where the overall rating for a particular outcome needs to be adjusted, as recommended by GRADE guidelines (Guyatt 2013a). For example, when data were so few that the results were highly susceptible to the random play of chance, or when a study used last observation carried forward (LOCF) imputation in circumstances of substantial differences in adverse event withdrawals (Moore 2012a), one would have no confidence in the result and would need to downgrade the quality of the evidence by three levels, to very low quality (Guyatt 2013a). In circumstances where no data were reported for an outcome, we would have reported the level of evidence as very low quality (Guyatt 2013b). We are aware that many Cochrane Reviews are based largely or wholly on small underpowered studies, and we know the danger of making conclusive assessments of evidence based on inadequate information (AlBalawi 2013; Brok 2009; Roberts 2015; Turner 2013).

'Summary of findings' tables

We have included five 'Summary of findings' tables as set out in the *PaPaS Author Guide* (PaPaS 2012), and as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 11; Schünemann 2011a). Four tables include outcomes of at least 30% and at least 50% pain intensity reduction, PGIC outcomes

of 'much or very much improved' and 'very much improved', lack of efficacy withdrawal, somnolence, dizziness, and adverse event withdrawal. These tables report on two daily doses of pregabalin (300 mg and 600 mg daily) for both PHN and PDN. The fifth table relates to participants experiencing at least one adverse event or one serious adverse event for pregabalin 300 mg or 600 mg daily, because these analyses used data from all studies and doses, across all conditions

For 'Summary of findings' tables, we used the following descriptors for levels of evidence (EPOC 2015).

- **High:** this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[a] is low.
- **Moderate:** this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[a] is moderate.
- **Low:** this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[a] is high.
- **Very low:** this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[a] is very high.

[a] Substantially different: a large enough difference that it might affect a decision.

Subgroup analysis and investigation of heterogeneity

We planned for all analyses to be based on individual painful conditions, because placebo response rates with the same outcome can vary between conditions, as can drug-specific effects (Moore 2009). We also planned subgroup analyses according to dose of pregabalin and study duration (eight weeks or longer), if sufficient data were available.

We did not plan subgroup analysis for partial enrichment, as this has been shown not to affect efficacy estimates (Straube 2008). We did plan a separate, qualitative analysis of EERW studies, as these are structurally different and probably produce a different estimate of efficacy (Moore 2015c).

Sensitivity analysis

We planned no specific sensitivity analyses.

Enriched enrolment randomised withdrawal (EERW) studies

Because we included several EERW studies, we judged risk of bias using a scheme for such studies in pain (Moore 2015c; Appendix 6). Additional items in this scheme involve study duration, outcomes used and their definition, and whether a taper period was used after randomisation for participants randomised to placebo. EERW studies differ from the usual parallel-group design, in which all participants in the active group receive active drug and all those in the placebo group receive placebo. In an EERW study, all participants receive active drug (usually in an open titration phase), and those who have adequate pain relief without intolerable adverse events (usually about half the initial number of participants) are subsequently randomised to continue on an effective dose or be switched in a double-blind manner to placebo.

These studies report different outcomes from those with a standard parallel-group design - usually loss of therapeutic response due to increasing pain or adverse event withdrawal. Often it is not possible to obtain comparable outcomes to those chosen for this review.

We made GRADE judgements about these studies based on the criteria above, along with additional criteria concerning the design, methods, and outcomes used in the EERW studies.

RESULTS

Description of studies

Results of the search

The earlier version of this review included 14 studies involving participants with chronic neuropathic pain having one or more of three different conditions: PHN, PDN, and central neuropathic pain (Moore 2009).

Updated database searches from January 2009 to 30 April 2018 identified 952 potentially relevant reports in MEDLINE, and 1407 in Embase. A full search of CENTRAL identified 288 potentially relevant studies. Searches of Pfizer's Clinical Study Synopses and clinical trials registries revealed 27 and 50 potentially relevant studies, respectively. We cross-referenced these reports with those identified in bibliographic databases when relevant.

After de-duplication and screening of titles and abstracts, we obtained full-text reports for 62 studies. We found no additional studies in reference lists of included studies or reviews, although we obtained some additional data from secondary publications. Of these 62, we included 31 studies and excluded 17 studies. A further eight studies appeared to satisfy our inclusion criteria and were completed (2098 participants in total: 1829 PDN, 105 PHN, 82 cancer treatment, and 82 spinal cord injury) but made no results available (see Characteristics of studies awaiting classification: IRCT201602112027N5; NCT00838799; NCT01314222; NCT01479556; NCT01504412; NCT01688947; NCT01939366; NCT02927951). Six studies appeared to satisfy our inclusion criteria but were ongoing (see Characteristics of ongoing studies: NCT01869569; NCT02394951; NCT02417935;

NCT02607254; NCT02868801; NCT03276689). Five of these studies were currently recruiting a total of 495 participants. Figure 1 illustrates the flow of studies for this update.

Included studies

This updated review includes 45 studies (1008-030; 1008-040; A0081030 [NCT00156078]; A0081071 [NCT00143156]; A0081244 [NCT01049217]; A0081279 [NCT01701362]; A9011015 [NCT01117766]; Arezzo 2008; Bansal 2009; Baron 2010; Cardenas 2013; Dou 2017; Dworkin 2003; Freynhagen 2005; Gilron 2011; González-Duarte 2016; Guan 2011; Hewitt 2011; Holbech 2015; Huffman 2015; Huffman 2017; Kim 2011; Lesser 2004; Liu 2017; Mishra 2012; Moon 2010; Mu 2018; NCT00785577; Ogawa 2010; Raskin 2014; Raskin 2016; Rauck 2013; Richter 2005; Rosenstock 2004; Sabatowski 2004; Satoh 2011; Siddall 2006; Simpson 2010; Smith 2014; Stacey 2008; Tölle 2008; van Seventer 2006; van Seventer 2010; Vinik 2014; Ziegler 2015).

We included 14 studies from the earlier review (3821 participants) and 31 new studies (8045 participants) in this update, with new studies accounting for 68% of the total number of participants (11,906).

We have provided details of individual studies in the Characteristics of included studies table. We originally found two studies on a European Medicines Agency (EMEA) website as part of a scientific discussion (1008-030; 1008-040), but we noted that they were subsequently mentioned in published papers examining placebo response (Freeman 2015). Although we identified these and some other studies, complete details of methods are not available beyond bare details. We had decided to include these studies in the 2009 version, and we also have included them in this update.

We assessed studies according to the type of neuropathic pain examined. Most studies enrolled participants with a single neuropathic pain condition, but a small number enrolled participants with two or more different conditions. We chose to assess these studies according to the condition experienced by the majority, if that majority consisted of 80% or more. We assessed the remaining studies, when no single condition represented at least 80% of the population, in the category of mixed or unclassified neuropathic pain (Gilron 2011; Hewitt 2011; Moon 2010). The 'Summary of included studies' table shows the numbers of studies and participants for each neuropathic pain condition in this 2018 update, and for equivalent conditions in the original 2009 review. For all neuropathic pain conditions, data show a substantial increase in the number of study participants; 85% of participants were included in studies of postherpetic neuralgia, painful diabetic neuropathy, or mixed neuropathic pain.

Summary of included studies

	Number of			
	2009[a]		2018	
Condition	**Studies**	**Participants**	**Studies**	**Participants**
PHN	5	1417	8	2308
PDN	7	2267	20	5943
Mixed neuropathic pain	0	0	8	1991
Central	2	177	3	575
HIV neuropathy	0	0	2	639
Back pain with radiculopathy	0	0	1	217
Neuropathic cancer pain	0	0	2	160
Painful polyneuropathy	0	0	1	73

(*Continued*)

Total	**14**	**3861**	**45**	**11,906**

[a] ***Not including Vranken 2008 (N = 40) in central neuropathic pain.***

PDN: painful diabetic neuropathy; PHN: postherpetic neuralgia.

General exclusions in included studies

Individual studies reported a range of criteria that would exclude participation. General exclusions were:

- being pregnant or breast-feeding;
- having creatinine clearance < 30 mL/min (in some studies, people with creatinine clearance of 30 to 60 mL/min received half-dose pregabalin);
- malignancy within two years;
- history of surgery or neurolysis for neuropathic pain;
- conditions that could affect assessment (e.g. severe skin condition in affected dermatome in PHN); and
- inadequate washout of excluded medication.

Most studies allowed ongoing use of stable pain medications given that a sufficiently high pain intensity remained to fulfil the entry criteria.

Postherpetic neuralgia (PHN)

Eight studies included 2308 participants with PHN in randomised comparisons with placebo (1008-030; Dworkin 2003; Huffman 2017; Liu 2017; Ogawa 2010; Sabatowski 2004; Stacey 2008; van Seventer 2006). Researchers administered pregabalin at doses ranging from 75 to 600 mg daily, usually as a divided dose, two or three times daily. Most studies used fixed doses with a titration period to achieve the target dose. One study used a titrated, flexible dosing regimen to determine the maximum tolerated dose, which was then fixed for the remainder of the study (Huffman 2017), and another study compared a flexible regimen with a fixed one (Stacey 2008). The duration of double-blind treatment periods ranged from 2 to 13 weeks. All studies used a parallel design.

Participants had moderate or severe pain (≥ 4/10) persisting for at least three months after healing of the rash. Mean age of study participants ranged from 65 to 72 years, and numbers of men and women were approximately equal. We judged three studies to have some degree of partial enrichment in recruitment (Dworkin 2003; Huffman 2017; Sabatowski 2004).

Peripheral diabetic neuropathy (PDN)

Twenty studies included 5943 participants with PDN in randomised comparisons. Fifteen studies had only placebo comparators, one had only active comparators (Bansal 2009), and six had both active and placebo comparators (1008-040; NCT00785577; Rauck 2013; Smith 2014; Vinik 2014; Ziegler 2015). Active comparators were amitriptyline, duloxetine, gabapentin, mirogabalin, and the experimental drugs carisbamate, LY545694, and ABT-639. Investigators gave pregabalin at doses ranging from 75 to 600 mg daily, usually as a divided dose, two or three times daily. Most studies used fixed doses with a titration period to achieve the target dose. Three studies used a titrated, flexible dosing regimen to determine the maximum tolerated dose, which was then fixed for the remainder of the study (Bansal 2009; Huffman 2015; Raskin 2016). The duration of double-blind treatment periods ranged from 4 to 15 weeks. Four studies used a cross-over design (Bansal 2009; González-Duarte 2016; Huffman 2015; Raskin 2016), and the remainder a parallel design. One used an EERW design (Raskin 2014).

Participants had moderate or severe pain (≥ 4/10) persisting for at least three months. Mean age of study participants ranged from 54 to 62 years, and studies included slightly fewer men than women (47%). Two studies used enriched enrolment (González-Duarte 2016; Raskin 2014), and we judged eight studies to have some degree of partial enrichment (Mu 2018; Huffman 2015; Lesser 2004; Rauck 2013; Rosenstock 2004; Smith 2014; Tölle 2008; Vinik 2014).

Mixed or unclassified neuropathic pain

Eight studies included 1991 participants with mixed types of neuropathic pain (< 80% participants with one type) or unclassified post-traumatic neuropathic pain in randomised comparisons with placebo. No studies used active comparators. Researchers administered pregabalin at daily doses of 150 to 600 mg, as a divided dose, usually twice daily. Most studies used a titrated, flexible dosing regimen to determine the maximum tolerated dose, which was then fixed for the remainder of the study. One study titrated to a fixed target dose (A9011015 [NCT01117766]), and one compared a flexible regimen with a fixed one (Freynhagen 2005). The duration of double-blind treatment periods ranged from 4 to 15 weeks. One

study used a cross-over design (A9011015 [NCT01117766]), and the remainder used a parallel design.
Participants had moderate or severe pain (≥ 4/10) persisting for at least three or six months. Mean age of study participants ranged from 52 to 61 years, and numbers of men and women were similar. Two studies used EERW (Gilron 2011; Hewitt 2011).

Central neuropathic pain

Three studies included 575 participants with central pain in randomised comparisons with placebo (Cardenas 2013; Kim 2011; Siddall 2006). Investigators gave pregabalin at daily doses of 150 to 600 mg, as a divided dose twice daily, using a titrated, flexible dosing regimen to determine the maximum tolerated dose, which was then fixed for the remainder of the study. The duration of double-blind treatment was 12 to 16 weeks, and all studies used a parallel-group design.
Participants had moderate or severe pain (≥ 4/10) persisting for at least three or six months (or remitting/relapsing for ≥ 6 months in Cardenas 2013). Two studies enrolled participants with spinal cord injury (Cardenas 2013; Siddall 2006), and one with post-stroke pain (Kim 2011). Mean age of study participants ranged from 46 to 58 years, and studies included more men than women (73%), particularly with spinal cord injuries. We judged one study to have some degree of partial enrichment (Cardenas 2013).

HIV neuropathy (HIV-associated painful sensory neuropathy)

Two studies included 639 participants with HIV neuropathy in comparisons with placebo (A0081244 [NCT01049217]; Simpson 2010). Researchers administered pregabalin at daily doses up to 600 mg, as a divided dose, using a titrated, flexible dosing regimen to determine the maximum tolerated dose, which was then fixed for the remainder of the study. The duration of double-blind treatment was 14 weeks, and both studies used a parallel design.
Participants in Simpson 2010 had moderate or severe pain (≥ 4/10) persisting for at least three months (not specified in A0081244 [NCT01049217]). The mean age of participants was 42 and 48 years, and these studies included slightly more men than women (56%).

Back pain with radiculopathy

One study included 217 participants with radicular, lumbar, or lumbosacral neuropathy in randomised comparisons with placebo in the withdrawal stage of an EERW design (Baron 2010). Investigators gave pregabalin at daily doses of 150 to 600 mg using a titrated, flexible dosing regimen to determine the maximum tolerated dose, which was then fixed for the remainder of the study.
Participants had moderate or severe pain (≥ 4/10) persisting for at least three months. The mean age of study participants was 45 and 53 years, respectively, and numbers of men and women were similar.

Neuropathic cancer pain

Two studies included 160 participants with neuropathic cancer pain (cancer-related or cancer treatment-related) in randomised comparisons with placebo. Dou 2017 stabilised participants on morphine to maintain PI < 4/10 and breakthrough pain < 3/d before the start of the study, and attempted morphine reduction on addition of pregabalin or placebo. Mishra 2012 included the active comparators gabapentin and amitriptyline. Pregabalin was titrated to 300 mg daily (Dou 2017), or to 600 mg daily (Mishra 2012), given as a divided dose. The duration of double-blind treatment was two or four weeks. Dou 2017 used a cross-over design, and Mishra 2012 used a parallel design.
Participants had moderate or severe pain (≥ 4/10) persisting for at least three months (duration not specified in Mishra 2012). The mean age of participants was 56 in Dou 2017, and numbers of men and women were similar. Mishra 2012 did not specify these details. We judged that neither study involved any enrichment.

Painful polyneuropathy

One study included 73 participants with polyneuropathy in comparisons with placebo, imipramine, and a combination of pregabalin and imipramine (Holbech 2015). Researchers titrated pregabalin to 300 mg daily, given as a divided dose. The study used a cross-over design, including four 5-week, double-blind treatment periods.
Participants had moderate or severe pain (≥ 4/10) persisting for at least six months, and the mean age of participants was 59 years, with slightly more men than women. We judged the study to have some degree of partial enrichment.

Excluded studies

We excluded 17 studies (A0081128; A0081187 [NCT00654940]; A0081296; Boyle 2012; CTRI/2013/05/003646; Mathieson 2017; NCT00787462; NCT00908375; NCT01058642; NCT01089556; NCT01180608; NCT01928381; NCT02215252; NCT02372578; Razazian 2014; Romano 2009; Vranken 2008). We have provided reasons for exclusion in the Characteristics of excluded studies table. We excluded one study previously included in the 2009 review due to its small size (Vranken 2008).
Reasons for exclusion were:

- three not neuropathic pain;
- three pregabalin not evaluable;
- four fewer than 25 per group;
- two not random;
- two suspended or terminated;
- one no pain;

- one no placebo comparator; and
- one other.

Risk of bias in included studies

For details of risk of bias, see Characteristics of included studies, Figure 2, and Figure 3. We have detailed below additional risks of bias specific to EERW designs. High risk of bias was due mainly to small size (nine studies), but many studies had unclear risk of bias, mainly due to incomplete outcome data, size, and allocation concealment. We considered only one study to be at low risk of bias across all items (Huffman 2017).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

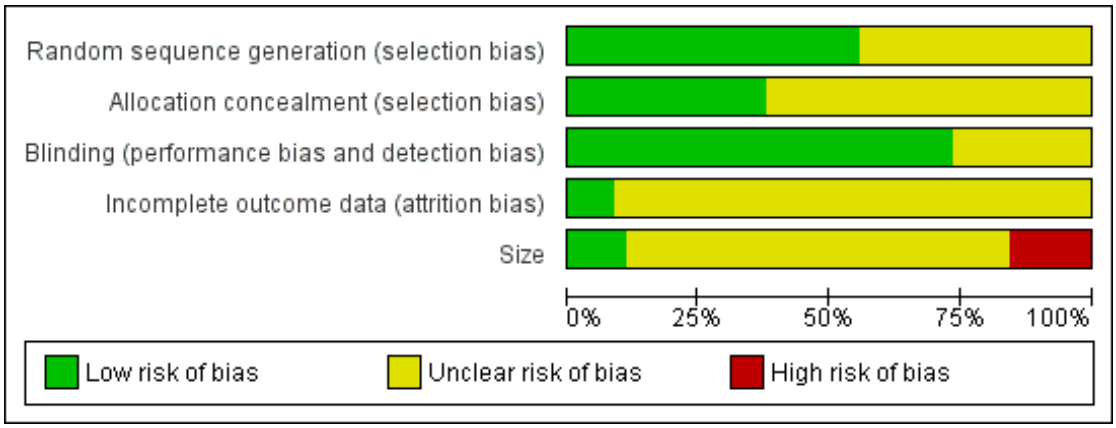
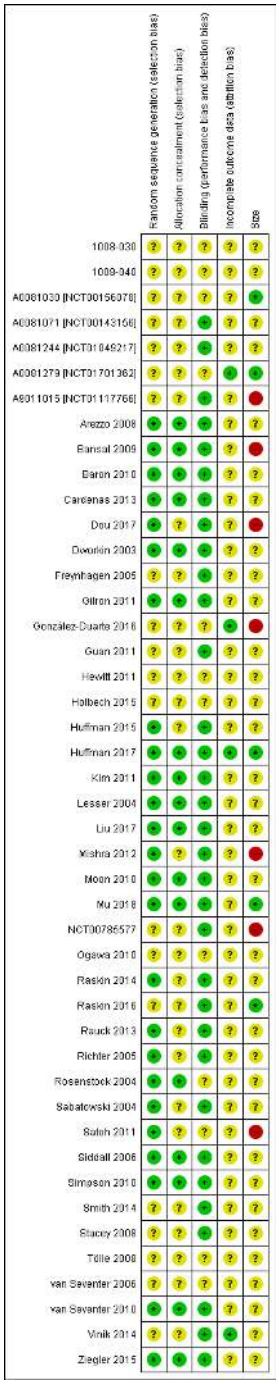


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

All studies were reported to be randomised, but only 25 adequately reported the method of random sequence generation, which we judged as having low risk of bias, and only 18 adequately reported the method of allocation, which we judged as having low risk of bias. We judged the remaining studies in both categories as having unclear risk of bias.

Blinding

All studies were reported to be double-blind, but only 33 adequately reported the method used to maintain blinding, which we judged as having low risk of bias.

Incomplete outcome data

Most studies either did not report how they dealt with data following withdrawal, or used LOCF, or a completer analysis. Four studies reported BOCF data analyses for some outcomes, which we judged as having low risk of bias (A0081244 [NCT01049217]; A0081279 [NCT01701362]; Cardenas 2013; Vinik 2014).

Other potential sources of bias

We judged five studies to be at low risk of bias due to size (included $\geq$ 200 participants per treatment arm) (A0081030 [NCT00156078]; A0081279 [NCT01701362]; Huffman 2017; Mu 2018; Raskin 2016), and we determined that seven studies were at high risk of bias (< 50 participants per treatment arm) (A9011015 [NCT01117766]; Bansal 2009; Dou 2017; González-Duarte 2016; Mishra 2012; NCT00785577; Satoh 2011). We judged the remaining studies to be at unknown risk of bias due to size (50 to 199 participants per treatment arm).

Effects of interventions

See: **Summary of findings for the main comparison** Pregabalin 300 mg compared with placebo for postherpetic neuralgia; **Summary of findings 2** Pregabalin 600 mg compared with placebo for postherpetic neuralgia; **Summary of findings 3** Pregabalin 300 mg compared with placebo for painful diabetic neuropathy; **Summary of findings 4** Pregabalin 600 mg compared with placebo for painful diabetic neuropathy; **Summary of findings 5** Pregabalin 300 mg or 600 mg compared with placebo for any neuropathic pain: any adverse event and serious adverse events

This updated review contains information on three doses of pregabalin, given in eight neuropathic pain conditions, each (at maximum) with results for up to 10 separate outcomes. To aid in comprehension, we use a number of inset summary tables.

Some studies used a flexible dosing regimen, with a pre-specified maximum daily dose. A period of dose adjustment was provided to establish the maximum tolerated dose, which was then maintained for the rest of the study. For these studies, we analysed according to the maximum daily dose. We undertook no separate analysis for flexible versus fixed-dose regimens because this would fragment the data and leave too little for sensible comparison.

Some studies used an enriched enrolment, randomised withdrawal design. We analysed these studies separately from those using the classic randomised design (McQuay 2008; Moore 2015c).

Our analysis concentrated on each condition separately, on efficacy or adverse event outcomes, and on dose (150 mg, 300 mg, and 600 mg daily). As formatted, results show examination of efficacy and adverse events separately, by condition. Analyses at the end of the document show the same data by dose, outcome, and condition, with analyses one to three containing data on pregabalin 150 mg, 300 mg, and 600 mg daily (Data and analyses).

Adverse event reporting typically was not comprehensive, often including only those events occurring in 3% to 5% of participants. Common adverse events consistently reported were somnolence and dizziness.

Efficacy analyses

We have provided detailed efficacy analyses for comparisons of pregabalin versus placebo in the following: Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; and Analysis 3.5. We have presented summaries of the results for each neuropathic pain condition in the tables below, only when data were available and more than 200 participants in two studies contributed to the analysis. For the summary of results tables, we calculated susceptibility to publication bias using a cut-off NNTB of 10, above which a result is not considered clinically relevant (for calculation purposes). Susceptibility is reported as the number of participants in trials with no difference between pregabalin and placebo that would be needed to raise an observed NNTB to 10 or above (Moore 2008).

We analysed EERW studies separately in a later section.

Data were insufficient for any analyses of comparisons of pregabalin versus an active comparator.

Postherpetic neuralgia efficacy

'Summary of results A' shows results for the four primary and two secondary efficacy outcomes for which data were available. Each case shows a greater response with a higher dose, with more participants achieving the outcomes, and with lower (better) NNTB values. At least 30% pain intensity reduction (moderate benefit)

tended to produce higher response rates and lower NNTB values than did at least 50% pain intensity reduction (substantial benefit). No studies reported a measure of substantial benefit (very much improved) on the PGIC scale. Limiting analyses to studies of eight weeks' duration or longer made no appreciable difference in the results.

Lack of efficacy withdrawals were fewer with 300-mg and 600-mg doses, but the number needed to treat to prevent (NNTp) one discontinuation was about the same for 300 mg and 600 mg daily. Results show no relevant differences in withdrawals for any cause between pregabalin at any dose and placebo.

We typically assessed the quality of evidence for pain outcomes as moderate for doses of 300 mg and 600 mg, and as low for the 150-mg dose. Results were generally consistent between studies. We downgraded evidence for all outcomes once to moderate quality because of doubts over the effects of using LOCF imputation on the definition of responders. For analyses of outcomes with susceptibility to publication bias, we downgraded evidence once more to low quality (see 'Summary of results A'; Summary of findings for the main comparison; and Summary of findings 2). For withdrawals, we rated the quality of evidence as high, as we noted adequate numbers of participants for these analyses, and we could not assess publication bias for these outcomes.

Summary of results A. Efficacy outcomes with different doses of pregabalin in postherpetic neuralgia

	Number of		Percent with outcome					
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Relative benefit (95% CI)**	**NNTB (95% CI)**	**Susceptibility to publication bias**	**GRADE assessment**
At least 30% pain intensity reduction								
300 mg	3	589	50	25	2.1 (1.6 to 2.6)	3.9 (3.0 to 5.6)	921	Moderate
600 mg	3	537	62	24	2.5 (2.0 to 3.2)	2.7 (2.2 to 3.4)	1452	Moderate
600 mg (≥ 8 weeks)	2	356	58	21	2.8 (2.0 to 3.8)	2.7 (2.2 to 3.7)	963	Moderate
At least 50% pain intensity reduction								
150 mg	4	699	24	13	2.0 (1.4 to 2.7)	8.3 (5.7 to 16)	143	Low
300 mg	4	713	32	13	2.5 (1.9 to 3.4)	5.1 (3.9 to 7.4)	685	Moderate
300 mg (≥ 8 weeks)	3	535	30	11	2.7 (1.9 to 4.0)	5.3 (3.9 to 8.1)	474	Moderate
600 mg	4	732	41	15	2.7 (2.0 to 3.5)	3.9 (3.1 to 5.1)	1145	Moderate
600 mg (≥ 8 weeks)	3	551	39	14	2.8 (2.0 to 3.9)	4.0 (3.1 to 5.5)	767	Moderate
PGIC much or very much improved								

(*Continued*)

150 mg	2	342	27	15	1.8 (1.2 to 2.8)	8.4 (4.9 to 30)	65	Low
300 mg	3	568	32	15	2.1 (1.5 to 2.9)	5.9 (4.2 to 9.8)	395	Low
Lack of efficacy withdrawal						**NNTp (95% CI)**		
150 mg	4	699	6	10	0.6 (0.4 to 0.97)	not calculated		High
300 mg	5	933	3	9	0.4 (0.2 to 0.7)	18 (12 to 41)		High
300 mg (≥ 8 weeks)	4	755	4	10	0.4 (0.2 to 0.7)	18 (11 to 47)		High
600 mg	4	732	3	11	0.2 (0.1 to 0.5)	13 (8.9 to 24)		High
600 mg (≥ 8 weeks)	3	551	3	12	0.3 (0.1 to 0.6)	11 (7.4 to 21)		High
All-cause withdrawal								
150 mg	4	699	22	17	0.8 (0.6 to 1.1)	not calculated		High
300 mg	5	933	22	21	1.0 (0.8 to 1.3)	not calculated		High
600 mg	4	732	26	20	1.3 (1.0 to 1.7)	16 (8.2 to 2300)		High

Painful diabetic neuropathy efficacy

'Summary of results B' shows results for the four primary and two secondary efficacy outcomes for which data were available. Each case shows greater response with a higher dose, with more participants achieving the outcomes, and with lower (better) NNTB values. At least 30% pain intensity reduction (moderate benefit) tended to produce higher response rates and lower NNTB values than did at least 50% pain intensity reduction (substantial benefit). Only two trials (both of less than eight weeks' duration) reported a measure of substantial benefit (very much improved) on the PGIC scale, showing no difference from placebo. For PGIC, much or very much improved NNTB values tended to be lower (better) than for 30% or 50% pain intensity reduction. Limiting analyses to studies of eight weeks' duration or longer made no appreciable difference in the results.

Lack of efficacy withdrawals were fewer with 600 mg pregabalin than with placebo, but not with lower doses. Data show no difference in withdrawals for any cause between pregabalin at any dose and placebo.

We typically assessed the quality of evidence for pain outcomes as moderate for doses of 300 mg and 600 mg using all trials, but

low when we only assessed trials lasting more than eight weeks. We assessed the quality of evidence for pain outcomes as low for the 150-mg dose. Results were generally consistent between studies. We downgraded evidence for all outcomes once to moderate quality because of doubts over the effects of using LOCF imputation on the definition of responders. For analyses of outcomes with susceptibility to publication bias, we downgraded evidence once more to low quality (see 'Summary of results B'; Summary of findings 3; and Summary of findings 4).

For withdrawals, we rated the quality of evidence as high, as typically adequate numbers of participants were available for analyses, and we could not assess publication bias for these outcomes.

Summary of results B. Efficacy outcomes with different doses of pregabalin in painful diabetic neuropathy

	Number of		Percent with outcome					
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Relative benefit (95% CI)**	**NNTB (95% CI)**	**Susceptibility to publication bias**	**GRADE assessment**
At least 30% pain intensity reduction								
300 mg	8	2320	47	42	1.1 (1.01 to 1.2)	22 (12 to 201)	NNTB above 10	Moderate
300 mg (≥ 8 weeks)	4	1304	51	47	1.1 (0.97 to 1.2)	not calculated	N/A	Moderate
600 mg	3	789	63	47	1.3 (1.2 to 1.5)	6.2 (4.3 to 11)	484	Moderate
600 mg (≥ 8 weeks)	2	611	63	52	1.2 (1.04 to 1.4)	9.6 (5.5 to 41)	25	Low
At least 50% pain intensity reduction								
150 mg	2	359	27	23	1.1 (0.8 to 1.6)	not calculated	N/A	Low
300 mg	11	2931	31	24	1.3 (1.2 to 1.5)	14 (9.7 to 26)	NNTB above 10	Moderate
300 mg (≥ 8 weeks)	7	1914	33	26	1.2 (1.1 to 1.4)	16 (9.6 to 44)	NNTB above 10	Moderate
600 mg	7	1360	42	25	1.6 (1.4 to 1.9)	6.1 (4.7 to 8.8)	870	Moderate

(*Continued*)

600 mg (≥ 8 weeks)	5	1015	41	28	1.4 (1.2 to 1.7)	7.8 (5.4 to 14)	286	Low
PGIC much or very much improved								
300 mg	5	1050	51	30	1.8 (1.5 to 2.0)	4.9 (3.8 to 6.9)	1093	Moderate
300 mg (≥ 8 weeks)	3	573	59	35	1.7 (1.5 to 2.0)	4.3 (3.2 to 6.6)	760	Moderate
600 mg	3	537	60	33	1.8 (1.5 to 2.2)	3.7 (2.8 to 5.3)	914	Moderate
600 mg (≥ 8 weeks)	2	364	56	38	1.5 (1.2 to 1.9)	5.3 (3.5 to 12)	323	Low
PGIC very much improved								
300 mg (≥ 8 weeks)	2	501	9.1	5.2	1.8 (0.91 to 3.4)	not calculated	N/A	Moderate
Lack of efficacy withdrawal						**NNTp (95% CI)**		
150 mg	2	359	4.5	6.6	0.7 (0.3 to 1.5)	not calculated		Moderate
150 mg (≥ 8 weeks)	1	195	8.1	11	0.7 (0.3 to 1.7)	not calculated		Low
300 mg	10	2430	2.0	2.9	0.7 (0.4 to 1.1)	not calculated		High
300 mg (≥ 8 weeks)	6	1612	2.7	4.1	0.6 (0.4 to 1.1)	not calculated		High
600 mg	5	879	2.7	6.1	0.5 (0.3 to 0.9)	30 (16 to 250)		High
600 mg (≥ 8 weeks)	3	544	3.3	7.4	0.4 (0.2 to 0.9)	24 (13 to 230)		High
All-cause withdrawal								
150 mg	2	359	12	17	0.7 (0.4 to 1.2)	not calculated		Moderate

(*Continued*)

300 mg	12	2823	18	17	1.1 (0.9 to 1.2)	not calculated		High
600 mg	8	1669	24	23	1.0 (0.9 to 1.2)	not calculated		High

Mixed or unclassified post-traumatic neuropathic pain efficacy

'Summary of results C' shows results for the four primary and two secondary efficacy outcomes for which data were available in the five studies that used a classic trial design. No useful efficacy data were available from the study using 300 mg pregabalin daily. More people with this type of neuropathic pain had greater response with pregabalin 600 mg daily than with placebo for both levels of pain intensity reduction and PGIC much or very much improved. This was not the case for the outcome of PGIC very much improved. Lack of efficacy withdrawals were fewer with 600 mg pregabalin than with placebo. Data show no difference in withdrawals for any cause between pregabalin at any dose and placebo.

We typically assessed the quality of evidence of efficacy as moderate for the 600-mg dose. Results were generally consistent between studies. We downgraded evidence for efficacy outcomes once to moderate quality because of doubts over the effects of using LOCF imputation on the definition of responders. For analyses of outcomes with susceptibility to publication bias, we downgraded evidence once more to low quality ('Summary of results C').

For withdrawals, we rated the quality of evidence as high, as adequate numbers of participants were included in analyses, and we could not assess publication bias for these outcomes.

Summary of results C. Efficacy outcomes with different doses of pregabalin in mixed or unclassified post-traumatic neuropathic pain

	Number of		Percent with outcome					
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Relative benefit (95% CI)**	**NNTB (95% CI)**	**Susceptibility to publication bias**	**GRADE assessment**
At least 30% pain intensity reduction								
600 mg	4	1367	48	36	1.2 (1.1 to 1.4)	8.2 (5.7 to 15)	300	Low
At least 50% pain intensity reduction								
600 mg	4	1367	34	20	1.5 (1.2 to 1.9)	7.2 (5.4 to 11)	532	Moderate
PGIC much or very much improved								
600 mg	3	1129	51	37	1.4 (1.2 to 1.6)	7.2 (5.1 to 12)	439	Moderate
PGIC very much improved								

(*Continued*)

600 mg	2	791	16	12	1.3 (0.95 to 1.9)	not calculated	N/A	Moderate
Lack of efficacy withdrawal						**NNTp (95% CI)**		
600 mg	4	1371	4.3	7.7	0.37 (0.24 to 0.57)	30 (17 to 140)		High
All-cause withdrawal								
600 mg	4	1371	23	24	0.81 (0.67 to 0.99)	not calculated		High

Central neuropathic pain efficacy

'Summary of results D' shows results for the four primary and two secondary efficacy outcomes for which data were available in studies using a classic trial design. Efficacy data were available only from studies using 600 mg pregabalin daily and lasting eight weeks or longer. More people with this type of neuropathic pain had greater response with pregabalin 600 mg daily than with placebo for both levels of pain intensity reduction, but not for either PGIC outcome.

Lack of efficacy withdrawals were fewer with pregabalin than with placebo, but data show no difference in all-cause discontinuations.

We assessed the quality of evidence as low for the 600-mg dose. Results were generally consistent between studies. We downgraded evidence for efficacy outcomes once to moderate quality because of doubts over the effects of using LOCF imputation on the definition of responders, and once more because of susceptibility to publication bias.

For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results D. Efficacy outcomes with different doses of pregabalin in central neuropathic pain

	Number of		**Percent with outcome**					
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Relative benefit (95% CI)**	**NNTB (95% CI)**	**Susceptibility to publication bias**	**GRADE assessment**
At least 30% pain intensity reduction								
600 mg	3	562	44	28	1.6 (1.3 to 2.0)	5.9 (4.1 to 11)	391	Low
At least 50% pain intensity reduction								
600 mg	3	562	26	15	1.7 (1.2 to 2.3)	9.8 (6.0 to 28)	11	Low
PGIC much or very much improved								

(*Continued*)

600 mg	1	210	29	26	1.1 (0.71 to 1.7)	not calculated	N/A	Low
PGIC very much improved								
600 mg	1	210	6.7	1.9	3.5 (0.74 to 16)	not calculated	N/A	Low
Lack of efficacy withdrawal						**NNTp (95% CI)**		
600 mg	3	575	2.1	8.1	0.27 (0.12 to 0.61)	17 (10 to 40)		High
All-cause withdrawal								
600 mg	3	575	20	23	0.85 (0.62 to 1.15)	not calculated		High-

HIV neuropathy efficacy

'Summary of results E' shows results for the four primary and two secondary efficacy outcomes for which data were available from two studies. We obtained only efficacy data from studies using 600 mg pregabalin daily and lasting eight weeks or longer. No more people with this type of neuropathic pain had greater response with pregabalin 600 mg daily than with placebo for either level of pain intensity reduction nor for either PGIC outcome.

There were no fewer lack of efficacy or all-cause withdrawals with pregabalin compared with placebo.

We assessed the quality of evidence as moderate for the 600-mg dose. Results were generally consistent between studies. We downgraded evidence for efficacy outcomes once to moderate quality because of doubts over the effects of using LOCF imputation on the definition of responders.

For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results E. Efficacy outcomes with different doses of pregabalin in HIV neuropathy

	Number of		**Percent with outcome**				
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Relative benefit (95% CI)**	**NNTB (95% CI)**	**GRADE assessment**
At least 30% pain intensity reduction							
600 mg	2	664	52	53	1.0 (0.87 to 1.2)	not calculated	Moderate
At least 50% pain intensity reduction							
600 mg	2	674	33	38	0.86 (0.70 to 1. 06)	not calculated	Moderate
PGIC much or very much improved							

(*Continued*)

600 mg	2	674	54	53	1.02 (0.88 to 1.17)	not calculated	Moderate
PGIC very much improved							
600 mg	2	674	21	23	0.91 (0.69 to 1.2)	not calculated	Moderate
Lack of efficacy withdrawal						**NNTp (95% CI)**	
600 mg	2	677	0.3	1.2	0.34 (0.05 to 2.13)	not calculated	High
All-cause withdrawal							
600 mg	1	302	21	19	not calculated	not calculated	High

Back pain with radiculopathy efficacy

We identified two studies for this condition (217 participants in total). One did not report any of our pre-specified efficacy outcomes nor withdrawals due to lack of efficacy, and data show no obvious difference in all-cause withdrawals. The other study used an enriched enrolment randomised withdrawal design, and we have considered it elsewhere in the review. We assessed the evidence as very low quality, downgraded three times due to small numbers.

Neuropathic cancer pain efficacy

Two studies examining this condition (160 participants in total) did not report any of our pre-specified efficacy outcomes nor withdrawals due to lack of efficacy or any cause. We assessed the evidence as very low quality, downgraded three times due to small numbers.

Painful polyneuropathy efficacy

We found one small study for this condition. More participants reported at least 30% and at least 50% pain intensity reduction with pregabalin 300 mg daily (16/73 and 8/73, respectively) than with placebo (10/73 and 4/73, respectively), but data were too few for analysis. Results show no difference in withdrawals due to lack of efficacy or for any cause. We assessed the evidence as very low quality, downgraded three times due to small numbers.

Efficacy analyses for EERW studies

Five studies used an EERW design, in PHN (Huffman 2017), in PDN (Raskin 2014), in mixed neuropathic pain (Gilron 2011; Hewitt 2011), and in back pain with radiculopathy (Baron 2010). As the summary of additional risk of bias evaluations below shows, only Raskin 2014 achieved low risk for the duration of the double-blind stage, where it was 13 weeks; for all others, the risk was unclear. For description of outcomes, all studies had unclear risk, mainly because they used 30%, not 50%, pain intensity reduction. Hewitt 2011 had high risk of bias for the taper period to placebo after randomisation, as it apparently provided no taper period; all others provided a one-week taper period, and we therefore judged them to be at low risk.

Summary of additional risk of bias evaluations

Risk of bias item	Huffman 2017	Raskin 2014	Gilron 2011	Hewitt 2011	Baron 2010
Duration	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Outcome	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Taper period	Low risk	Low risk	Low risk	High risk	Low risk

It was not possible to perform any pooled analysis of the EERW studies because of their methodological heterogeneity, so instead we provided a qualitative description, using outcomes reported in the studies themselves, as they did not report our pre-specified outcomes.

Postherpetic neuralgia

Huffman 2017 was a large multi-centre study comprising a six-week single-blind evaluation (801 participants) followed by double-blind treatment with pregabalin (up to 600 mg daily) or placebo after randomisation for 13 weeks (413 participants). The primary outcome was loss of therapeutic response, defined as < 30% pain response relative to the single-blind phase baseline, or withdrawal due to lack of efficacy or adverse events in the double-blind phase of the study, after ≥ 50% pain intensity reduction was achieved initially.

Half (52%) of those entering the single-blind phase achieved ≥ 50% response. Improvements were greater for mean daily and weekly pain scores, and for sleep, anxiety, depression, and the physical component of the Short Form (SF)-36 quality of life instrument via LOCF imputation. The proportion maintaining their response for 13 weeks after randomisation was 86% with pregabalin and 69% with placebo based on a true responder outcome without imputation. These results yielded an RR of 1.24 (95% CI 1.1 to 1.4), with an NNTB of 6.0 (95% CI 4.0 to 11), for maintenance of pain response compared with placebo over 13 weeks.

We assessed the evidence as moderate quality, downgraded once, because this was a single study with more than 200 participants in the randomised, double-blind phase.

Painful diabetic neuropathy

Raskin 2014 was a large multi-centre study comprising a six-week single-blind evaluation followed by double-blind treatment with pregabalin or placebo for 13 weeks after randomisation. Participants had to be receiving one of several drugs, with treatment failure due to inadequate pain control (pain ≥ 40/100). In the single-blind phase (665 participants with mean pain scores of around 7/10), researchers titrated pregabalin to 150 mg or 300 mg daily; they classified those with ≥ 30% pain reduction on optimal dosing as responders who entered the double-blind phase after randomisation (294 participants). The primary outcome was mean pain intensity (last seven days); other outcomes included loss of pain response (< 15% pain reduction from study baseline) and proportions of 30% and 50% pain responders, among others.

Half (50%) of those entering the single-blind phase achieved ≥ 30% response. Mean pain scores were not different between groups. The proportion maintaining their response for 13 weeks after randomisation was 83% with pregabalin and 79% with placebo via a true responder outcome without imputation.

We assessed the evidence as low quality, downgraded twice, because this was a single study with fewer than 200 participants in the randomised, double-blind phase.

Mixed neuropathic pain

Gilron 2011 recruited 256 participants into a single-blind flexible pregabalin dosing stage, up to 600 mg daily (mean initial pain score 6/10). Participants with ≥ 30% improvement in their weekly mean pain score were eligible to be randomised to remain on their optimised pregabalin dose or switch to matching placebo (158 participants). The primary outcome was mean pain score at the end of the double-blind phase.

The majority (65%) of those entering the single-blind phase achieved ≥ 30% response. At the endpoint, mean pain scores were lower with pregabalin than with placebo, by about 0.6/10; mean sleep, anxiety, and depression scores were also better with pregabalin. The proportion of participants who maintained at least 30% pain intensity reduction and continued on pregabalin was 65%; with placebo, it was 64%.

Hewitt 2011 was a modest proof of concept study using a short (four-day, 274 participants, mean pain score 6/10) screening period, 12-day titration with pregabalin (140 participants), and then nine-day maintenance following randomisation to continuation or placebo (104 participants). The primary outcome was mean pain intensity change, although maintenance of ≥ 30% pain intensity reduction over baseline was also reported.

The majority (74%) of those entering the single-blind phase achieved ≥ 30% response. Greater pain reduction was evident with pregabalin than with placebo (by about 1/10), and although the proportion maintaining their response after randomisation was

similar in both groups (about 60%), data show a large difference in terms of time to loss of therapeutic response. This might be accounted for by use of different imputation methods.
We assessed the evidence as low quality, downgraded twice, because each study included fewer than 200 participants in the randomised, double-blind phase.

Neuropathic pain associated with chronic lumbosacral radiculopathy

Baron 2010 recruited 544 participants into an initial screening phase, followed by trials with placebo to eliminate placebo responders, and then with pregabalin (to 600 mg daily) for 28 days (initial pain about 6/10); researchers randomised 218 participants to continuation or placebo for five weeks if they observed ≥ 30% reduction in pain intensity. The primary outcome was loss of therapeutic response (≥ 1/10 increase in pain from randomisation) or discontinuation for any reason.
The majority (60%) of those entering the single-blind phase achieved ≥ 30% response. The proportion maintaining their response after randomisation was similar in both pregabalin and placebo groups (28%).
We assessed the evidence as moderate quality, downgraded once, because this was a single study with more than 200 participants in the randomised, double-blind phase.

Adverse event analyses

For analysis of adverse events, we chose to pool participants experiencing at least one adverse event (very common) and those experiencing at least one serious adverse event (uncommon) across all doses.
We have provided detailed analyses in the following: Analysis 1.5; Analysis 1.6; Analysis 1.7; Analysis 1.8; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 4.1; and Analysis 5.1.

Participants experiencing at least one adverse event or serious adverse event (all-trials analysis)

Results for participants experiencing at least one adverse event or serious adverse event were not reported in all studies. Consequently, the analysis in 'Summary of results F' is by dose only, not by dose and condition. Most participants given pregabalin and placebo reported at least one adverse event over the period, with no indication of a dose-response relationship. A small proportion reported at least one adverse event considered serious (almost certainly based on pre-set criteria of seriousness). Data show no difference in the incidence of serious adverse events between pregabalin and placebo, and no indication of any dose response.
We rated the quality of evidence for experiencing at least one adverse event as high; these are often poorly reported (Edwards 1999), but numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes. Serious adverse events are usually well reported.

Summary of results F. Participants experiencing at least one adverse event or serious adverse event

	Number of		Percent with outcome				
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Risk ratio (95% CI)**	**NNTH (95% CI)**	**GRADE assessment**
At least one adverse event							
300 mg	15	3697	60	51	1.2 (1.2 to 1.3)	11 (8.0 to 16)	High
600 mg	15	3963	69	57	1.3 (1.2 to 1.4)	8.1 (6.5 to 11)	High
At least one serious adverse event							
150 mg	3	542	4.1	4.0	1.0 (0.5 to 2.4)	not calculated	High
300 mg	17	4112	3.1	2.6	1.2 (0.8 to 1.7)	not calculated	High
600 mg	16	3995	3.4	3.4	1.1 (0.8 to 1.5)	not calculated	High

Specific adverse events and adverse event withdrawal in postherpetic neuralgia

We present results for somnolence, dizziness, and adverse event withdrawal in 'Summary of results G'. Higher doses produced higher adverse event rates with pregabalin and lower (worse) NNTH values. Between one participant in 10 and one in five withdrew because of an adverse event. Only for somnolence did 150 mg produce higher adverse event rates than placebo.

We assessed the quality of evidence for somnolence and dizziness as moderate, downgraded once because of uncertainty over reporting of common adverse events (Edwards 1999). For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results G. Somnolence, dizziness, and adverse event withdrawal in postherpetic neuralgia

	Number of		Percent with outcome				
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Risk ratio (95% CI)**	**NNTH (95% CI)**	**GRADE assessment**
Somnolence							
150 mg	3	527	15	7.0	2.2 (1.4to 3.7)	12 (7.3 to 34)	Moderate
300 mg	5	933	16	5.5	3.0 (1.9 to 4.5)	9.5 (7.0 to 15)	Moderate
600 mg	4	732	25	5.8	4.4 (2.8 to 6.8)	5.2 (4.1 to 7.0)	Moderate
Dizziness							
150 mg	3	527	13	10	1.3 (0.80 to 2.1)	not calculated	Moderate
300 mg	5	933	29	8.1	3.6 (2.6 to 5.1)	4.8 (3.9 to 6.2)	Moderate
600 mg	4	732	35	8.8	4.0 (2.8 to 5.7)	3.8 (3.2 to 4.9)	Moderate
Adverse event withdrawal							
150 mg	4	699	8.0	6.7	1.2 (0.70 to 2.0)	not calculated	High
300 mg	5	933	14	5.3	2.7 (1.8 to 4.2)	11 (7.8 to 19)	High
600 mg	4	732	19	5.2	3.7 (2.3 to 6.0)	7.1 (5.3 to 11)	High

Specific adverse events and adverse event withdrawal in painful diabetic neuropathy

Results for somnolence, dizziness, and adverse event withdrawal are shown in 'Summary of results H'. Higher doses produced higher adverse event rates with pregabalin and lower (worse) NNTH values. Between one participant in 25 and one in seven discontinued because of an adverse event. Pregabalin 150 mg produced adverse event rates no different from placebo.

We assessed the quality of evidence for somnolence and dizziness as moderate, downgraded once because of uncertainty over reporting of common adverse events (Edwards 1999). For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results H. Somnolence, dizziness, and adverse event withdrawal in painful diabetic neuropathy

	Number of		Percent with outcome				
Outcome - daily dose	Studies	Participants	Pregabalin	Placebo	Risk ratio (95% CI)	NNTH (95% CI)	GRADE assessment
Somnolence							
150 mg	2	359	5.1	2.2	2.3 (0.72 to 7.5)	not calculated	Moderate
300 mg	12	3315	11	3.1	3.5 (2.6 to 4.8)	13 (11 to 17)	Moderate
600 mg	7	1501	15	4.5	4.3 (2.9 to 6.3)	9.6 (7.5 to 13)	Moderate
Dizziness							
150 mg	2	359	6.2	2.2	2.8 (0.93 to 8.7)	not calculated	Moderate
300 mg	12	3315	13	3.8	3.5 (2.7 to 4.6)	10 (8.6 to 13)	Moderate
600 mg	8	1885	22	4.4	5.6 (4.1 to 7.7)	5.6 (4.8 to 6.7)	Moderate
Adverse event withdrawal							
150 mg	2	359	3.9	3.9	1.0 (0.36 to 2.9)	not calculated	Moderate
300 mg	13	3384	8.0	5.1	1.6 (1.2 to 2.1)	35 (22 to 82)	High
600 mg	8	1669	14	5.6	2.7 (1.9 to 3.7)	12 (9.2 to 19)	High

Specific adverse events and adverse event withdrawal in mixed or unclassified post-traumatic neuropathic pain

Results for somnolence, dizziness, and adverse event withdrawal are shown in 'Summary of results I'. Rates of somnolence and dizziness were higher with pregabalin 600 mg than with placebo, but data show no difference in withdrawals due to adverse events. We assessed the quality of evidence for somnolence and dizziness as moderate, downgraded once because of uncertainty over reporting of common adverse events (Edwards 1999). For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results I. Somnolence, dizziness, and adverse event withdrawal in mixed or unclassified post-traumatic neuropathic pain

	Number of		Percent with outcome				
Outcome - daily dose	Studies	Participants	Pregabalin	Placebo	Risk ratio (95% CI)	NNTH (95% CI)	GRADE assessment
Somnolence							
600 mg	4	1371	12	3.9	3.2 (2.0 to 5.1)	12 (9.2 to 19)	Moderate

(*Continued*)

Dizziness							
600 mg	4	1371	23	6.2	3.8 (2.6 to 5.4)	5.9 (4.9 to 7.4)	Moderate
Adverse event withdrawal							
600 mg	4	1371	8.4	5.0	1.1 (0.6 to 1.7)	not calculated	High

Specific adverse events and adverse event withdrawal in central neuropathic pain

Results for somnolence, dizziness, and adverse event withdrawal are shown in 'Summary of results J'. Pregabalin 600 mg produced more somnolence and dizziness but did not produce higher rates of adverse event withdrawal.

We assessed the quality of evidence for somnolence and dizziness as moderate, downgraded once because of uncertainty over reporting of common adverse events (Edwards 1999). For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results J. Somnolence, dizziness, and adverse event withdrawal in central neuropathic pain

	Number of		Percent with outcome				
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Risk ratio (95% CI)**	**NNTH (95% CI)**	**GRADE assessment**
Somnolence							
600 mg	3	575	32	11	3.5 (2.3 to 5.2)	4.9 (3.7 to 7.0)	Moderate
Dizziness							
600 mg	3	575	25	8.6	3.5 (2.2 to 5.5)	6.1 (4.5 to 9.4)	Moderate
Adverse event withdrawal							
600 mg	3	575	11	7.9	1.5 (0.9 to 2.5)	not calculated	High

Specific adverse events and adverse event withdrawal in HIV neuropathy

Results for somnolence, dizziness, and adverse event withdrawal are shown in 'Summary of results K'. Pregabalin 600 mg produced more somnolence and dizziness but did not produce higher rates of adverse event withdrawal.

We assessed the quality of evidence for somnolence and dizziness as moderate, downgraded once because of uncertainty over reporting of common adverse events (Edwards 1999). For withdrawals, we rated the quality of evidence as high, as numbers of participants were adequate for the analyses, and we could not assess publication bias for these outcomes.

Summary of results K. Somnolence, dizziness, and adverse event withdrawal in HIV neuropathy

	Number of		Percent with outcome				
Outcome - daily dose	**Studies**	**Participants**	**Pregabalin**	**Placebo**	**Risk ratio (95% CI)**	**NNTH (95% CI)**	**GRADE assessment**
Somnolence							
600 mg	2	677	14	5.0	2.9 (1.7 to 4.8)	11 (7.2 to 20)	Moderate
Dizziness							
600 mg	2	677	16	7.6	2.1 (1.4 to 3.3)	12 (7.5 to 27)	Moderate
Adverse event withdrawal							
600 mg	2	677	3.6	1.5	2.4 (0.9 to 6.8)	not calculated	High

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Pregabalin 600 mg compared with placebo for postherpetic neuralgia

Patient or population: adults with moderate or severe pain associated with postherpetic neuralgia
Settings: community
Intervention: oral pregabalin 600 mg, typically for 8 weeks or longer after initial titration
Comparison: oral placebo

Outcome	Probable outcome with pregabalin	Probable outcome with placebo	RR and NNTB or NNTH (95% CI)	No. of studies (participants)	Quality of the evidence (GRADE)	Comments
At least 30% pain intensity reduction	620 per 1000	240 per 1000	RR 2.5 (2.0 to 3.2) NNTB 2.7 (2.2 to 3.7)	3 (537)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
At least 50% pain intensity reduction	410 per 1000	150 per 1000	RR 2.7 (2.0 to 3.5) NNTB 3.9 (3.1 to 5.5)	4 (732)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
Patient Global Impression of Change - much or very much improved	No data	No data	No data	No data	Very low	Downgraded 3 times due to no data
Lack of efficacy withdrawal	30 per 1000	110 per 1000	RR 0.2 (0.1 to 0.5) NNTB 13 (8.9 to 24)	4 (732)	High	
Somnolence	250 per 1000	58 per 1000	RR 4.4 (2.8 to 6.8) NNTH 5.2 (4.1 to 7.0)	4 (732)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events

Dizziness	350 per 1000	88 per 1000	RR 4.0 (2.8 to 5.7) NNTH 3.8 (3.2 to 4.9)	4 (732)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events
Adverse event withdrawal	190 per 1000	52 per 1000	RR 3.7 (2.3 to 6.0) NNTH 7.1 (5.3 to 11)	4 (732)	High	

CI: confidence interval; LOCF: last observation carried forward; NNTB: number needed to treat for an additional beneficial outcome compared with placebo; NNTH: number needed to treat for an additional harmful outcome compared with placebo; RR: risk ratio

Descriptors for levels of evidence (EPOC 2015).
High quality: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[a] is low.
Moderate quality: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[a] is moderate.
Low quality: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[a] is high.
Very low quality: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[a] is very high.
[a]Substantially different: a large enough difference that it might affect a decision

Pregabalin 300 mg compared with placebo for painful diabetic neuropathy

Patient or population: adults with moderate or severe pain associated with painful diabetic neuropathy
Settings: community
Intervention: oral pregabalin 300 mg, typically for 8 weeks or longer after initial titration
Comparison: oral placebo

Outcome	Probable outcome with pregabalin	Probable outcome with placebo	RR and NNTB or NNTH (95% CI)	No. of studies (participants)	Quality of the evidence (GRADE)	Comments
At least 30% pain intensity reduction	470 per 1000	420 per 1000	RR 1.1 (1.01 to 1.2) NNTB 22 (12 to 200)	8 (2320)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
At least 50% pain intensity reduction	310 per 1000	240 per 1000	RR 1.3 (1.2 to 1.5) NNTB 14 (9.7 to 26)	11 (2931)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
Patient Global Impression of Change - much or very much improved	510 per 1000	300 per 1000	RR 1.8 (1.5 to 2.0) NNTB 4.9 (3.8 to 6.9)	5 (1050)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
Patient Global Impression of Change - very much improved	91 per 1000	52 per 1000	RR 1.8 (0.9 to 3.4) NNTB not calculated	2 (501)	Low	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders, and once because of susceptibility to publication bias

Lack of efficacy withdrawal	20 per 1000	29 per 1000	RR 0.7 (0.4 to 1.1) NNTB not calculated	10 (2430)	High	
Somnolence	110 per 1000	31 per 1000	RR 3.5 (2.6 to 4.8) NNTH 13 (11 to 17)	12 (3315)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events
Dizziness	130 per 1000	38 per 1000	RR 3.5 (2.7 to 4.6) NNTH 10 (8.6 to 13)	12 (3315)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events
Adverse event withdrawal	80 per 1000	51 per 1000	RR 1.6 (1.2 to 2.1) NNTH 35 (22 to 82)	13 (3384)	High	

CI: confidence interval; LOCF: last observation carried forward; NNTB: number needed to treat for an additional beneficial outcome compared with placebo; NNTH: number needed to treat for an additional harmful outcome compared with placebo; RR: risk ratio

Descriptors for levels of evidence (EPOC 2015).
High quality: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[a] is low.
Moderate quality: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[a] is moderate.
Low quality: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[a] is high.
Very low quality: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[a] is very high.
[a]Substantially different: a large enough difference that it might affect a decision

Pregabalin 600 mg compared with placebo for painful diabetic neuropathy

Patient or population: adults with moderate or severe pain associated with painful diabetic neuropathy
Settings: community
Intervention: oral pregabalin 600 mg, typically for 8 weeks or longer after initial titration
Comparison: oral placebo

Outcome	Probable outcome with pregabalin	Probable outcome with placebo	RR and NNTB or NNTH (95% CI)	No. of studies (participants)	Quality of the evidence (GRADE)	Comments
At least 30% pain intensity reduction	630 per 1000	470 per 1000	RR 1.3 (1.2 to 1.5) NNTB 9.6 (5.5 to 41)	3 (789)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
At least 50% pain intensity reduction	420 per 1000	250 per 1000	RR 1.6 (1.4 to 1.9) NNTB 6.1 (4.7 to 8.8)	7 (1360)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
Patient Global Impression of Change - much or very much improved	600 per 1000	330 per 1000	RR 1.8 (1.5 to 2.2) NNTB 3.7 (2.8 to 5.3)	3 (537)	Moderate	Downgraded once due to doubts over effects of using LOCF imputation on the definition of responders
Lack of efficacy withdrawal	27 per 1000	61 per 1000	RR 0.5 (0.3 to 0.90) NNTB 30 (16 to 230)	5 (879)	High	
Somnolence	150 per 1000	45 per 1000	RR 4.3 (2.9 to 6.3) NNTH 9.6 (7.5 to 13)	7 (1501)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events

Dizziness	220 per 1000	44 per 1000	RR 5.6 (4.1 to 7.7) NNTH 5.6 (4.8 to 6.7)	8 (1885)	Moderate	Downgraded once because of uncertainty over reporting of common adverse events
Adverse event withdrawal	140 per 1000	56 per 1000	RR 2.7 (1.9 to 3.7) NNTH 12 (9.2 to 19)	8 (1669)	High	

CI: confidence interval; LOCF: last observation carried forward; NNTB: number needed to treat for an additional beneficial outcome compared with placebo; NNTH: number needed to treat for an additional harmful outcome compared with placebo; RR: risk ratio

Descriptors for levels of evidence (EPOC 2015).
High quality: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[a] is low.
Moderate quality: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[a] is moderate.
Low quality: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[a] is high.
Very low quality: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[a] is very high.
[a]Substantially different: a large enough difference that it might affect a decision

Pregabalin 300 mg or 600 mg compared with placebo for any neuropathic pain: any adverse event and serious adverse events

Patient or population: adults with moderate or severe neuropathic pain
Settings: community
Intervention: oral pregabalin 300 mg or 600 mg
Comparison: oral placebo

Outcome	Probable outcome with pregabalin	Probable outcome with placebo	RR and NNTB or NNTH (95% CI)	No. of studies (participants)	Quality of the evidence (GRADE)	Comments
300 mg pregabalin						
At least 1 AE	600 per 1000	510 per 1000	RR 1.2 (1.2 to 1.3) NNTH 11 (8.0 to 16)	15 (3697)	High	
Serious AE	31 per 1000	26 per 1000	RR 1.2 (0.8 to 1.7) NNTH not calculated	17 (4112)	High	
600 mg pregabalin						
At least 1 AE	690 per 1000	570 per 1000	RR 1.3 (1.2 to 1.4) NNTH 8.1 (6.5 to 11)	15 (3963)	High	
Serious AE	34 per 1000	34 per 1000	RR 1.1 (0.8 to 1.5) NNTH not calculated	16 (3995)	High	

AE: adverse event; CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome compared with placebo; NNTH: number needed to treat for an additional harmful outcome compared with placebo; RR: risk ratio

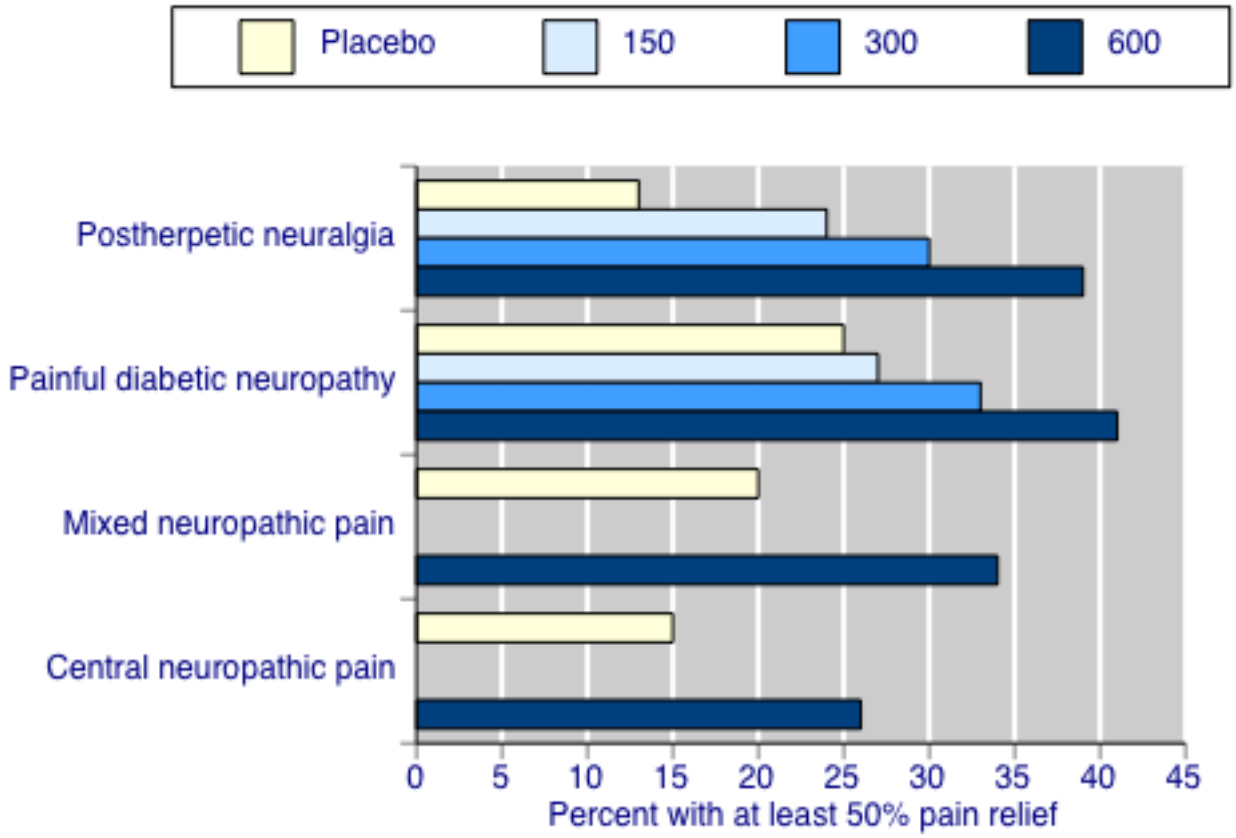
Descriptors for levels of evidence (EPOC 2015).
High quality: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different[a] is low.
Moderate quality: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different[a] is moderate.
Low quality: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different[a] is high.
Very low quality: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different[a] is very high.
[a]Substantially different: a large enough difference that it might affect a decision

DISCUSSION

A previous Cochrane Review titled "Pregabalin for acute and chronic pain in adults", published in 2009 (Moore 2009), examined neuropathic pain amongst other types of pain. That review has now been split, and this update considers only neuropathic pain because of the large amount of information now available on this topic, and because of the Cochrane policy to separate fibromyalgia into separate reviews. A separate updated review of pregabalin for fibromyalgia has been published (Derry 2016a).

Approximately 50 systematic reviews in the Cochrane Library are concerned with pharmacological therapy for neuropathic pain; many have provided scant or no useable data. This review involves the largest number of participants (almost 12,000), larger even than the next two largest reviews combined - those on duloxetine and gabapentin (Lunn 2014; Wiffen 2017a). This review includes studies involving eight different neuropathic pain conditions; we have followed the convention of not combining efficacy data from these different pain conditions. Figure 4 shows very different response rates with placebo and different doses of pregabalin in four neuropathic pain conditions, with comparable trial designs, durations, and outcomes; data show considerable variation, demonstrating differences between conditions in the extent of response to placebo and response to drug.

Figure 4. Percentage of participants with at least 50% pain relief with placebo or four daily pregabalin doses at trial end for four painful conditions (dose of pregabalin in milligrams).



We note that data in studies completed but not reported were substantial (2098 participants in total: 1829 painful diabetic neuropathy (PDN), 105 postherpetic neuralgia (PHN), 82 cancer treatment, and 82 spinal cord injury). The quantity of unavailable data may have the potential to substantially alter the results reported here for these conditions.

Summary of main results

Pregabalin at oral doses of 300 mg and 600 mg daily produced

useful benefit for patients with PHN, PDN, mixed neuropathic pain, and central neuropathic pain. Pregabalin at 150 mg daily was generally ineffective, except in PHN. We found no evidence of efficacy for the 600-mg dose in HIV neuropathy, and we obtained little consistent information for three other conditions - back pain with radiculopathy, neuropathic cancer pain, and painful polyneuropathy. This was the case for several dichotomous efficacy outcomes equating to moderate or substantial pain relief, as defined by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) Group (Dworkin 2008), many of which are of importance to people with neuropathic pain (Moore 2013c), as well as being of economic importance (Moore 2014a). In parallel-group studies lasting eight weeks or longer, the numbers needed to treat for an additional beneficial outcome (NNTB) for pregabalin 300 mg or 600 mg compared with placebo were in the range of 3 to 6 for several efficacy outcomes at both doses in PHN, with broadly similar values for ≥ 30% and ≥ 50% pain intensity reduction, and for Patient Global Impression of Change Scale (PGIC) much or very much improved. For PDN, by contrast, data show greater variability between different outcomes; NNTBs ranged from 5 to 22 for ≥ 30% and ≥ 50% pain intensity reduction, but ranged from 4 to 6 for PGIC much or very much improved.

Only one of the studies using an enriched enrolment randomised withdrawal (EERW) design was free of risk of bias issues (Huffman 2017). This produced an NNTB for loss of therapeutic response after 13 weeks of double-blind comparison with placebo of about 6 for pregabalin doses up to 600 mg in the double-blind phase, based on only 50% with an initial pain response. This suggests far lower efficacy than the NNTBs of 4 and below reported in parallel-group studies.

'Summary table 1' summarises results of the 2009 review (Moore 2009), along with results of this 2018 update, across doses and conditions. This shows the comparison across dose, study duration, and outcome. No changes in NNTB estimates are evident between 2009 and 2018, despite the availability of increased study and participant data, although reported numerical changes might be considered clinically important.

Summary table 1 . Comparison of NNTBs for efficacy outcomes (empty cells denote no useable data)

Condition and pregabalin dose	≥ 30% pain intensity reduction (95% CI)		≥ 50% pain intensity reduction (95% CI)		PGIC much or very much improved (95% CI)	
	2009 original	2018 update	2009 original	2018 update	2009 original	2018 update
Postherpetic neuralgia						
300 mg	4.0 (2.9 to 6.5)	3.9 (3.0 to 5.6)	5.1 (3.9 to 7.4)	5.1 (3.9 to 7.4)	5.8 (3.9 to 12)	5.9 (4.2 to 9.8)
300 mg ≥ 8 weeks			5.3 (3.9 to 8.1)	5.3 (3.9 to 8.1)		
600 mg	2.7 (2.2 to 3.4)	2.7 (2.2 to 3.4)	3.9 (3.1 to 5.1)	3.9 (3.1 to 5.1)		
Painful diabetic neuropathy						
300 mg	6.8 (4.3 to 17)	22 (12 to 201)	7.5 (5.1 to 14)	14 (9.7 to 26)	5.6 (3.6 to 13)	4.9 (3.8 to 6.9)
300 mg ≥ 8 weeks		not calculated	11 (6.0 to 54)	16 (9.6 to 44)		4.3 (3.2 to 6.6)
600 mg	5.1 (3.8 to 7.8)	6.2 (4.3 to 11)	5.0 (4.0 to 6.6)	6.1 (4.7 to 8.8)	4.2 (3.3 to 5.8)	3.7 (2.8 to 5.3)
600 mg ≥ 8 weeks	6.8 (4.4 to 15)	9.6 (5.5 to 41)	6.3 (4.6 to 10)	7.8 (5.4 to 14)	5.4 (3.9 to 9.2)	5.3 (3.5 to 12)
Central neuropathic pain						

(*Continued*)

300 mg ≥ 8 weeks				5.9 (4.1 to 11)		
600 mg ≥ 8 weeks			5.6 (3.5 to 14)	8.7 (5.6 to 20)		

Benefit was balanced by an increase in common adverse events and withdrawals due to adverse events compared with placebo ('Summary table 2'). Adverse events were more frequent with higher pregabalin doses, leading to lower (worse) number needed to treat for an additional harmful outcome (NNTH) values. Generally, the 150-mg dose did not produce an excess of adverse events (except somnolence in PHN). Data show little difference statistically or numerically between results from 2009 and 2018, with the exception of dizziness at 300 mg in PDN; here, a lesser effect was seen in 2018 compared with the 2009 original review ($z = 3.35$; $P < 0.001$).

Summary table 2 . Comparison of NNTHs for adverse event outcomes (empty cells denote no useable data)

Condition and pregabalin dose	Somnolence (95% CI)		Dizziness (95% CI)		AE withdrawal (95% CI)	
	2009 original	2018 update	2009 original	2018 update	2009 original	2018 update
Postherpetic neuralgia						
150 mg	12 (7.3 to 34)	12 (7.3 to 34)	null effect	null effect	null effect	null effect
300 mg	7.4 (5.5 to 11)	9.5 (7.0 to 15)	4.7 (3.7 to 6.5)	4.8 (3.9 to 6.2)	9.3 (6.5 to 16)	11 (7.8 to 19)
600 mg	5.2 (4.1 to 7.0)	5.2 (4.1 to 7.0)	3.8 (3.2 to 4.9)	3.8 (3.2 to 4.9)	7.1 (5.3 to 11)	7.1 (5.3 to 11)
Painful diabetic neuropathy						
150 mg	null effect	null effect	null effect	null effect	null effect	null effect
300 mg	7.8 (6.0 to 11)	13 (11 to 17)	5.5 (4.4 to 7.4)	10 (8.6 to 13)	16 (9.9 to 37)	35 (22 to 82)
600 mg	8.8 (7.0 to 12)	9.6 (7.5 to 13)	4.7 (4.0 to 5.6)	5.6 (4.8 to 6.7)	8.8 (6.8 to 12)	12 (9.2 to 19)
Central neuropathic pain						
600 mg	4.0 (2.6 to 8.3)	4.9 (3.7 to 7.0)	7.8 (4.1 to 82)	6.1 (4.5 to 9.4)	null effect	null effect

[Note that the data for dizziness with 300 mg pregabalin in PHN were entered incorrectly in tables in the 2009 review, where data from fibromyalgia were entered in error.]
Across all conditions, results show a minimal increase in the rate of occurrence of at least one adverse event at 600 mg compared with 300 mg pregabalin. No differences in the occurrence of serious adverse events were found. Again, data show no differences between the 2009 and 2018 reviews.

Overall completeness and applicability of evidence

Despite a considerable increase in the numbers of studies and participants, problems remain concerning completeness and applicability of evidence. Most available data (85%) related to two neuropathic pain conditions - PHN and PDN - which also predominated in the mixed neuropathic pain group. For some conditions - back pain with radiculopathy, neuropathic cancer pain, and painful polyneuropathy - data were few. For HIV neuropathy (HIV-associated painful sensory neuropathy), results show no evidence of effect.
All the larger studies (typically those with more than 100 participants) reported some efficacy outcome equivalent to one or both of the IMMPACT outcomes of at least moderate or substantial benefit. Clearly, analysis at the level of the individual participant would facilitate a more robust estimate (Moore 2013a). Such analysis could also demonstrate a link between benefit in terms of pain and benefit in terms of other outcomes, including quality of life (Hoffman 2010).
Possible sources of bias that could have affected results of this review include the following.

- Duration of studies may have an effect. NNTB estimates of efficacy in chronic pain studies tend to increase (get worse) with increasing duration (Moore 2010e). However, limiting studies to those lasting eight weeks or longer did not change the main efficacy outcomes, mainly because most participants were included in longer-duration studies.
- Outcomes may affect estimates of efficacy, but the efficacy outcomes chosen were participants achieving the equivalent of IMMPACT-defined moderate or substantial improvement, and it is likely that lesser benefits, such as 'any benefit' or 'any improvement', are potentially related to lesser outcomes, although this remains to be clarified.
- The dose of pregabalin differed between studies, in terms of maximum allowable dose and whether the dose was fixed, titrated to effect, or titrated up to the maximum, irrespective of beneficial or adverse effects.
- In some circumstances, cross-over trials have been shown to exaggerate treatment effects in comparison with trials of parallel-group design (Khan 1996); this may not always be the source of major bias (Elbourne 2002), but the extent of exaggeration of treatment effect can be up to 74% (Khan 1996). Only seven of the 47 studies used a cross-over design, and many did not contribute data to analyses.
- Absence of publication bias (unpublished trials showing no benefit of pregabalin over placebo) can never be proven. However, we calculated the number of participants in studies of zero benefit (risk ratio of 1) required for the absolute benefit to reduce beneficial effects to a negligible amount and made a judgement about its potential for impact (Moore 2008).
- Data show the effects of imputation when participants withdraw from studies. Many studies used last observation carried forward (LOCF) imputation, which could have affected the results (Moore 2012a). LOCF tends to overestimate treatment effects when adverse event withdrawals with drug are greater than with placebo. For pregabalin, the excess adverse withdrawal over placebo was about 3%. This is not likely to result in a significant overestimation of treatment effect (Moore 2012a). In a similar situation, duloxetine produced few different NNTBs based on LOCF and baseline observation carried forward (BOCF) in four different chronic pain conditions (Moore 2014b).
- Small study size has become a particular issue, with increasing association of small study size with positive bias (Dechartres 2013; Dechartres 2014; Fanelli 2017; Nguyen 2017). Cochrane Reviews have been criticised for being overly confident with inadequate data (AlBalawi 2013; Brok 2009; Roberts 2015; Turner 2013). In this updated review, which includes largely modern studies, the average trial size was 250 participants. Smaller studies tended to examine less common neuropathic pain conditions and to not contribute to analyses. Moreover, we used study size as part of our risk of bias assessment.

In this review, we found no way to incorporate important observations on the timing and consistency of analgesia with pregabalin in neuropathic pain. For PHN, individual participant-level pooled analyses of several large trials have demonstrated that, judged by the proportion of participants with a 1 out of 10-point pain intensity reduction, around 20 to 40 days is needed for effects to be seen (Rauck 2013c). Early response, defined as 30% pain intensity reduction or greater, was predictive of response after 10 weeks, and pain intensity reduction less than 10% at week 5 was the best early predictor of lack of response at week 10 (Jensen 2012). Much the same is seen in arthritis (Karabis 2016).
Neuropathic pain and chronic pain in general tend to be more prevalent among older people. We have little evidence concerning the use of pregabalin in the older elderly (Gaskell 2014), and probably among those with multiple co-morbidities.
Adverse events present a particular problem. Reporting of particular adverse events was typically curtailed, so that only adverse events affecting 5% or so of participants were reported. To adequately access this information, data from clinical trial reports are usually needed (Edwards 2004; Moore 2005). The problem of reporting adverse events has been commented on before (Edwards 1999; Ioannidis 2001; Loke 2001). Although considerable information is available on withdrawals and adverse events, these studies

could not address rare but serious adverse events. We are aware that erectile dysfunction has been a cause of 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 was not present, and effects of pregabalin on sexual function may not be well represented. Nor did these trials address the issue of substance abuse with pregabalin (Evoy 2017; Schjerning 2016).

Quality of the evidence

All studies included in this review were described as randomised and double-blind, were predominantly of six weeks' duration or longer, and generally reported clinically useful outcomes in people with moderate or severe neuropathic pain. Studies also tended to be large, with reasonable group sizes, and total numbers of participants and events were larger than needed to minimise chance effects (Moore 1998); only seven studies were at high risk of bias due to small size. Risk of bias was otherwise almost uniformly low or unclear for all trials. Diagnostic criteria for inclusion were reasonable and were based on appropriate definitions and duration of pain, and all participants in chronic pain studies had to have pain that was 40% of maximum, indicating that they had pain of at least moderate intensity. This means that studies would be sensitive enough to measure any analgesic effect. The studies themselves appear to be well conducted, and individual participant analyses could overcome some of the shortcomings of reporting. Our GRADE evaluations for efficacy typically revealed moderate-quality evidence, and then only because of concerns about the effect of the LOCF imputation method on efficacy estimates (Moore 2012a). For some doses and some outcomes, for which number of participants and size of effect combined to produce a high likelihood of publication bias, we judged the evidence to be of low quality. For adverse events, with large numbers of participants we typically judged the evidence to be of high quality.

Potential biases in the review process

We know of no potential biases in the review process.

Agreements and disagreements with other studies or reviews

As detailed above, results of the 2018 update were generally in agreement with those of the original 2009 review. Many recent guidelines based on systematic reviews have concluded that pregabalin is helpful in neuropathic pain (Finnerup 2015; Moulin 2014; NICE 2013; SIGN 2013), and UK NICE guidance on pharmacological management of neuropathic pain includes pregabalin as one of four drugs to be tried initially, with early switching if pain relief is not forthcoming (NICE 2013). We are unaware of any systematic reviews or meta-analyses published since 2013 that have come to different conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

For people with neuropathic pain

Pregabalin at daily oral doses of 300 to 600 mg can provide good levels of pain relief for some people with postherpetic neuralgia and painful diabetic neuropathy. Evidence for other types of neuropathic pain is very limited. Pregabalin appears not to be effective for HIV-associated painful peripheral neuropathy. The outcome of at least 50% pain intensity reduction is regarded as a useful outcome of treatment by people with chronic neuropathic pain, and achievement of this degree of pain relief is associated with important beneficial effects on sleep interference, fatigue, and depression, as well as quality of life, function, and work. Around 3 to 4 out of 10 achieved this degree of pain relief with pregabalin, compared with 1 to 2 out of 10 for placebo. More than half of those treated with pregabalin will not attain worthwhile pain relief. Around 6 or 7 out of 10 will experience at least one adverse event with pregabalin (somnolence and dizziness are common), compared with 5 or 6 out of 10 with placebo. Serious adverse events are rare and are of similar proportions with pregabalin and placebo.

The level of efficacy found for pregabalin is consistent with efficacy estimates for other drug therapies for these conditions.

For clinicians

Pregabalin at daily oral doses of 300 to 600 mg can provide good levels of pain relief for some people with postherpetic neuralgia and painful diabetic neuropathy. Evidence for other types of neuropathic pain is very limited. Pregabalin appears not to be effective for HIV-associated painful peripheral neuropathy. The outcome of at least 50% pain intensity reduction is regarded as a useful outcome of treatment by people with chronic neuropathic pain, and achievement of this degree of pain relief is associated with important beneficial effects on sleep interference, fatigue, and depression, as well as quality of life, function, and work. Around 3 to 4 out of 10 achieved this degree of pain relief with pregabalin, compared with 1 to 2 out of 10 for placebo. More than half of those treated with pregabalin will not have achieved worthwhile pain relief. Around 6 or 7 out of 10 will experience at least one adverse event with pregabalin (somnolence and dizziness are common), compared with 5 or 6 out of 10 with placebo. Serious adverse events are rare and are of similar proportions with pregabalin and placebo.

The level of efficacy found for pregabalin is consistent with efficacy estimates for other drug therapies for these conditions.

For policy makers

Pregabalin at daily oral doses of 300 to 600 mg can provide good levels of pain relief for some people with postherpetic neuralgia and painful diabetic neuropathy. Evidence for other types of neuropathic pain is very limited. Pregabalin appears not to be effective for HIV-associated painful peripheral neuropathy. The outcome of at least 50% pain intensity reduction is regarded as a useful outcome of treatment by people with chronic neuropathic pain, and achievement of this degree of pain relief is associated with important beneficial effects on sleep interference, fatigue, and depression, as well as quality of life, function, and work. Around 3 to 4 out of 10 achieved this degree of pain relief with pregabalin, compared with 1 to 2 out of 10 for placebo. More than half of those treated with pregabalin will not attain worthwhile pain relief. Around 6 or 7 out of 10 will experience at least one adverse event with pregabalin (somnolence and dizziness are common), compared with 5 or 6 out of 10 with placebo. Serious adverse events are rare and are of similar proportions with pregabalin and placebo.
The level of efficacy found for pregabalin is consistent with efficacy estimates for other drug therapies for these conditions.

For funders of the intervention

Pregabalin at daily oral doses of 300 to 600 mg can provide good levels of pain relief for some people with postherpetic neuralgia and painful diabetic neuropathy. Evidence for other types of neuropathic pain is very limited. Pregabalin appears not to be effective for HIV-associated painful peripheral neuropathy. The outcome of at least 50% pain intensity reduction is regarded as a useful outcome of treatment by people with chronic neuropathic pain, and achievement of this degree of pain relief is associated with important beneficial effects on sleep interference, fatigue, and depression, as well as quality of life, function, and work. Around 3 to 4 out of 10 achieved this degree of pain relief with pregabalin, compared with 1 to 2 out of 10 for placebo. More than half of those treated with pregabalin will not attain worthwhile pain relief. Around 6 or 7 out of 10 will experience at least one adverse event with pregabalin (somnolence and dizziness are common), compared with 5 or 6 out of 10 with placebo. Serious adverse events are rare and are of similar proportions with pregabalin and placebo.
The level of efficacy found for pregabalin is consistent with efficacy estimates for other drug therapies for these conditions.

Implications for research

General

The design and outcomes of studies in neuropathic pain are well understood, but as the number of people experiencing good pain relief with pregabalin over the longer term (12 weeks) is likely to be small, an enriched-enrolment randomised-withdrawal (EERW) design might provide the highest sensitivity to detect a signal (Moore 2015c).

Use of combinations of drugs for neuropathic pain is common and may be more effective than monotherapy (Chaparro 2012). Future studies might examine combinations, especially the combined use of pregabalin with tricyclic antidepressants, weak opioids, or tramadol. Studies might specifically examine the the timing and sequencing of these drugs with pregabalin.

More research is warranted to examine the efficacy of pregabalin in painful neuropathic pain conditions for which current information is inadequate. These conditions tend to be uncommon, and studies can be difficult and can include few possible participants. We have little evidence concerning use of pregabalin among the older elderly (Gaskell 2014).

Design

Reporting of clinically relevant outcomes using appropriate imputation for withdrawal would improve the relevance of findings for clinical practice. Use of EERW designs for comparison with classic trial designs indicates that good quality EERW designs of long duration may be appropriate for neuropathic pain.
Stratification by phenotype (observable to testable characteristics) might be an interesting possibility for future studies (Baron 2017), as well as the possibility of measuring pain scores with activity (including dynamic tactile allodynia) versus at rest or on average/worst/best over the prior 24 hours. Participant-level data might be of importance for identifying responder clusters and characteristics.
Although pain is important, other outcomes related to function, sleep, fatigue, and quality of life are also important, and are probably closely linked (Hoffman 2010). Participant-level data could shed light on these relationships.
However, the main issue is not whether pregabalin is effective, but rather how it can best be used in clinical practice to generate the best results for most people with a chronic neuropathic pain condition, in the shortest time, and at the lowest cost. New study designs have been proposed to examine this (Moore 2010f).

Measurement (endpoints)

Assessment of neuropathic pain and associated symptoms such as sleep, fatigue, depression, and quality of life should be based on dichotomous participant-reported outcomes of proven clinical utility.

Comparison between active treatments

There seems little point in comparing pregabalin directly with other treatments; the issue is what works for whom. Although the quality and weight of evidence supporting pregabalin in these conditions probably surpass that available for other interventions, this information has been generated largely for regulatory purposes. We need more information about which patients are likely to benefit most from this drug, how dose can best be titrated to effect to minimise adverse events, and whether patients who experienced treatment failure on other drugs can still benefit from pregabalin.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

1008-030

Methods	Randomised, double-blind, placebo-controlled, parallel-group study Duration: 5 weeks (including initial titration)
Participants	Postherpetic neuralgia ≥ 6 months after rash healing, PI ≥ 4/10, age range not known Excluded: no exclusion criteria known N = 256 M/F not available Mean age 71 years (SD 10)
Interventions	Pregabalin 75 mg, n = 84 Pregabalin 150 mg, n = 84 Placebo, n = 88 Medication given as divided dose, 3 times daily Rescue medication: paracetamol Low-dose prophylactic aspirin allowed
Outcomes	PI Participants with ≥ 50% reduction in PI over baseline PGIC Sleep QoL Mood
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Pfizer sponsored No researchers mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not available
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not available - probably LOCF

1008-030 (*Continued*)

Size	Unclear risk	50 to 199 participants per treatment arm

1008-040

Methods	Randomised, double-blind, placebo- and active-controlled, parallel-group study Duration: 6 weeks (2-week titration, 4-week fixed dose)
Participants	Painful diabetic neuropathy ≥ 1 year, PI ≥ 4/10, stable antidiabetic medication, age range not known Excluded: other conditions that might confound assessments N = 256 M/F not available Mean age 60 years (SD 12)
Interventions	Pregabalin 600 mg daily, n = 87 Amitriptyline 75 mg daily, n = 88 Placebo, n = 81 Medication given as divided dose, 3 times daily Rescue medication: paracetamol Low-dose prophylactic aspirin allowed
Outcomes	PI Participants with ≥ 50% reduction in PI over baseline PGIC Sleep QoL Anxiety and depression
Notes	Oxford Quality Score: R1, DB1, W0 = 2/5 Pfizer sponsored No researchers mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not available
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not available - probably LOCF

1008-040 (*Continued*)

Size	Unclear risk	50 to 199 participants per treatment arm

A0081030 [NCT00156078]

Methods	Multi-centre, randomised, double-blind, parallel-group study, with no obvious enrichment Duration: 1-week baseline, 6-week titration, 6-week maintenance, 1-week taper
Participants	Painful diabetic neuropathy 1 to 12 years, optimised glycaemic control, HbA1c ≤ 11%, age ≥ 18 years, PI ≥ 40/100 Excluded: other neurological disorders or pain conditions that could confound results; symptoms confined to upper extremities; markedly asymmetrical symptoms; history of drug or alcohol abuse; amputation other than toes N = 406 (401 in ITT) M 156, F 245 Mean age 57 years (SD 10)
Interventions	Pregabalin 150 to 600 mg daily, n = unknown Placebo, n = unknown
Outcomes	PI (0 to 10) PGIC AEs Withdrawals Sleep QoL Depression
Notes	Oxford Quality Score: R1, DB1, W0 = 2/5 Pfizer sponsored No researchers mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method of blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not available

A0081030 [NCT00156078] (*Continued*)

Size	Low risk	Probably about 200 participants per treatment arm

A0081071 [NCT00143156]

Methods	Randomised, double-blind, placebo-controlled, parallel-group study, with no obviously enriched enrolment Duration: 1-week dose escalation, 12-week fixed dose, 1-week taper
Participants	Painful diabetic neuropathy ≥ 3 months, PI ≥ 40/100, age ≥ 18 years Excluded: other neurological disorders that might affect assessments, severe pain due to other conditions that might affect assessments N = 456 M 260, F 196, majority white Mean age 59 years
Interventions	Pregabalin 300 mg daily, n = 153 Pregabalin 600 mg daily, n = 152 Placebo daily, n = 151 Medication given as divided dose, twice daily
Outcomes	PI Participants with ≥ 30% or ≥ 50% decrease from baseline in mean pain score PGIC (7-point scale) Sleep Anxiety Depression
Notes	Oxford Quality Score: R1, DB2, W1 = 4/5 Pfizer sponsored No researchers mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation

A0081071 [NCT00143156] (*Continued*)

Size	Unclear risk	50 to 199 participants per treatment arm

A0081244 [NCT01049217]

Methods	Multi-centre, randomised, double-blind, parallel-group study, with no obvious enrichment Duration: 2-week single-blind placebo run-in, 2-week double-blind dose adjustment, 12-week maintenance, 1-week taper
Participants	Neuropathic pain associated with HIV neuropathy, age ≥ 18 years, life expectancy > 12 months Excluded: untreated or recently treated vitamin B deficiency; diabetes requiring regular medical treatment or HbA1c > 6.9; peripheral neuropathic pain not associated with HIV; autoimmune disease; malignancy N = 375 (treated) M 138, F 237 Mean age 42 years (range 21 to 73) Baseline PI not reported, no minimum reported, but large average changes reported, consistent with moderate or severe pain at baseline
Interventions	Pregabalin to 450 mg daily, n = 183 Placebo, n = 192 If inadequate control with 450 mg, but well tolerated, dose could be increased to 600 mg daily Medication given as divided dose, twice daily
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders PGIC AEs Withdrawals Sleep QoL Anxiety and depression
Notes	Oxford Quality Score: R1, DB2, W1 = 4/5 Study terminated early: interim analysis indicated completion unlikely to result in statistically significant demonstration of efficacy vs placebo Pfizer sponsored No researchers mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported

A0081244 [NCT01049217] (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo capsule"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF and modified BOCF imputation (used mBOCF for data extraction/analysis)
Size	Unclear risk	50 to 199 participants per treatment arm

A0081279 [NCT01701362]

Methods	Multi-centre, randomised, double-blind, parallel-group study, with no obvious enrichment Duration: 3-week titration, 12-week maintenance, 1-week taper
Participants	Post-traumatic peripheral neuropathic pain ≥ 6 months, PI ≥ 4/10, age ≥ 18 years Excluded: no specific criteria provided N = 539 (treated) M 275, F 267 (randomised) Mean age 53 years (range 20 to 85)
Interventions	Pregabalin 150 to 600 mg daily, n = 274 Placebo, n = 265 Medication given as divided dose, twice daily; started at 150 mg daily and titrated to 600 mg or maximum tolerated dose over 3 weeks Rescue medication: paracetamol ≥ 3 g daily
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders PGIC (7-point scale) AEs Withdrawals Sleep QoL
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Pfizer sponsored No researchers mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported

A0081279 [NCT01701362] (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	BOCF for participants who discontinued due to AE or LoE
Size	Low risk	> 199 participants per treatment arm

A9011015 [NCT01117766]

Methods	Multi-centre, randomised, double-blind, cross-over study, with no obvious enrichment Duration: 2 × 4 weeks with 2-week washout between
Participants	Peripheral neuropathic pain with spontaneous ongoing pain and dynamic mechanical allodynia to brush stimuli ≥ 6 months, PI ≥ 4/10, stable analgesic medication (excluding pregabalin) > 1 month Excluded: no specific criteria provided N = 31 M 13, F 18 Mean age 55 years (range 30 to 86)
Interventions	Pregabalin 300 mg daily, n = 28 Placebo, n = 30 Medication given in divided dose, twice daily; titrated from 150 mg daily to 300 mg daily over first 2 weeks; dose reduced to 150 mg daily for renally impaired participants
Outcomes	PI (0 to 10) PGIC (7-point scale) AEs Withdrawals QST
Notes	Oxford Quality Score: R1, DB2, W1 = 3/5 Sponsor closed study after 31 participants randomised (40 planned) due to "operational difficulties of subject recruitment and retention" Pfizer sponsored No researchers mentioned

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported

A9011015 [NCT01117766] (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo" "as blister packed capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Size	High risk	< 50 participants per treatment arm

Arezzo 2008

Methods	Randomised, double-blind, parallel-group study, with no enriched enrolment Duration: 13 weeks (1-week dose titration, then 12-week fixed dose)
Participants	Painful diabetic neuropathy ≥ 3 months, PI ≥ 40/100, HbA1c ≤ 11%, stable (≥ 30 days) treatment Excluded: creatinine clearance ≤ 60 mL/min; conditions that could confound pain assessment; antidepressants (except stable SSRIs for anxiety and depression), antiepileptics, NSAIDs, other pain medication, or supplements without adequate washout N = 167 M 103, F 64, 73% white Mean age 58 years (SD 10)
Interventions	Pregabalin 600 mg daily, n = 82 Placebo daily, n = 85 Medication given as divided dose, twice daily Paracetamol ≤ 4 g daily and prophylactic low-dose aspirin allowed
Outcomes	≥ 50% decrease in mean pain score between endpoint and baseline PGIC AEs Withdrawals Sleep
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated random code"
Allocation concealment (selection bias)	Low risk	Remote administration

Arezzo 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"identical capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly stated
Size	Unclear risk	50 to 199 participants per treatment arm

Bansal 2009

Methods	Randomised, double-blind, active-control, cross-over study, with no obvious enrichment Duration: 2 × 5 weeks with 1-week run-in and 3-week washout between
Participants	Painful diabetic neuropathy ≥ 1 month, stable diabetic medication, PI ≥ 50/100 Excluded: clinically significant or unstable medical or psychiatric illness; renal (< 132 µmol/L) or liver disease; epilepsy; malignancy; uncontrolled hypertension; substance abuse; other causes of neuropathy; current use of antiepileptics, antidepressants, local anaesthetics, or opioids (previous exposure allowed) N = 51 M 19, F 25 (completers) Mean age 55 years (range 48 to 61) (completers) Duration of pain 3 to 24 months (mean 12)
Interventions	Pregabalin 150 to 600 mg daily, n = 48 Amitriptyline 10 to 50 mg daily, n = 47 Medication up-titrated after 1 and 3 weeks to achieve maximum effect and tolerability. Pregabalin given as divided dose, twice daily; amitriptyline given once daily at bedtime Rescue medication: paracetamol up to 3 g daily during run-in period and washout, except night before assessment
Outcomes	Patient VAS PGIC Participants reporting improvement Treatment preference AEs Withdrawals Depression Sleep
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Cipla Pharmaceuticals and Wockhardt Pharmaceuticals provided free samples of pregabalin and amitriptyline Study authors declared no conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Bansal 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	"using random number tables"
Allocation concealment (selection bias)	Low risk	"Drugs were packed, blinded and numbered serially"; "administered to patients serially according to the patients' reporting sequence"; "Blinding and randomisation were carried out by an independent person unrelated to the study"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matched placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not reported; probably LOCF
Size	High risk	< 50 participants per treatment arm

Baron 2010

Methods	Multi-centre, enriched enrolment, randomised, double-blind, placebo-controlled, withdrawal, parallel-group study Duration: 1-week placebo run-in (SB, to exclude placebo responders (≥ 50%)), 4-week flexible dose pregabalin (SB, to identify responders (≥ 30%)), 5-week randomised withdrawal (DB)
Participants	Chronic lumbosacral radiculopathy (due to spinal stenosis or disc herniation) ≥ 3 months, stable for ≥ 4 weeks, PI < 4/10, age ≥ 18 years Exclusion: lumbosacral radiculopathy > 4 years; surgery for condition ≤ 6 months or epidural injection ≤ 6 weeks; > 1 previous surgery for L5-S1 pain or radiculopathy; use of antiepileptics, nerve blocks, high-potency opioids, and opioid combinations N = 378 (placebo run-in), 364 (flexible dosing), 217 (withdrawal) M 181, F 183 (flexible dosing); M 104, F 113 (withdrawal) Mean age 53 years (SD 12)
Interventions	Randomised withdrawal Pregabalin 150 to 600 mg daily, n = 110 Placebo, n = 107 (SB dose tapered over 1 week) Medication given as divided dose, twice daily. Initial dose 150 mg daily, increased to balance efficacy and tolerability in flexible dosing phase, then maintained in withdrawal phase Stable non-prohibited medication allowed Rescue medication: paracetamol ≤ 4 g or paracetamol + codeine ≤ 4 g/≤ 60 mg daily, limited to once daily on ≤ 2 consecutive days, not during randomised withdrawal

Baron 2010 (*Continued*)

Outcomes	Participants with ≥ 30% PI reduction Time to loss of therapeutic response (≥ 1-point increase in PI, discontinuation, use of rescue medication) PGIC AEs Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 A0081007 Pfizer sponsored Study authors were Pfizer employed or declared various conflicts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A central Internet/telephone randomization system (IMPALA) was used to assign patient identification numbers, to assign all study medication, and to randomize patients to double-blind treatment"
Allocation concealment (selection bias)	Low risk	"A central Internet/telephone randomization system (IMPALA) was used to assign patient identification numbers, to assign all study medication, and to randomize patients to double-blind treatment"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo capsule"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation
Size	Unclear risk	50 to 199 participants per treatment arm

Cardenas 2013

Methods	Multi-centre, randomised, double-blind, parallel-group, partial enrichment study Duration: 4-week dose optimisation; 12-week dose maintenance; 1-week taper
Participants	Spinal cord injury (C2-T12, complete or incomplete), ≥ 12 months, below-level neuropathic pain continuously for ≥ 3 months or remitting/relapsing for ≥ 6 months, PI ≥ 4/10 Excluded: other condition that could confound assessment of spinal cord injury neuropathic pain; previous participation in trial of pregabalin; intolerance to pregabalin or gabapentin; retinal abnormalities N = 219

Cardenas 2013 (*Continued*)

	M 176, F 43 Mean age 46 years (SD 13) Mean baseline PI 6.5
Interventions	Pregabalin 150 mg to 600 mg daily, n = 112 Placebo, n = 107 Pregabalin started at 150 mg daily, increased to 300 mg (day 8), 450 mg (day 15), 600 mg (day 22) based on tolerability. Medication given as divided dose, twice daily NSAIDs and paracetamol allowed as rescue medication; antidepressants allowed if dose stable ≥ 30 days
Outcomes	PI (0 to 10) ≥ 30% reduction in PI PGIC AEs Withdrawals Mean change at endpoint Sleep Depression
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Study authors were Pfizer employed or declared various conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated"
Allocation concealment (selection bias)	Low risk	Remote allocation; "investigators used the sponsor's interactive response technology system to screen, randomize, and assign treatment to patients in a double-blind manner"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"; "Both placebo and pregabalin were in the form of gray capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified BOCF for mean pain score, LOCF for other analyses
Size	Unclear risk	50 to 199 participants per treatment arm

Dou 2017

Methods	Randomised, double-blind, placebo-controlled, cross-over study, with no obvious enrichment Duration: 2 × 2 weeks, with 1-week washout between (3-day taper)
Participants	Severe neuropathic cancer pain (cancer-related or cancer treatment-related), treated with morphine ≥ 3 months, PI ≥ 4/10 before analgesia, Karnofsky score ≥ 40/100, and QoL ≥ 30/60 Excluded: current oncological treatment; creatinine clearance < 60 mL/min or plasma creatinine > 1.5 mg/mL; non-opioid analgesics or other adjuvant drugs N = 40 M 24, F 16 Mean age 56 years (range 33 to 80) Mean PI before morphine treatment 7/10 (SD 1)
Interventions	All participants took stable dose morphine SR and IR, optimised and stable for 1 week before entering the study (PI < 4/10 and breakthrough pain < 3/d) Pregabalin 300 mg daily Placebo Pregabalin given as divided dose, twice daily, started at 150 mg daily, increased to 300 mg daily on day 4 Morphine optimised dose decreased by 30% on day 4, maintained if adequate pain control for 1 to 2 days (PI 0 to 3/10 and breakthrough < 3/d). If not controlled, returned to optimised dose and 1 further reduction attempted when pain under control again. Optimised dose given during washout
Outcomes	PI (0 to 10) Decrease in morphine dosage AEs Withdrawals Sleep
Notes	Oxford Quality Score: R2, DB2, W0 = 4/5 Grant from Department of Health of Guangxi Zhuang Autonomous Region Study authors declared no conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Similar looking corn starch capsules were used as the PL treatment, which were administered in the same schedule as the PGB

Dou 2017 (*Continued*)

		treatment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported, but no useable data provided
Size	High risk	< 50 participants per treatment arm

Dworkin 2003

Methods	Multi-centre, randomised (stratified), double-blind, parallel-group study, with partially enriched enrolment Duration: 9 weeks (1-week dose titration, 8-week fixed dose)
Participants	PHN, pain ≥ 3 months after healing of herpes zoster skin rash, PI ≥ 40/100, NRS ≥ 4/11 Excluded: history of neurolytic or neurosurgical therapy for PHN, creatinine clearance ≤ 30 mL/min, other severe pain that could affect assessment, previous participation in pregabalin trial, non-response to gabapentin N = 173 M 81, F 92, 95% white Mean age 71 years (SD 11)
Interventions	Pregabalin 600 mg daily (300 mg daily for reduced creatinine clearance), n = 89 Placebo daily, n = 84 Medication given as divided dose, 3 times daily
Outcomes	PI (11-point NRS) Participants with ≥ 30% and ≥ 50% reduction in PI from baseline to endpoint PGIC (7-point scale) AEs Withdrawals
Notes	Oxford Quality Score: R2, D2, W1 = 5/5 Pfizer sponsored One study author declared various conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Low risk	Protocol for concealment; "sequential randomization numbers"
Blinding (performance bias and detection bias) All outcomes	Low risk	"capsules were identical in appearance"

Dworkin 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation when large difference in AE and LoE withdrawals were evident between groups
Size	Unclear risk	50 to 199 participants per treatment arm

Freynhagen 2005

Methods	Multi-centre, randomised, double-blind, parallel-group study, with no enriched enrolment. Fixed and flexible dosing regimens Duration: 12 weeks
Participants	Chronic neuropathic pain (painful diabetic neuropathy, postherpetic neuralgia) ≥ 3 months, PI ≥ 40/100 Excluded: clinically significant or unstable medical or psychiatric condition; malignancy ≤ 2 years; abnormal ECG or haematology; creatinine clearance < 60 mL/min; history of drug or alcohol abuse ≤ 2 years N = 338 M 183, F 155, 98% white Mean age 62 years (SD 11)
Interventions	Flexible regimen of pregabalin 150, 300, 450, or 600 mg daily based on individual response, n = 141 Fixed 300 mg/d for 1 week followed by 600 mg daily (12 weeks in total), n = 132 Placebo, n = 65 Medication given as divided dose, twice daily Rescue medication: paracetamol
Outcomes	≥ 30% and ≥ 50% decrease in mean pain score PGIC AEs Withdrawals Sleep QoL
Notes	Oxford Quality Score: R1, D2, W1 = 4/5 Pfizer funded Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported

Freynhagen 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Size	Unclear risk	50 to 199 participants per treatment arm

Gilron 2011

Methods	Multi-centre, enriched enrolment, randomised, double-blind, placebo-controlled, withdrawal, parallel-group study Duration: 4-week flexible dosing (SB, to identify responders (≥ 30%)), 5-week randomised withdrawal (DB)
Participants	Peripheral neuropathic pain ≥ 6 months, PI ≥ 4/10, age ≥ 18 years Excluded: cervical or lumbosacral radiculopathy; chronic low back pain; carpel tunnel or other entrapment-related neuropathic pain; complex regional pain syndrome; fibromyalgia N = 256 (flexible dose), 157 (withdrawal) M 128, F 128 (flexible dose) Mean age 58 years (SD 10)
Interventions	Pregabalin 150 to 600 mg daily, n = 80 Placebo, n = 77 (SB dose tapered over 1 week) Medication given as divided dose, twice daily. Initial dose 150 mg daily, increased to balance efficacy and tolerability in flexible dosing phase, then maintained in withdrawal phase
Outcomes	≥ 30% PI reduction Participants with and time to loss of therapeutic response (≥ 1-point increase in PI, discontinuation, use of rescue medication) PI (0 to 10) PGIC AEs Withdrawals Sleep Anxiety and depression
Notes	Oxford Quality Score: R1, DB2, W1 = 4/5 Pfizer funded Several study authors were Pfizer employees
Risk of bias	

Gilron 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"sequential randomization numbers according to the randomization schedule that was computer generated"
Allocation concealment (selection bias)	Low risk	"telerandomization system sequentially generated a randomization number and a unique patient identifier to patients as they were determined to be eligible for study treatment"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF
Size	Unclear risk	50 to 199 participants per treatment arm

González-Duarte 2016

Methods	Enriched enrolment, randomised, double-blind, placebo-controlled, cross-over study Duration: 1-week placebo (SB, to identify and exclude placebo responders), 4-week titration and maintenance (SB, to identify responders (≥ 30%)), 2 × 4-week treatment (1-week up-titration, 2-week fixed dose, 1-week down-titration) with 1-week washout between (DB)
Participants	Pre-diabetes small-fibre neuropathy, impaired fasting glucose, or glucose intolerance Excluded: use of opioids N = 45 (SB), 26 (randomised DB) M 11, F 34 Mean age 54 years (range 33 to 85) Mean baseline PI 8.2 (SD 1)
Interventions	Pregabalin 600 mg daily Placebo Medication titrated to maximum 600 mg daily over 1 week, given as divided dose, twice daily Rescue medication: paracetamol (500-mg tablets - dose not specified)
Outcomes	PI (0 to 10) PGIC (7-point scale) AEs Withdrawals Sleep

González-Duarte 2016 (*Continued*)

Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Pfizer funded One study author declared various conflicts

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description of blinding maintenance in cross-over phase
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported during double-blind period
Size	High risk	< 50 participants per treatment arm

Guan 2011

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study, with no obvious enrichment Duration: 1-week single-blind run-in; 8 weeks treatment
Participants	PDN > 1 to 5 years, HbA1c ≤ 11% or PHN ≥ 3 months after rash, PI ≥ 40/100, age 18 to 75 years Chinese Excluded: neurological disorders unrelated to PDN or PHN; significant or unstable medical or psychiatric condition; abnormal ECG; creatinine clearance < 60 mL/min; abnormal haematology N = 309 (308 took medication); ~ 70% PDN M 143, F 165 Mean age 60 years (SD 10) Mean baseline PI 6.3 (SD 1.6)
Interventions	Pregabalin up to 600 mg daily, n = 206 Placebo, n = 102 Pregabalin given as divided dose, twice daily; started at 75 mg daily, increased by 150 mg daily at weekly increments to maximum tolerated dose if ≤ 30% improvement in pain score at weekly visit. Down-titration allowed for adverse events. Dose maintained after 4 weeks of adjustment

Guan 2011 (*Continued*)

Outcomes	PI (0 to 10 and 100-mm VAS) PGIC AEs Withdrawals Sleep
Notes	Oxford Quality Score: R1, DB2, W1 =4/5 Pfizer funded Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Matched placebo capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation
Size	Unclear risk	50 to 199 participants per treatment arm

Hewitt 2011

Methods	Enriched enrolment; single-blind titration; randomised, double-blind, placebo-controlled, withdrawal, parallel-group study Duration: titration up to 12 days, maintenance 9 days, withdrawal approximately 19 days
Participants	Painful diabetic neuropathy (HbA1c ≤ 11%), postherpetic neuralgia (≥ 3 months after healing of rash), small-fibre neuropathy, idiopathic sensory neuropathy PI ≥ 5 and < 10 at screening; age ≥ 18 years Excluded: other pain that was more severe than neuropathic pain, clinically significant unstable or serious medical or psychiatric condition, creatinine clearance < 30 mL/min N = 140 (entered titration), 104 (entered double-blind withdrawal) M 74, F 66 Mean age 59 years Baseline PI before titration 6.4/10, before randomised withdrawal 4.0/10

Hewitt 2011 (*Continued*)

Interventions	Pregabalin 150 mg daily increased to 600 mg or maximum tolerated dose over 12 days, then maintained for 9 days, n = 140 Pregabalin at maximum tolerated dose, n = 53 Placebo, n = 51 Medication given as divided dose, 3 times daily Rescue medication during titration period only: paracetamol ≤ 4000 mg daily or paracetamol + hydrocodone ≤ 1000/10 mg for ≤ 3 days
Outcomes	Primary responders, ≥ 30% decrease in PI from baseline Secondary responders, ≥ 10% to < 30% decrease in PI from baseline Non-responders, < 10% in PI from baseline Additionally, participants had to have ≥ 75% compliance Time to efficacy failure (first of 3 consecutive days when PI ≥ 4/10 and ≥ 30% increase in PI relative to randomisation at baseline) AEs Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Merck funded Several study authors were Merck employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind; method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for responder analysis; BOCF for loss of therapeutic response
Size	Unclear risk	50 to 199 participants per treatment arm

Holbech 2015

Methods	Multi-centre, randomised, double-blind (double-dummy), placebo-controlled, cross-over, study with partial enrichment (for tolerance) Duration: 1-week baseline, 4 × 5-week treatment periods with 1-week washouts between

Holbech 2015 (*Continued*)

Participants	Painful polyneuropathy (mixed etiologies), symptoms > 6 months, age 20 to 85 years, PI ≥ 4/10, pain ≥ 4 days/week. Primary cause (if applicable) stable ≥ 3 months (diabetes) or ≥ 6 months (other) Excluded: other significant causes of pain; previous allergic reaction or AEs to test drugs; cardiac contraindications; severe terminal illness; inability to stop current treatment with antidepressants, anticonvulsants, or opioids N = 69 M 41, F 28 Mean age 59 years (range 29 to 82) Mean baseline PI 6.4 (range 4 to 10)
Interventions	Pregabalin 300 mg daily Imipramine 75 mg daily Medication titrated to target dose over first week, then stable for 4 weeks; pregabalin given as divided dose, twice daily; imipramine given once daily Participants > 70 years given pregabalin 150 mg daily or imipramine 25 mg daily; poor metabolisers of CYP2C19 and CYP2D6 given imipramine 25 mg daily Participants with no effect after 2 weeks could switch to washout and next treatment Rescue medication: ≤ 6 × 500 mg paracetamol daily
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders PR (6-point VRS) QoL Depression AEs Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 = 4/5 Funded by Pfizer and Odense Hospital Several study authors declared various conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Matched placebos of identical appearance to the 2 trial drugs were dosed similarly using double-dummy technique"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF

Holbech 2015 (*Continued*)

Size	Unclear risk	50 to 199 participants per treatment arm

Huffman 2015

Methods	Multi-centre, randomised, double-blind, placebo-controlled, cross-over study, probably with partial enrichment (intolerance of pregabalin excluded) Duration: 2 × 6 weeks (2-week dose titration, 4-week fixed dose) with 2-week (with pregabalin taper) washout between
Participants	Painful diabetic neuropathy ≥ 3 months, pain exacerbated on walking, PI ≥ 4/10, HbA1c ≤ 11%, ≥ 18 years Excluded: inability to walk 50 feet on flat surface, need for walking aid, difficulty standing upright; pain on walking due to other conditions; highly variable pain during baseline period; intolerance to pregabalin; other medical condition that might interfere with assessments; creatinine clearance ≤ 60 mL/min N = 203 M 132, F 71 Mean age 59 years (SD 8.9)
Interventions	Pregabalin 150 mg to 300 mg daily, n = 198 Placebo, n = 186 Medication given in 3 divided doses, titrated over first 2 weeks, then maintained Rescue medication: paracetamol ≤ 3 g daily Current neuropathic pain medications washed out before study; antidiabetic medication stable ≥ 30 days before randomisation; prophylactic low-dose aspirin allowed; NSAIDs for other pain conditions allowed ≤ 2 weekly; stable doses of sleep medication and SSRIs allowed
Outcomes	PI (0 to 10) 30% and 50% responders PGIC (7-point scale) AEs Withdrawals Daytime activity Sleep QoL Walk questionnaire
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Funded by Pfizer Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated pseudo-random code"

Huffman 2015 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo capsules given in 3 divided doses"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation
Size	Unclear risk	50 to 199 participants per treatment arm

Huffman 2017

Methods	Multi-centre, enriched enrolment, randomised withdrawal study Duration: 6-week single-blind phase (4-week dose optimisation, 2-week fixed dose), 13-week double-blind withdrawal phase (for '50% responders')
Participants	PHN ≥ 3 months after healing of herpes zoster skin rash, PI ≥ 4/10, age ≥ 18 years Excluded: other condition that could affect assessments; creatinine clearance < 30 mL/min; previous non-response to pregabalin or related medication; creatinine clearance ≤ 30 mL/min; clinically significant and unstable condition; history of alcohol or substance dependence ≤ 1 year; planned neurolytic surgery N = 801 (entered SB phase), 413 (entered DB phase) M 157, F 256 (DB phase) Age: 48% ≥ 65 years; 40% 45 to 64 years (DB phase)
Interventions	In SB phase: Pregabalin CR 165 to 660 mg once daily, n = 801 In DB phase: Pregabalin 165 to 660 mg once daily, n = 208 Placebo, n = 205 Medication titrated according to efficacy and tolerability during SB phase, dose maintained during DB phase (tapered for those taking placebo); given as single daily dose after evening meal Participants with creatinine clearance > 30 to < 60 mL/min received 82.5 to 330 mg once daily Rescue medication: paracetamol ≤ 3 g daily Stable dose of analgesics, NSAIDs, antidepressants, sedatives allowed
Outcomes	LTR: ≥ 30% increase in 7-day rolling average PI during DB relative to same for baseline score (participants who withdrew for LoE or AEs count as LTR) Secondary LTR: ≥ 30% increase in 5-day rolling average relative to 5 day randomisation baseline score, or PI ≥ 4/10 (participants who withdrew for LoE or AEs count as LTR) Participants with ≥ 30% and ≥ 50% reduction in mean PI from SB baseline to DB endpoint PGIC (7-point scale) AEs

Huffman 2017 (*Continued*)

	Withdrawals Sleep QoL Anxiety and depression
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Most study authors were Pfizer employees

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed by an interactive voice response system and patients were randomly assigned to continue treatment with pregabalin CR or receive placebo"; judged by review authors to be adequate
Allocation concealment (selection bias)	Low risk	"Randomization was performed by an interactive voice response system and patients were randomly assigned to continue treatment with pregabalin CR or receive placebo"; judged by review authors to be adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	True responder for primary outcome of LTR; LOCF only for mean data
Size	Low risk	> 200 participants per treatment arm

Kim 2011

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study, with no obvious enrichment Duration: 2-week screening and washout, 4-week dose adjustment, 8-week maintenance, 1-week taper
Participants	Central post-stroke pain ≥ 3 months, PI ≥ 40/100, age ≥ 18 years Excluded: other potential causes of pain not readily discriminated from post-stroke pain; unstable medical, psychological, or psychiatric conditions; severe cognitive impairment N = 219 M 137, F 82

Kim 2011 (*Continued*)

	Mean age 58 years (range 34 to 85)
Interventions	Pregabalin 150 to 600 mg daily, n = 110 Placebo, n = 109 Medication given as divided dose, twice daily; 150 mg daily for 7 days, then 300 mg daily for 7 days, then further increased to maximum 600 mg daily over following 2 weeks, based on response and tolerance, then maintained for 8 weeks
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% reduction in pain PGIC AEs Withdrawals Sleep QoL
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated schedule with a randomized permuted block design"
Allocation concealment (selection bias)	Low risk	remote allocation "centralized telerandomization system (IMPALA)"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matched placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation (early termination; not considered failure in responder analysis)
Size	Unclear risk	50 to 199 participants per treatment arm

Lesser 2004

Methods	Randomised, double-blind, parallel-group study, with partially enriched enrolment Duration: 5 weeks (including titration when necessary)
Participants	Painful diabetic neuropathy for 1 to 5 years, PI ≥ 40/100, age ≥ 18 years Excluded: HbA1c > 11%; clinically significant or unstable hepatic, respiratory, haematological, cardiac, or peripheral vascular disease; creatinine clearance ≤ 60 mL/min; any condition that might confound pain assessment; previous failed response to gabapentin

Lesser 2004 (*Continued*)

	(≥ 1200 mg daily) N = 337 M 202, F 135, 95% white Mean age 60 years (SD 10)
Interventions	Pregabalin 75 mg daily, n = 77 Pregabalin 300 mg daily, n = 81 Pregabalin 600 mg daily, n = 82 Placebo daily, n = 97 Medication given as divided dose, 3 times daily. Pregabalin 75 mg and 300 mg started at full dose, pregabalin 600 mg titrated over first 6 days Rescue medication: paracetamol ≤ 3 g daily. Stable treatment with selective serotonin reuptake inhibitors allowed
Outcomes	≥ 50% decrease in mean pain score PGIC AEs Withdrawals Mood QoL
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random number table"
Allocation concealment (selection bias)	Low risk	Remote administration; "assigned the next sequential random number at the site"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo capsules"; double-dummy technique
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation not reported
Size	Unclear risk	50 to 199 participants per treatment arm

Liu 2017

Methods	Multi-centre, randomised (stratified), double-blind, parallel-group study, with no obvious enrichment Duration: 1-week placebo run-in, 1-week titration, 7-week fixed dose, 1-week taper
Participants	Postherpetic neuralgia, PI ≥ 40/100 Chinese Excluded: ≥ 30% decrease or high variability in PI during placebo run-in, other neurological disorder that might impact assessment of pain N = 220 M 119, F 101 Mean age 65 years (SD 9, range 26 to 84)
Interventions	Pregabalin 2 × 150 mg daily, n = 111 Placebo, n = 109 Medication given twice daily. Pregabalin started at 2 × 75 mg daily, increased after first week to target dose Stable use of SSRIs for depression or anxiety, NSAIDs or cyclo-oxygenase-2 inhibitors, and hypnotics for insomnia permitted without change Other pharmacological and non-pharmacological treatments for pain not permitted
Outcomes	PI (100-mm VAS and 6-point VRS) Participants with ≥ 30% reduction in PI from baseline to endpoint PGIC (7-point scale) AEs Withdrawals Sleep
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stated to be randomised; method of randomisation not reported; judged adequate due to method used to conceal allocation
Allocation concealment (selection bias)	Low risk	Independent, remote allocation; "interactive voice response system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matched placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation for missing data (early termination; not considered failure for responder analysis)

Liu 2017 (*Continued*)

Size	Unclear risk	50 to 199 participants per treatment arm

Mishra 2012

Methods	Randomised, double-blind, placebo- and active controlled, parallel-group study, with no obvious enrichment Duration: 4 weeks
Participants	Neuropathic cancer pain, age ≥ 18 years Excluded: unstable cardiovascular, respiratory, hepatic, or haematological disease or psychological disorder; history of drug abuse N = 120 M, F not reported Mean age not reported Baseline PI ≥ 7.5 (SD 2.2)
Interventions	Pregabalin 600 mg daily, n = 30 Gabapentin 1800 mg daily, n = 30 Amitriptyline 100 mg daily, n = 30 Placebo, n = 30 Doses increased over 3 weeks. Pregabalin started at 150 mg daily and given as divided dose, twice daily; gabapentin started at 900 mg daily and given as divided dose, 3 times daily; amitriptyline started at 50 mg daily and given as single dose at bedtime Rescue medication: immediate-release morphine
Outcomes	PI (100-mm VAS; mild, moderate, severe) Patient Global Satisfaction (5-point VRS) AEs Function
Notes	Oxford Quality Score: R2, DB2, W0 = 4/5 Grant from from Institute Research Grant of All India Institute of Medical Sciences Study authors declared no conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computerized random list"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"All drugs were placed in gelatin capsules prepared by the pharmacist", although use of dummy doses for different schedules was not specifically mentioned

Mishra 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Size	High risk	< 50 participants per treatment arm

Moon 2010

Methods	Multi-centre, randomised, double-blind, placebo-controlled study, with no obvious enrichment Duration: 10 weeks (1-week screening, 4-week dose titration, 4-week dose maintenance, 1-week taper)
Participants	Peripheral neuropathic pain (61% PHN, 7.5% PDN, 32% post-traumatic neuropathic pain), PI ≥ 4/10 on walking, HbA1c ≤ 11% for PDN, age ≥ 18 years Korean Excluded: unstable or significant medical condition; clinically significant orthostatic hypotension or diarrhoea; creatinine clearance < 30 mL/min; abnormal liver function (≥ 3 upper limit), ECG, haematology; anticipated need for surgery; history of drug abuse; treatment with drug known to affect retina or visual field N = 240 M 111, F129 Mean age 61 years (range 19 to 84)
Interventions	Pregabalin 150 to 600 mg daily, n = 162 Placebo, n = 78 Pregabalin started at 150 mg daily, increased to maximum tolerated dose (maximum for creatinine clearance 30 to 60 mL/min was 300 mg daily) Selected analgesics permitted for neuropathic pain, if dose stable
Outcomes	PI ≥ 30% and ≥ 50% responders PGIC (7-point scale) AEs Withdrawals Sleep QoL Depression and anxiety
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Study authors declared no conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed with the IMPALA system, a central web-telephone computerised telerandomization system"

Moon 2010 (*Continued*)

Allocation concealment (selection bias)	Low risk	Remote allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for discontinuations
Size	Unclear risk	50 to 199 participants per treatment arm

Mu 2018

Methods	Multi-centre, randomised, double-blind, parallel-group, partially enriched study Duration: 1-week single-blind placebo run-in, 1-week titration, 8-week fixed-dose maintenance, 1-week taper
Participants	Painful diabetic neuropathy 6 months to 2 years, PI ≥ 50/100, HbA1c ≤ 9%, stable diabetes medication Chinese Excluded: previous use of pregabalin and high (≥ 30%) placebo response rate, highly variable pain scores during screening (≥ 1 score < 3/10) N = 623 (620 treated) M/F not reported Age not reported
Interventions	Pregabalin 300 mg daily, n = 313 Placebo, n = 307 Medication given as divided dose, twice daily
Outcomes	PI ≥ 50% and ≥ 30% responder rates PGIC AE Withdrawals Sleep Anxiety and depression
Notes	Oxford Quality Score: R1, D2, W1 = 4/5 Pfizer sponsored Chinese language paper, with no mention of conflicts in the available translation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mu 2018 (*Continued*)

Random sequence generation (selection bias)	Low risk	"interactive voice response system"
Allocation concealment (selection bias)	Low risk	"interactive voice response system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF
Size	Low risk	> 199 participants per treatment arm

NCT00785577

Methods	Randomised, double-blind (double-dummy), placebo- and active-controlled study, with no obvious enrichment Duration: 6 weeks (including 1-week taper at the end)
Participants	Painful diabetic neuropathy > 6 months, PI ≥ 4/10 symmetrical onset in feet, stable glycaemic control, HbA1c ≤ 10%, age 18 to 70 years Excluded: other potential cause of neuropathy; condition that might interfere with assessment of diabetic neuropathic pain; history (< 1 year) of psychiatric or psychotic condition or alcohol or eating disorder; serious or unstable medical condition that might compromise participation; significant renal or hepatic abnormality; history of glaucoma, substance abuse or dependence, seizures, gastroparesis; judged at suicidal risk N = 273 (134 took pregabalin or placebo) M 80, F 54 Mean age 56 years (SD 9)
Interventions	Pregabalin 300 mg daily, n = 45 Placebo, n = 89 Experimental drug LY545694 (ionotropic glutamate receptor antagonist) also used at 3 doses Pregabalin titrated to 300 mg daily over 3 weeks; given as divided dose 3 times daily; taper in final week
Outcomes	PI (0 to 10) (not reported for pregabalin) ≥ 30% responders (not reported for pregabalin) Time to response PGIC (mean data only) AEs Withdrawals Sleep QoL Disability

NCT00785577 (*Continued*)

Notes	Oxford Quality Score: R1, DB2, W1 = 4/5 Eli Lilly sponsored No study authors mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy method described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Size	High risk	< 50 participants per treatment arm

Ogawa 2010

Methods	Randomised (stratified), double-blind, parallel-group study, with no obviously enriched enrolment Duration: 13 weeks
Participants	Painful diabetic neuropathy, pain ≥ 3 months after healing of herpes zoster skin rash, with average daily PI ≥ 40/100 Japanese Excluded: history of neurolytic or neurosurgical therapy for PHN, creatinine clearance ≤ 30 mL/min, other severe pain that could affect assessment N = 371 (safety), 369 (efficacy) Mean age 70 years (SD 10, range 24 to 92) 54% male
Interventions	Pregabalin 150 mg daily, n = 87 Pregabalin 300 mg daily, n = 89 Pregabalin 600 mg daily, n = 97 Placebo daily, n = 98 Medication given twice daily. Dose titration over first week; fixed dose for remaining 12 weeks
Outcomes	≥ 50% reduction in PI PGIC (7-point scale) AEs

Ogawa 2010 (*Continued*)

	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind; method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation when withdrawals due to AEs and LoE differ
Size	Unclear risk	50 to 199 participants per treatment arm

Raskin 2014

Methods	Multi-centre, double-blind, placebo-controlled, enriched enrolment, randomised withdrawal study Duration: 20 weeks: 6 weeks single-blind (3-week switch from current medication to pregabalin and optimised dose, 3-week stable), then 13-week double-blind withdrawal (for ≥ 30% responders, 1-week taper for placebo group)
Participants	Painful diabetic neuropathy > 3 months; currently receiving tramadol, gabapentin, venlafaxine, duloxetine, a tricyclic antidepressant, or combination of any 2 agents, with inadequate pain control (PI ≥ 4/10); HbA1c ≤ 11%; stable antidiabetic medication; age ≥ 18 years Excluded: previous failure with pregabalin; PI 10/10 at baseline; other pain that could affect assessment; malignancy ≤ 5 years; creatinine clearance ≤ 60 mL/min; psychiatric condition; unstable diabetes N = 665 (single-blind), 294 (entered double-blind) M 363, F 302 (single-blind); M 155, F 139 (double-blind) Age 58 (SD 10), range 20 to 84 (single-blind), 26 to 81 (double-blind)
Interventions	Pregabalin 150 to 300 mg daily, n = 147 Placebo, n = 147 Medication given as divided dose, 3 times daily Rescue medication: paracetamol ≤ 4 g daily

Raskin 2014 (*Continued*)

Outcomes	Loss of therapeutic response (< 15% relative to baseline: n and median time to) ≥ 30% and ≥ 50% responders at endpoint relative to single-blind baseline PGIC (7-point scale) SB and DB AEs Withdrawals Sleep Anxiety and depression QoL
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer funded Study authors declared several conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was undertaken according to a computer generated pseudo-random code"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for some outcomes
Size	Unclear risk	50 to 199 participants per treatment arm

Raskin 2016

Methods	Multi-centre, randomised, double-blind, placebo-controlled, cross-over study Duration: 2 × 6 weeks (2-week titration, 4-week fixed dose), with 2-week (single-blind) taper and washout between phases
Participants	Painful diabetic neuropathy, currently treated with 1 NSAID (regular dose, ≥ 4 days/week, stable) for a co-morbid, non-PDN condition, PI ≥ 4/10, ≥ 18 years, HbA1c ≤ 11% Excluded: criteria similar to Huffman 2015 N = 301 M 164, F 137 Mean age 59 years (SD 10, range 27 to 84)

Raskin 2016 (*Continued*)

Interventions	Pregabalin 150 to 300 mg daily Placebo Medication given as divided dose, 3 times daily, titrated to effect and tolerability
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders (compared with SB baseline) LTR PGIC (7-point scale) at end of period 1 AEs Withdrawals Sleep Anxiety and depression QoL
Notes	Oxford Quality Score: R1, DB2, W0 = 3/5 Pfizer funded Study authors declared several conflicts

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF
Size	Low risk	> 200 participants per treatment arm

Rauck 2013

Methods	Multi-centre, randomised, double-blind (double-dummy), placebo-controlled, parallel-group study Duration: 14 weeks (1-week titration, 12-week fixed-dose maintenance, 1-week taper)
Participants	Painful diabetic neuropathy > 6 months and ≤ 5 years, PI ≥ 4/10, stable glycaemic control, HbA1c ≤ 11% Exclusion: chronic pain that could not be differentiated from PDN; condition or medication that could interfere with assessment of neuropathic pain (including unstable depression, alcohol, substance abuse); liver, renal, cardiovascular disease, epilepsy or seizures,

Rauck 2013 (*Continued*)

	other condition that could interfere with accurate assessment; recent exposure or previous allergic reaction to study drugs or paracetamol N = 420 M 249, F 171 Mean age 59 years (SD 10, range 29 to 85)
Interventions	Pregabalin 300 mg daily, n = 66 Gabapentin encarbil 1200 mg daily, n = 66 Gabapentin encarbil 2400 mg daily, n = 62 Gabapentin encarbil 3600 mg daily, n = 116 Placebo, n = 120 Medication given in divided doses, 3 times daily Rescue medication: paracetamol (maximum 3 g/daily) except within 24 hours of any assessment
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders PGIC AEs Withdrawals Mood QoL
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 GSK funded Several study authors were GSK employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated schedule"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"; "identical in appearance" placebo tablets or capsules; double-dummy method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF for responder rates
Size	Unclear risk	50 to 199 participants per treatment arm

Richter 2005

Methods	Randomised, double-blind, parallel-group study, with no enriched enrolment Duration: 6 weeks (2-week titration, 4-week fixed dose)
Participants	Painful diabetic neuropathy for 1 to 5 years, PI ≥ 40/100, age ≥ 18 years Excluded: neurological disorder unrelated to diabetes; any condition that could confound study assessments; serious medical condition N = 246 M 149, F 97, 84% white Mean age 57 years (SD 10)
Interventions	Pregabalin 150 mg daily, n = 79 Pregabalin 600 mg daily, n = 82 Placebo daily, n = 85 Medication given as divided dose, 3 times daily Rescue medication paracetamol ≤ 3 g daily. Stable doses of SSRIs and prophylactic low-dose aspirin allowed
Outcomes	≥ 50% decrease in mean pain score PGIC AEs Withdrawals Sleep Mood QoL
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Patients with missing data for a given parameter at baseline or at the time point to be analyzed were automatically excluded from that analysis"
Size	Unclear risk	50 to 199 participants per treatment arm

Rosenstock 2004

Methods	Randomised, double-blind, parallel-group study, with partially enriched enrolment Duration: 8 weeks (no titration)
Participants	Painful diabetic neuropathy for 1 to 5 years, PI ≥ 40/100, HbA1c ≤ 11%, stable medication, age ≥ 18 years Excluded: serious or unstable medical or psychiatric disorders; conditions that could confound pain assessments; creatinine clearance ≤ 60 mL/min; haematological abnormalities; failure to respond to gabapentin (≥ 1200 mg daily) N = 146 M 82, F 64, 88% white Mean age 60 years (64% ≤ 64 years)
Interventions	Pregabalin 300 mg daily, n = 76 Placebo daily, n = 70 Medication given as divided dose, 3 times daily Rescue medication: paracetamol ≤ 4 g daily. Prophylactic low-dose aspirin and stable SSRIs allowed
Outcomes	≥ 50% decrease in mean pain score PGIC AEs Withdrawals Sleep Mood QoL
Notes	Oxford Quality Score: R2, DB1, W1 = 4/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomisation schedule"
Allocation concealment (selection bias)	Low risk	"Study medication was packaged and labeled with sequential randomization numbers according to a randomization schedule"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not reported

Rosenstock 2004 (*Continued*)

Size	Unclear risk	50 to 199 participants per treatment arm

Sabatowski 2004

Methods	Multi-centre, randomised, double-blind, parallel-group study, with partially enriched enrolment Duration: 8 weeks (1-week titration, 7-week fixed dose)
Participants	PHN ≥ 6 months after healing of herpes zoster skin rash, PI ≥ 40/100, age ≥ 18 years Excluded: clinically significant disease, failure to respond to gabapentin, neurolytic or neurosurgical therapy for PHN, creatinine clearance < 30 mL/min N = 238 Mean age 72 years (SD 10, range 32 to 96) 45% male, 99% white
Interventions	Pregabalin 150 mg daily, n = 81 Pregabalin 300 mg daily, n = 76 Placebo daily, n = 81 Dose titrated over 1 week, fixed dose for remaining 7 weeks Stable regimens of paracetamol (≤ 3 g daily); NSAIDs, opioids, antidepressants permitted. New analgesic therapies prohibited. Benzodiazepines and anticonvulsants discontinued ≥ 2 weeks before treatment
Outcomes	PI (0 to 10) Participants with ≥ 50% reduction in PI from baseline to endpoint PGIC AEs Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Parke-Davis (Pfizer) funded Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated code"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"capsules identical in size and appearance"

Sabatowski 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not mentioned
Size	Unclear risk	50 to 199 participants per treatment arm

Satoh 2011

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study, with no obvious enrichment Duration: 13 weeks (1-week titration, 12-week fixed dose)
Participants	Painful diabetic neuropathy, PI ≥ 40/100, age ≥ 18 years Japanese Excluded: malignant tumour within 2 years, creatinine clearance ≤ 30 mL/min, pain or skin conditions that might affect evaluation of pain N = 314 M 237, F 77 Mean age 62 years (SD 10, range 35 to 85)
Interventions	Pregabalin 300 mg daily, n = 134 Pregabalin 600 mg daily, n = 45 Placebo, n = 135 Medication started at 150 mg daily, given as divided dose twice daily, increased over first week to target dose, and maintained for 12 weeks, then tapered over 1 week (or participants continued to open-label extension). Participants with creatinine clearance < 60 mL/min and allocated pregabalin 600 mg daily received 300 mg daily
Outcomes	PI (0 to 10) ≥ 50% responders PGIC AEs Withdrawals QoL Sleep
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer funded Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"centrally organized using a validated web-based system"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described

Satoh 2011 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"matching placebo" (clinical trials record)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation
Size	High risk	< 50 participants per treatment arm

Siddall 2006

Methods	Randomised, double-blind, parallel-group study, with no enriched enrolment Duration: 12 weeks (up to 3-week dose titration and adjustment, then fixed)
Participants	Spinal cord injury (paraplegia or tetraplegia) at least 1 year previously, non-progressive for 6 months, with chronic pain ≥ 3 months, PI ≥ 40/100, age ≥ 18 years Excluded: severe pain of other origin that could confound assessments, creatinine clearance < 60 mL/min N = 137 M 114, F 23, 97% white Mean age 50 years (range 21 to 80)
Interventions	Pregabalin up to 600 mg daily, n = 70 Placebo, n = 67 Medication given as divided dose, twice daily Stable doses of NSAIDs, opioid and non-opioid analgesics, antiepileptics (other than gabapentin), and antidepressants allowed
Outcomes	Participants with ≥ 50% reduction in PI from baseline to endpoint PGIC AEs Withdrawals Sleep Anxiety and depression
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated"

Siddall 2006 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Study medication was packaged and labeled with sequential randomization numbers according to the randomization schedule"
Blinding (performance bias and detection bias) All outcomes	Low risk	"identical size, colour, taste, and smell"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation
Size	Unclear risk	50 to 199 participants per treatment arm

Simpson 2010

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study, with no obvious enrichment Duration: 14 weeks (2-week titration, 12-week maintenance)
Participants	HIV distal sensory polyneuropathy ≥ 3 months, PI moderate to severe, Karnofsky Performance ≥ 60, stable dose of any antiretroviral drug (≥ 3 months) and any other pain medication (≥ 1 month), any non-pharmacological therapy stable ≥ 30 days, age ≥ 18 years Excluded: use of antiepileptic or serotonin norepinephrine reuptake inhibitor drugs; significant pain unrelated to HIV neuropathy; abnormalities in major organ function N = 302 M 245, F 57 Mean age 48 years (SD 8)
Interventions	Pregabalin 150 to 300 mg daily, n = 151 Placebo, n = 151 Medication started at 75 mg daily, increased to maximum tolerated dose (maximum 600 mg daily) over 2 weeks, given as divided dose, twice daily
Outcomes	PI (0 to 10) > 30% and ≥ 50% responders PGIC AEs Withdrawals Sleep Anxiety and depression
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Simpson 2010 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated
Allocation concealment (selection bias)	Low risk	"central computerized telerandomization system, such that investigators remained blinded to treatment assignments during the study"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Study drug and placebo were identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation
Size	Unclear risk	50 to 199 participants per treatment arm

Smith 2014

Methods	Multi-centre, randomised, double-blind (double-dummy), placebo- and active-controlled, parallel-group study, with partial enrichment Duration: 15 weeks (3-week titration, 12-week maintenance)
Participants	Painful diabetic neuropathy ≥ 6 months, lower extremity pain on a nearly daily basis ≥ 3 months, PI ≥ 4/10, HbA1c < 11%, stable (≥ 3 months) diabetic treatment and willingness to discontinue all pain medication except paracetamol, age 18 to 75 years Excluded: poor response to 3 or more medications for neuropathic pain; use of capsaicin ≤ 6 months, systemic corticosteroids ≤ 3 months; use of tricyclic antidepressants or warfarin; history of neurolytic treatment; clinically important medical disorders N = 386 M 225, F 161 Mean age 58 years (range 27 to 75, 22.5% ≥ 65 years)
Interventions	Pregabalin 300 mg daily, n = 99 Carisbamate 800 mg daily, n = 94 Carisbamate 1200 mg daily, n = 98 Placebo, n = 95 Medication titrated to maximum tolerated dose over 3 weeks, given as divided dose, twice daily Rescue medication: paracetamol ≤ 1 g daily and not within 3 hours of daily assessments
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders PGIC AEs Withdrawals

Smith 2014 (*Continued*)

	Sleep QoL
Notes	Oxford Quality Score: R1, DB2, W1 = 4 IVRS/5 Janssen sponsored Several study authors were Janssen employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo tablets"; "matching placebo capsules"; double-dummy method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF
Size	Unclear risk	50 to 199 participants per treatment arm

Stacey 2008

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study, with no enriched enrolment Duration: 4 weeks
Participants	PHN ≥ 3 months after healing of herpes zoster skin rash, PI ≥ 40/100, age ≥ 18 years Excluded: history of neurolytic or neurosurgical therapy for PHN, other condition that could confound assessment of pain N = 269 Mean age 67 years 50% male, 96% white Mean baseline PI 6.5/10
Interventions	Pregabalin flexible dose (150 to 600 mg daily), n = 91 Fixed-dose pregabalin 300 mg, n = 88 Placebo, n = 90 Medication given twice daily. Dose titration over ≤ 2 weeks for flexible dose Stable concomitant pain therapy permitted (not gabapentin, oxycodone, non-pharmacological therapy using needles, local and topical anaesthetics, musculoskeletal relaxants)

Stacey 2008 (*Continued*)

Outcomes	Participants with ≥ 30% and ≥ 50% reduction in PI from baseline to endpoint PGIC (7-point scale) AEs Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 = 4/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF imputation for missing data (except for survival analyses)
Size	Unclear risk	50 to 199 participants per treatment arm

Tölle 2008

Methods	Randomised, double-blind, parallel-group study, perhaps with partially enriched enrolment Duration: 12 weeks (including 1-week titration for 300/600 mg, withdrawal of those not able to reach target dose)
Participants	Painful diabetic neuropathy ≥ 1 year, PI ≥ 40/100, HbA1c ≤ 11% Excluded: serious or unstable medical or psychiatric disorders; conditions that could confound pain assessments; creatinine clearance ≤ 30 mL/min; haematological abnormalities. Note that published paper says exclusion similar to Lesser, Richter, Rosenstock - 1 of which includes failure to respond to gabapentin ≥ 1200 mg daily as an exclusion criterion N = 395 M 219, F 176, 96% white Mean age 59 years (SD 11)
Interventions	Pregabalin 150 mg daily, n = 99 Pregabalin 300 mg daily, n = 99 Pregabalin 600 mg daily, n = 101

Tölle 2008 (*Continued*)

	Placebo daily, n = 96 Medication given as divided dose, twice daily. Participants with creatinine clearance > 30 but ≤ 60 mL/min and randomised to pregabalin 600 mg daily received maximum dosage of 300 mg daily Stable dose of SSRIs for anxiety or depression allowed. All other medications for relief of pain discontinued
Outcomes	Proportion of patients with ≥ 50% decrease in mean pain score between endpoint and baseline PGIC AEs Withdrawals QoL Sleep
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation method not reported, probably LOCF
Size	Unclear risk	50 to 199 participants per treatment arm

van Seventer 2006

Methods	Randomised (stratified), double-blind, parallel-group study, with no enriched enrolment Duration: 13 weeks (1-week titration, 12-week maintenance)
Participants	PHN ≥ 3 months after healing of herpes zoster skin rash, PI ≥ 40/100 at baseline, mean daily PI ≥ 4/10 during screening, age ≥ 18 years Excluded: malignancy ≤ 2 years; significant abnormal haematology; significant or unstable medical or psychological condition; history of chronic hepatitis B or C, hepatitis B or C ≤ 3 months, HIV infection; immunocompromise; alcohol or illicit drug abuse

	≤ 2 years; previous trial of pregabalin; creatinine clearance ≤ 30 mL/min; previous surgical therapy for PHN; use of prohibited medication; participant in a previous trial of pregabalin N = 368 Mean age 71 years (SD 11, range 18 to 92) M 168, F 200 Mean baseline PI 6.7/10
Interventions	Pregabalin 150 mg daily, n = 87 Pregablin 300 mg daily, n = 98 Pregablin 600 mg daily, n = 90 Placebo daily, n = 93 Medication given twice daily; 1-week titration for 300/600 mg (withdrawal of those not able to reach target dose); fixed dose for remaining 12 weeks Stable regimens of opioids, non-narcotic analgesics, anti-inflammatories, antidepressants permitted
Outcomes	PI (0 to 10) Participants with ≥ 30% and ≥ 50% reduction in PI from baseline to endpoint PGIC (7-point scale) AEs Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be double-blind; method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation for missing data not mentioned
Size	Unclear risk	50 to 199 participants per treatment arm

van Seventer 2010

Methods	Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study, with no obvious enrichment Duration: 8 weeks, with 2-week single-blind placebo run-in
Participants	Post-traumatic peripheral neuropathic pain ≥ 3 months, PI ≥ 4/10, age 18 to 80 years Excluded: painful diabetic neuropathy, postherpetic neuralgia, radiculopathy, trigeminal neuralgia, carpel tunnel syndrome, central neuropathic pain, CRPS I or II, creatinine clearance ≤ 60 mL/min, positive urine illicit drug screen, previous exposure to pregabalin N = 254 (safety), 252 (efficacy) M 125, F 129 Mean age 52 (SD 14)
Interventions	Pregabalin 150 to 600 mg daily, n = 127 Placebo, n = 127 Medication given twice daily. Starting dose 150 mg daily in week 1, increased to 300 mg daily in week 2, and to 600 mg daily in week 3 if required. One dose reduction permitted Stable (≥ 1 month) NSAIDs, opioid and non-opioid analgesics, antiepileptics, antidepressants allowed
Outcomes	PI (0 to 10) Participants with ≥ 30% and ≥ 50% reduction in PI from baseline to endpoint PGIC (7-point scale) AEs Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 Pfizer sponsored Several study authors were Pfizer employees

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"interactive Voice Recognition System used to randomise patients"
Allocation concealment (selection bias)	Low risk	Interactive Voice Recognition System - remote allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"capsules of identical size, colour, taste, and smell"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Imputation for missing data not mentioned
Size	Unclear risk	50 to 199 participants per treatment arm

Vinik 2014

Methods	Multi-centre, randomised, double-blind (double-dummy), placebo- and active-controlled, parallel-group study, with partially enriched enrolment Duration: 5 weeks
Participants	Painful diabetic neuropathy ≥ 6 months, PI ≥ 4/10, HbA1c ≤ 10% with stable medication, age ≥ 18 years Excluded: creatinine clearance < 60 mL/min; significant or unstable medical condition; other pain that could confound assessments; malignancy ≤ 2 years; hypersensitivity to or previous therapeutic failure with gabapentinoids; abuse of prescription medication, street drugs, or alcohol < 1 year N = 452 M 242, F 210 Mean age 60 years (SD 9)
Interventions	Pregabalin 300 mg daily, n = 56 Mirogabalin 5 mg (n = 57), 10 mg (n = 57), 15 mg (n = 57), 20 mg (n = 56), 30 mg (n = 57) daily Placebo, n = 112 Pregabalin started at 150 mg daily, increased to 300 mg daily after 1 week, given as divided dose, twice daily. Mirogabalin 30 mg started at 15 mg daily, increased after 1 week; given as single dose at bedtime for 5-mg and 10-mg doses, and as divided dose, twice daily, for 30-mg dose Stable doses of selective serotonin reuptake inhibitors allowed; all other pain medication discontinued
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders AEs Withdrawals Sleep Anxiety and depression QoL
Notes	Oxford Quality Score: R1, DB1, W1 = 3/5 Daiichi funded Several study authors were Daiichi employees

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"placebo capsule matching over-encapsulated pregabalin"

Vinik 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be BOCF for responder analysis
Size	Unclear risk	50 to 199 participants per treatment arm

Ziegler 2015

Methods	Multi-centre, randomised, double-blind, placebo- and active-controlled, parallel-group study Duration: 6 weeks
Participants	Painful diabetic neuropathy ≥ 6 months, ≥ 4/10, age 18 to 75 years Excluded: pain conditions that cannot be distinguished or might interfere with assessments; newly diagnosed significant medical conditions or mental disorders; significant abnormalities in laboratory tests N = 194 (179 for analyses: 1 centre excluded due to concerns about data quality) M 103, F 91 Mean age 59 years (SD 8.5)
Interventions	Pregabalin 300 mg daily, n = 70 ABT-639 200 mg daily, n = 62 Placebo, n = 62 Pregabalin started at 150 mg daily, increased to 300 mg daily after 1 week, given as divided dose, twice daily. ABT-639 given as divided dose, twice daily All current medication for neuropathic pain discontinued ABT-639 is a peripherally acting selective T-type calcium channel blocker
Outcomes	PI (0 to 10) ≥ 30% and ≥ 50% responders PGIC Rescue medication AEs Withdrawals QoL Sleep
Notes	Oxford Quality Score: R2, DB2, W1 = 5/5 AbbVie funded Several study authors were employees of AbbVie

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated IVRS/IWRS system"

Ziegler 2015 (*Continued*)

Allocation concealment (selection bias)	Low risk	"computer-generated IVRS/IWRS system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo capsules for ABT-639 were identical in appearance to the ABT-639 capsules. Pregabalin tablets were overencapsulated into capsules that were identical in appearance to ABT-639 capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data not imputed
Size	Unclear risk	50 to 199 participants per treatment arm

AE: adverse event; BOCF: baseline observation carried forward; CR: controlled-release; CRPS: chronic regional pain syndrome; DB: double-blind; ECG: echocardiogram; F: female; Hb: haemoglobin; HbA1c: glycosylated haemoglobin; IR: immediate-release; ITT: intention-to-treat; IVRS/IWRS: Interactive Voice Recognition System; LOCF: last observation carried forward; LoE: lack of efficacy; LTR: loss of therapeutic response; M: male; mBOCF: modified BOCF: n: number of participants per treatment arm; N: number of participants in study; NRS: numerical rating scale; NSAID: non-steroidal anti-inflammatory drug; PDN: painful diabetic neuropathy; PGB: pregabalin; PGIC: Patient Global Impression of Change; PHN: postherpetic neuralgia; PI: pain intensity; PR: pain relief; QoL: quality of life; QST: quantitative sensory testing; R: randomised; SB: single-blind; SD: standard deviation; SR: sustained-release; SSRI: selective serotonin reuptake inhibitor; VAS: visual analogue scale; VRS: verbal rating scale; W: withdrawal.

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

Study	Reason for exclusion
A0081128	Not clearly neuropathic pain
A0081187 [NCT00654940]	Fewer than 25 participants per treatment arm
A0081296	No treatment arm that allows evaluation of pregabalin
Boyle 2012	Insufficient baseline pain intensity
CTRI/2013/05/003646	Epalrestat is an aldose reductase inhibitor available only in Asia; no placebo comparator; no results
Mathieson 2017	Not clearly chronic pain
NCT00787462	Last updated September 2010; study recruitment suspended due to "restrictive inclusion criteria and a limited pool of suitable subjects with SFN"; no results posted
NCT00908375	Fewer than 25 participants per group

(*Continued*)

NCT01058642	Fewer than 25 participants per treatment arm; terminated with no reason given
NCT01089556	Data for pregabalin and duloxetine groups pooled
NCT01180608	Both treatment arms received pregabalin. Recruitment status unknown; last updated August 2010; no results posted Functional imaging study - unclear if any useable data for pain intensity were collected
NCT01928381	Participants underwent 'pain training' using experimental pain and were selected based on 'accuracy' of reporting
NCT02215252	Possible combination of placebo groups in reported results; 4 treatments in methods, but 3 treatment groups reported
NCT02372578	Terminated due to futility analysis; no results posted
Razazian 2014	Participants withdrawing due to adverse events were replaced - not true randomisation
Romano 2009	Quasi-randomised; states single-blind in one place and double-blind in another - no clear evidence of adequate blinding of investigators
Vranken 2008	Fewer than 25 participants per group

Characteristics of studies awaiting assessment *[ordered by study ID]*

IRCT201602112027N5

Methods	Single-centre, randomised, double-blind, parallel-group study Duration: 7 weeks
Participants	Peripheral neuropathy induced by taxane-containing chemotherapy regimens for breast cancer, ≥ grade 1 sensory pain ≥ 4/10, age ≥ 18 years Excluded: other conditions that cause neuropathies; alcohol abuse; CNS diseases; heart, hepatic, or renal failure; psychiatric disorders; other neurotoxic chemotherapy drugs; test drug taken within 15 days N = 82 All F
Interventions	Pregabalin 150 mg daily Duloxetine 60 mg daily Medication given at half target dose, once daily for first week, then at target dose as divided dose twice daily for 6 weeks (pregabalin could be given as 75 mg × 3 daily, so possible blinding issues) Stable doses of selected analgesics allowed
Outcomes	PI Sensory neuropathy QoL

IRCT201602112027N5 (*Continued*)

Notes	Recruitment complete; no results identified

NCT00838799

Methods	Randomised, double-blind, active- and placebo-controlled, parallel-group study Duration: 14 weeks
Participants	Painful diabetic neuropathy, "controlled blood glucose", age 18 to 75 years Excluded: past use of pregabalin, other significant medical conditions N = 458
Interventions	Pregabalin 3 × 100 mg daily RGH-896 3 × 15 mg daily RGH-896 3 × 30 mg daily RGH-896 3 × 45 mg daily Placebo RGH-896 (radiprodil) is a selective NMDA (N-methyl-D-aspartate) NR2B receptor antagonist. Development for neuropathic pain conditions has been discontinued due to lack of effect
Outcomes	50% reduction in pain
Notes	Study completed; record last updated July 2011; no results posted

NCT01314222

Methods	Randomised (stratified), double-blind, active- and placebo-controlled, cross-over study Duration: 10 weeks
Participants	Painful diabetic neuropathy ≥ 6 months, PI ≥ 4/10, age 18 to 85 years Excluded: previous lack of response to pregabalin or gabapentin, HbA1c > 9%, Hb ≤ 9 g/dL, significant renal impairment N = 178
Interventions	Pregabalin 3 × 100 mg daily Placebo Also compared 2 doses of experimental compound BMS-954561 vs placebo in separate cross-over arm
Outcomes	Not specified for pregabalin For BMS-954561: PI AEs AE withdrawals
Notes	Last updated December 2015 Estimated final data collection date for primary outcome measure March 2012; study completed; no results posted

NCT01479556

Methods	Randomised (stratified), double-blind, placebo-controlled, cross-over study
Participants	Neuropathic pain secondary to SCI, persistent from 1 to 6 months after injury, non-evoked at-level PI ≥ 2/10; age 18 to 70 years Excluded: previous use of gabapentin, impaired renal function, other neuropathic pain condition or significant medical condition Estimated N = 82
Interventions	Pregabalin 2 × 150 mg daily Placebo
Outcomes	PI Rescue medication AEs
Notes	Last updated November 2011; 'not yet recruiting' at that stage Estimated final data collection date for primary outcome measure May 2014 Study status unknown; no results posted Inclusion criteria: participants with PI ≤ 2/10, but PI of those actually recruited not known (if anyone)

NCT01504412

Methods	Randomised, double-blind (double-dummy), active- and placebo-controlled, parallel-group study Duration: 7 weeks
Participants	Painful diabetic neuropathy, PI ≥ 4/10, age ≥ 20 years Japanese Excluded: HbA1c ≥ 9.0
Interventions	Pregabalin 2 × 150 mg daily DS-5565 10 mg daily, 15 mg daily, 20 mg daily, 30 mg daily Placebo N = 450
Outcomes	PI
Notes	Last updated December 2013; study completed Estimated final data collection date for primary outcome measure June 2013; no results posted

NCT01688947

Methods	Randomised, double-blind, active- and placebo-controlled, parallel-group study Duration: 4 weeks
Participants	Postherpetic neuralgia ≥ 3 months after healing of rash; ≥ moderate PI, with pain every day; age 21 to 90 years Excluded: other predominant chronic pain condition, taking opioids > 4 days/week or unwilling to stop current medication, Hx seizure or other unstable medical condition N = 105

NCT01688947 (*Continued*)

Interventions	Pregabalin 2 × 1 to 2 capsules daily V116517 2 × 30 mg daily V116517 2 × 50 mg daily Placebo V116517 is a TRPV1 agonist
Outcomes	PI PGIC Rescue medication
Notes	Last updated May 2014; study completed Estimated final data collection date for primary outcome measure March 2014; no results posted

NCT01939366

Methods	Randomised, double-blind, placebo-controlled, parallel-group study Duration: 6 weeks
Participants	Painful diabetic neuropathy ≥ 3 months, PI ≥ 5/10, dissatisfied with current medication, HbA1c ≤ 11%, age 18 to 80 years Excluded: significant other condition that might interfere with study, impaired renal or hepatic function N = 699
Interventions	Pregabalin 2 × 300 mg daily Cebranopadol 100 µg daily, 300 µg daily, 600 µg daily Placebo Pregabalin titrated over 2 weeks; cebranopadol titrated over 4 to 7 days Cebranopadol is a dual opioid and a nociceptin/orphanin FQ receptor agonist analgesic that was not commercially available
Outcomes	PI
Notes	Last updated February 2015; study completed Estimated final data collection date for primary outcome measure January 2015; no results posted

NCT02927951

Methods	Randomised, double-blind, placebo-controlled, cross-over study Duration: 2 × 6 weeks with 2-week washout between
Participants	Painful diabetic neuropathy, type 2 diabetes, age 40 to 75 years Excluded: type 1 diabetes, diabetic nephropathy, various characteristics that could compromise walking and balance N = 44
Interventions	Pregabalin 2 × 150 mg daily Placebo

NCT02927951 (*Continued*)

Outcomes	PI (0 to 10) PGIC AEs Risk of fall
Notes	Possibly a subgroup of Vinik 2014 Last updated October 2016; results submitted to ClinicalTrials.gov but not yet posted (February 2018)

AE: adverse event; CNS: central nervous system; F: female; Hb: haemoglobin; HbA1c: glycosylated haemoglobin; N: number of participants in study; NMDA: N-methyl-D-aspartate; PGIC: Patient Global Impression of Change; PI: pain intensity; QoL: quality of life; SCI: spinal cord injury.

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

NCT01869569

Trial name or title	Effect of pregabalin in patients with radiation-induced peripheral neuropathic pain: a randomized double-blind placebo-controlled trial
Methods	Randomised (factorial assignment), double-blind, placebo-controlled, parallel-group study Duration: 12 weeks (4-week titration, 8-week maintenance)
Participants	Nasopharyngeal carcinoma and radiation-induced peripheral neuropathic pain ≥ 4 weeks, PI ≥ 4/10, age 18 to 65 years Chinese Estimated N = 60
Interventions	Pregabalin 2 × 300 mg daily Placebo Pregabalin started at 2 × 75 mg daily, titrated during first 4 weeks, stable for remaining 8 weeks
Outcomes	PI
Starting date	February 2013
Contact information	Yamei Tang, MD, PhD Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University
Notes	Last update July 2017; recruiting participants Estimated final data collection date for primary outcome measure August 2017

NCT02394951

Trial name or title	Investigation of somatosensory predictors of response to pregabalin in painful chemotherapy-induced peripheral neuropathy (CIPN)
Methods	Randomised, double-blind, placebo-controlled, cross-over study Duration 2 × 4 weeks (washout not reported)
Participants	Chemotherapy-induced peripheral neuropathy, symmetrical, > 2 months appearing ≥ 12 weeks after chemotherapy, PI ≥ 3/10, age ≥ 18 years, N = 35
Interventions	Pregabalin titrated to maximum 600 mg daily Placebo
Outcomes	PI AEs Neuropathic symptoms
Starting date	April 2015
Contact information	Simon Haroutounian, PhD Washington University School of Medicine
Notes	Last update November 2017; recruiting participants Estimated final data collection date for primary outcome measure December 2018

NCT02417935

Trial name or title	A Japanese post-marketing, randomized, double-blind, parallel-group, flexible dose comparative study to assess the non-inferiority of duloxetine compared with pregabalin in patients with diabetic peripheral neuropathic pain
Methods	Randomised, double-blind, placebo-controlled, parallel-group study Duration: 12 weeks
Participants	PDN, PI ≥ 4/10, HbA1c ≤ 9.4%, age 20 to 79 years Japanese N = 100 (originally estimated at 410)
Interventions	Pregabalin to maximum 2 × 600 mg daily by 8 weeks Duloxetine to maximum 1 × 60 mg daily by week 4 or 8 Starting dose of pregabalin 2 × 150 mg daily; duloxetine 1 × 20 mg daily
Outcomes	PI (0 to 10) 30% and 50% responders PGIC AEs
Starting date	April 2015

NCT02417935 (*Continued*)

Contact information	Eli Lilly and Company, USA (1-877-285-4559)
Notes	Last update June 2017; recruitment completed Estimated final data collection date for primary outcome measure May 2017

NCT02607254

Trial name or title	Efficacy and safety of pregabalin in treatment of neuropathic pain in patients with idiopathic small-fibre neuropathy
Methods	Responders (≥ 1 point improvement) to participant-blinded pregabalin entered randomised, placebo-controlled, withdrawal phase Duration: screening and washout, 8-week single-blind phase, 4-week randomised withdrawal phase
Participants	Idiopathic small-fibre neuropathy, ≥ 3 months, PI > 3 < 8, increase in PI during washout, age > 18 years Estimated N = 20
Interventions	Pregabalin Placebo No indication of dose or titration
Outcomes	Loss of therapeutic response
Starting date	September 2015
Contact information	Mohammad Khoshnoodi, MD Johns Hopkins University
Notes	Last update March 2017; recruiting participants Estimated final data collection date for primary outcome measure October 2017 Unclear if randomised withdrawal phase is double-blind

NCT02868801

Trial name or title	Efficacy and safety of pregabalin sustained release tablet for postherpetic neuralgia - a multicenter, randomized, double-blind, placebo-controlled trial
Methods	Randomised, double-blind, placebo-controlled, parallel-group study Duration: 14 weeks + 1-week taper
Participants	PHN, > 3 months after healing of rash, PI ≥ 40/100, age ≥ 18 years Chinese Estimated N = 280
Interventions	Pregabalin SR 1 × 165 mg daily Pregabalin SR 1 × 330 mg daily Pregabalin SR 1 × 660 mg daily

NCT02868801 (*Continued*)

	Placebo
Outcomes	30% and 50% responders
Starting date	March 2015
Contact information	Lu Qianjin, MD Central South University Jiangsu HengRui Medicine Co. Ltd.
Notes	Last update August 2016; recruiting participants Estimated final data collection date for primary outcome measure June 2017

NCT03276689

Trial name or title	'Fix the Dysfunction' concept for mechanism-based pharmacological treatment of neuropathic pain by drug
Methods	Randomised, quadruple-blind, placebo-controlled, parallel-group study Duration: 8 weeks
Participants	PDN, age ≥ 18 years, no other significant chronic pain conditions
Interventions	Pregabalin 2 × 150 mg daily (2 × 75 mg daily for first 7 days) Duloxetine 2 × 60 mg daily (2 × 30 mg daily for first 7 days) Placebo
Outcomes	PI
Starting date	Not yet recruiting (May 2018)
Contact information	David Yarnitsky, MD (d_yarnitsky@rambam.health.gov.il)
Notes	

AE: adverse event; CIPN: chemotherapy-induced peripheral neuropathy; HbA1c: glycosylated haemoglobin; N: number of participants in study; PDN: peripheral diabetic neuropathy; PGIC: Patient Global Impression of Change; PHN: postherpetic neuralgia; PI: pain intensity; SR: sustained release.

DATA AND ANALYSES

Comparison 1. Pregabalin 150 mg daily versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 30% pain intensity reduction	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Postherpetic neuralgia	1	180	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [1.35, 3.81]
2 At least 50% pain intensity reduction	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Postherpetic neuralgia	4	699	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.41, 2.74]
2.2 Painful diabetic neuropathy	2	359	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.80, 1.63]
3 PGIC much or very much improved	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Postherpetic neuralgia	2	342	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.16, 2.77]
3.2 Painful diabetic neuropathy	1	195	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.96, 1.95]
4 Withdrawal - lack of efficacy	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Postherpetic neuralgia	4	699	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.97]
4.2 Painful diabetic neuropathy	2	359	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.53]
5 Withdrawal - adverse event	6	1058	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.72, 1.83]
5.1 Postherpetic neuralgia	4	699	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.70, 2.01]
5.2 Painful diabetic neuropathy	2	359	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.36, 2.86]
6 Withdrawal - all cause	6	1058	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 0.98]
6.1 Postherpetic neuralgia	4	699	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.05]
6.2 Painful diabetic neuropathy	2	359	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.42, 1.18]
7 Somnolence	5	886	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.38, 3.57]
7.1 Postherpetic neuralgia	3	527	Risk Ratio (M-H, Fixed, 95% CI)	2.20 [1.31, 3.70]
7.2 Painful diabetic neuropathy	2	359	Risk Ratio (M-H, Fixed, 95% CI)	2.32 [0.72, 7.47]
8 Dizziness	5	886	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.97, 2.27]
8.1 Postherpetic neuralgia	3	527	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.80, 2.05]
8.2 Painful diabetic neuropathy	2	359	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [0.93, 8.69]

Comparison 2. Pregabalin 300 mg daily versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 30% pain intensity reduction	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Postherpetic neuralgia	3	589	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [1.63, 2.57]
1.2 Painful diabetic neuropathy	8	2320	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.01, 1.21]
1.3 Polyneuropathy	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.78, 3.29]
2 At least 50% pain intensity reduction	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Postherpetic neuralgia	4	713	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [1.86, 3.42]
2.2 Painful diabetic neuropathy	11	2931	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.15, 1.46]
2.3 Polyneuropathy	1	146	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.63, 6.35]
3 PGIC much or very much improved	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Postherpetic neuralgia	3	568	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.54, 2.94]
3.2 Painful diabetic neuropathy	5	1050	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.51, 2.03]
4 Very much improved	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Painful diabetic neuropathy	2	501	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.91, 3.39]
5 Withdrawal - lack of efficacy	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Postherpetic neuralgia	5	933	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.22, 0.65]
5.2 Painful diabetic neuropathy	10	2430	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.39, 1.09]
5.3 Mixed neuropathic pain	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Polyneuropathy	1	123	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.07, 15.89]
6 Withdrawal - adverse event	18	4317	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.49, 2.33]
6.1 Postherpetic neuralgia	5	933	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [1.75, 4.22]
6.2 Painful diabetic neuropathy	13	3384	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.24, 2.09]
7 Withdrawal - all cause	17	3756	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.19]
7.1 Postherpetic neuralgia	5	933	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.28]
7.2 Painful diabetic neuropathy	12	2823	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.24]
8 Somnolence	17	4248	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [2.62, 4.26]
8.1 Postherpetic neuralgia	5	933	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [1.93, 4.53]
8.2 Painful diabetic neuropathy	12	3315	Risk Ratio (M-H, Fixed, 95% CI)	3.54 [2.63, 4.76]
9 Dizziness	17	4248	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [2.86, 4.35]
9.1 Postherpetic neuralgia	5	933	Risk Ratio (M-H, Fixed, 95% CI)	3.61 [2.57, 5.05]
9.2 Painful diabetic neuropathy	12	3315	Risk Ratio (M-H, Fixed, 95% CI)	3.48 [2.67, 4.55]

Comparison 3. Pregabalin 600 mg daily versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 30% pain intensity reduction	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Postherpetic neuralgia	3	537	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [2.01, 3.18]
1.2 Painful diabetic neuropathy	3	789	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.16, 1.51]
1.3 Mixed neuropathic pain	4	1367	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.08, 1.43]
1.4 Central neuropathic pain	3	562	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.28, 2.03]
1.5 HIV neuropathy	2	664	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
2 At least 50% pain intensity reduction	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Postherpetic neuralgia	4	732	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [2.04, 3.48]
2.2 Painful diabetic neuropathy	7	1360	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.37, 1.88]
2.3 Mixed neuropathic pain	4	1367	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.23, 1.85]
2.4 Central neuropathic pain	3	562	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.19, 2.34]
2.5 HIV neuropathy	2	674	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.06]
3 PGIC much or very much improved	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Postherpetic neuralgia	1	183	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [1.33, 3.89]
3.2 Painful diabetic neuropathy	3	537	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.50, 2.21]
3.3 Mixed neuropathic pain	3	1129	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.18, 1.59]
3.4 Central neuropathic pain	1	210	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.73]
3.5 HIV neuropathy	2	674	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.88, 1.17]
4 PGIC very much improved	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Mixed neuropathic pain	2	791	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.95, 1.90]
4.2 Central neuropathic pain	1	210	Risk Ratio (M-H, Fixed, 95% CI)	3.5 [0.74, 16.46]
4.3 HIV neuropathy	2	674	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.69, 1.22]
5 Withdrawal - lack of efficacy	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Postherpetic neuralgia	4	732	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.53]
5.2 Painful diabetic neuropathy	5	879	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.28, 0.93]
5.3 Mixed neuropathic pain	4	1371	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.24, 0.57]
5.4 Central neuropathic pain	3	575	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.12, 0.61]
5.5 HIV neuropathy	2	677	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.05, 2.13]
6 Withdrawal - adverse event	21	5024	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.78, 2.68]
6.1 Postherpetic neuralgia	4	732	Risk Ratio (M-H, Fixed, 95% CI)	3.71 [2.28, 6.03]
6.2 Painful diabetic neuropathy	8	1669	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [1.92, 3.65]
6.3 Mixed neuropathic pain	4	1371	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.64, 1.73]
6.4 Central neuropathic pain	3	575	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.87, 2.47]
6.5 HIV neuropathy	2	677	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.87, 6.77]
7 Withdrawal - all cause	20	4649	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.09]
7.1 Postherpetic neuralgia	4	732	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.01, 1.71]
7.2 Painful diabetic neuropathy	8	1669	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]

7.3 Mixed neuropathic pain	4	1371	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.67, 0.99]
7.4 Central neuropathic pain	3	575	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.15]
7.5 HIV neuropathy	1	302	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.70, 1.73]
8 Somnolence	20	4856	Risk Ratio (M-H, Fixed, 95% CI)	3.68 [3.02, 4.47]
8.1 Postherpetic neuralgia	4	732	Risk Ratio (M-H, Fixed, 95% CI)	4.36 [2.79, 6.82]
8.2 Painful diabetic neuropathy	7	1501	Risk Ratio (M-H, Fixed, 95% CI)	4.29 [2.94, 6.26]
8.3 Mixed neuropathic pain	4	1371	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [1.95, 5.07]
8.4 Central neuropathic pain	3	575	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [2.30, 5.23]
8.5 HIV neuropathy	2	677	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [1.69, 4.83]
9 Dizziness	21	5240	Risk Ratio (M-H, Fixed, 95% CI)	3.95 [3.34, 4.68]
9.1 Postherpetic neuralgia	4	732	Risk Ratio (M-H, Fixed, 95% CI)	3.98 [2.78, 5.70]
9.2 Painful diabetic neuropathy	8	1885	Risk Ratio (M-H, Fixed, 95% CI)	5.60 [4.06, 7.72]
9.3 Mixed neuropathic pain	4	1371	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [2.64, 5.39]
9.4 Central neuropathic pain	3	575	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [2.16, 5.50]
9.5 HIV neuropathy	2	677	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.36, 3.29]

Comparison 4. Participants with at least one adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least one adverse event	26		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pregabalin 600 mg	15	3963	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.24, 1.37]
1.2 Pregabalin 300 mg	15	3697	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.15, 1.28]
1.3 Pregabalin 150 mg	1	185	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.97, 1.43]

Comparison 5. Participants with at least one serious adverse event

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least one serious adverse event	27		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pregabalin 150 mg	3	542	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.45, 2.38]
1.2 Pregabalin 300 mg	17	4112	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.83, 1.70]
1.3 Pregabalin 600 mg	16	3995	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.77, 1.48]

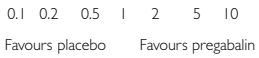
Analysis 1.1. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 1 At least 30% pain intensity reduction.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 1 At least 30% pain intensity reduction

Study or subgroup	Pregabalin 150 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
van Seventer 2006	34/87	16/93		100.0 %	2.27 [1.35, 3.81]
Subtotal (95% CI)	**87**	**93**		**100.0 %**	**2.27 [1.35, 3.81]**
Total events: 34 (Pregabalin 150 mg), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.11 (P = 0.0019)					

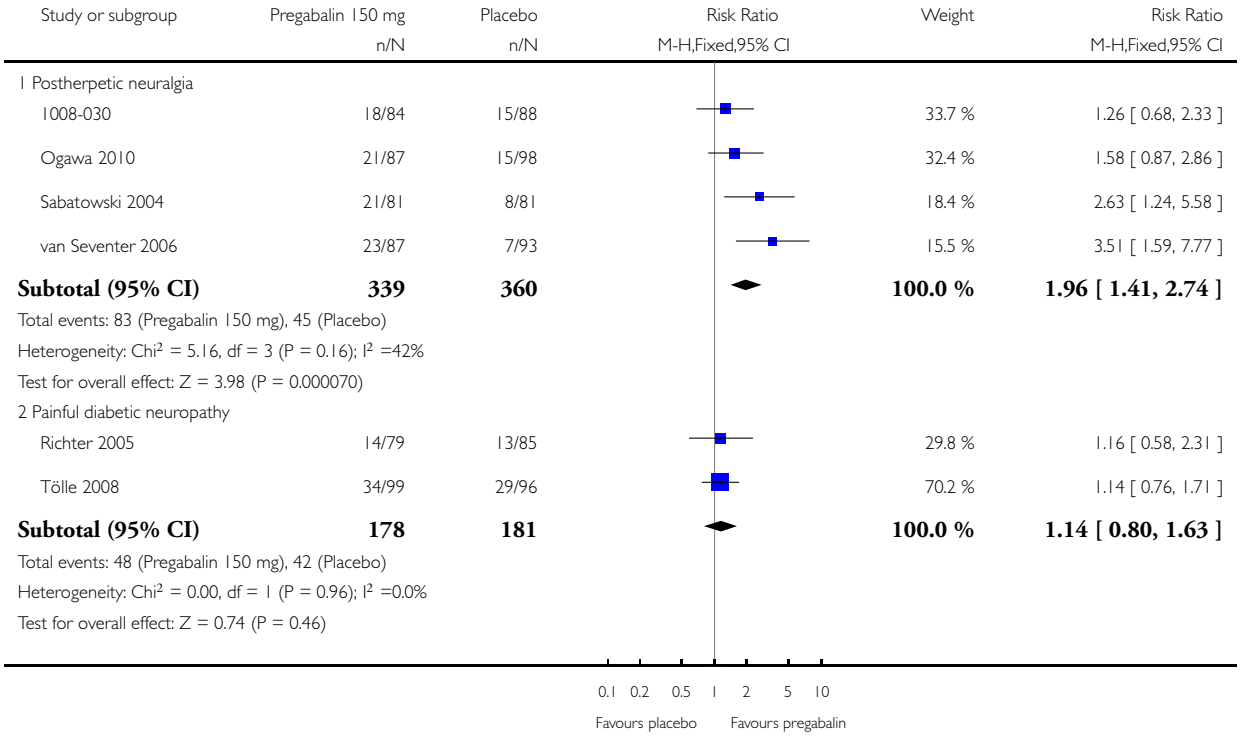


Analysis 1.2. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 2 At least 50% pain intensity reduction.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 2 At least 50% pain intensity reduction

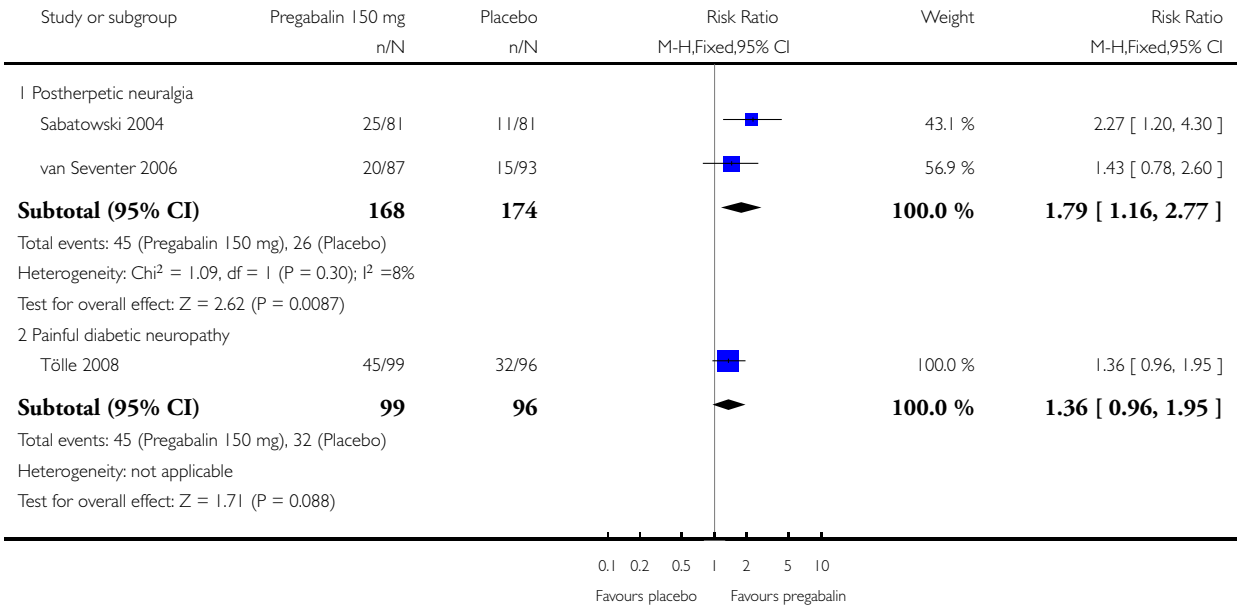


Analysis 1.3. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 3 PGIC much or very much improved.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 3 PGIC much or very much improved

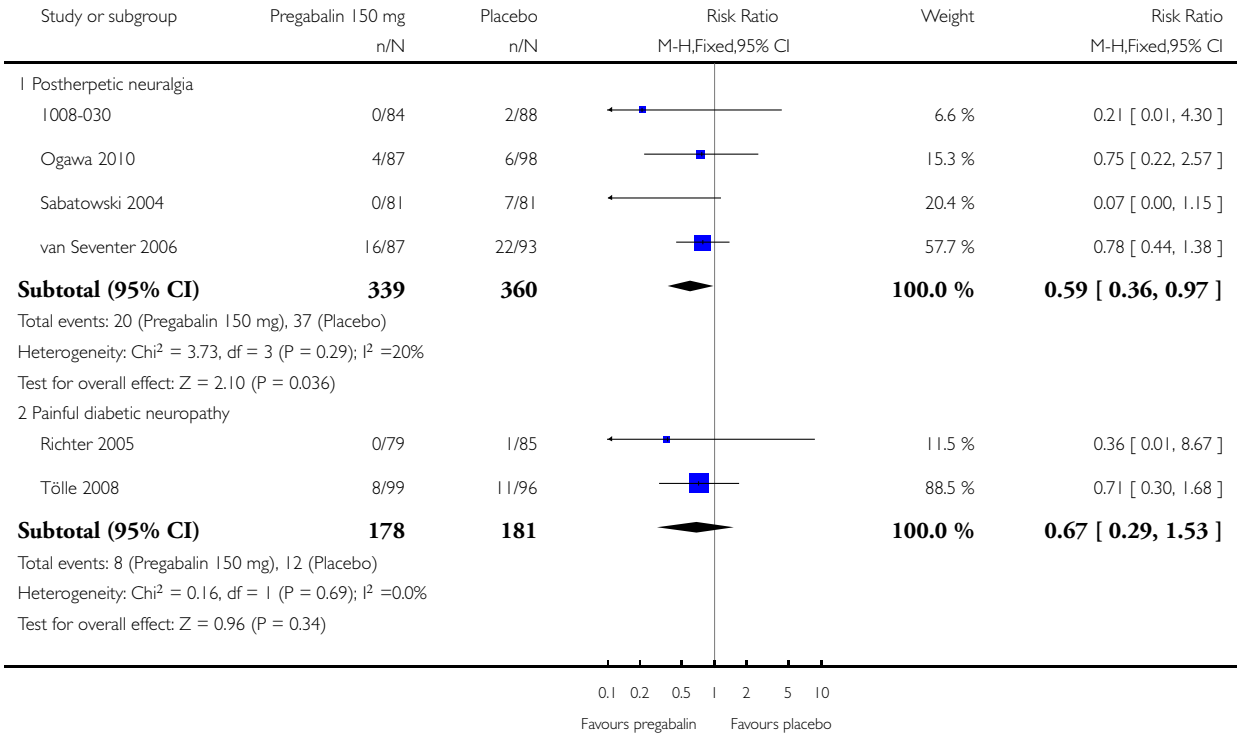


Analysis 1.4. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 4 Withdrawal - lack of efficacy.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 4 Withdrawal - lack of efficacy

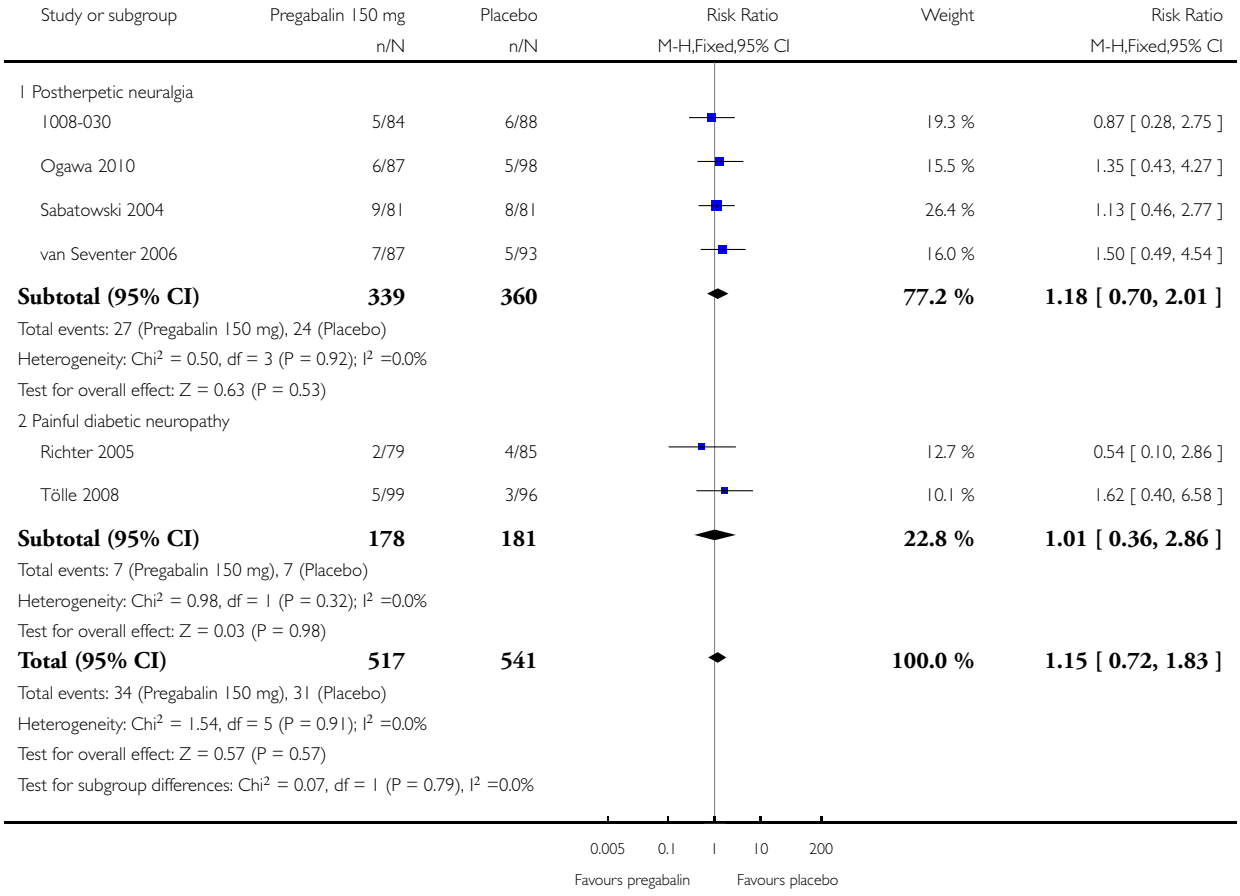


Analysis 1.5. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 5 Withdrawal - adverse event.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 5 Withdrawal - adverse event

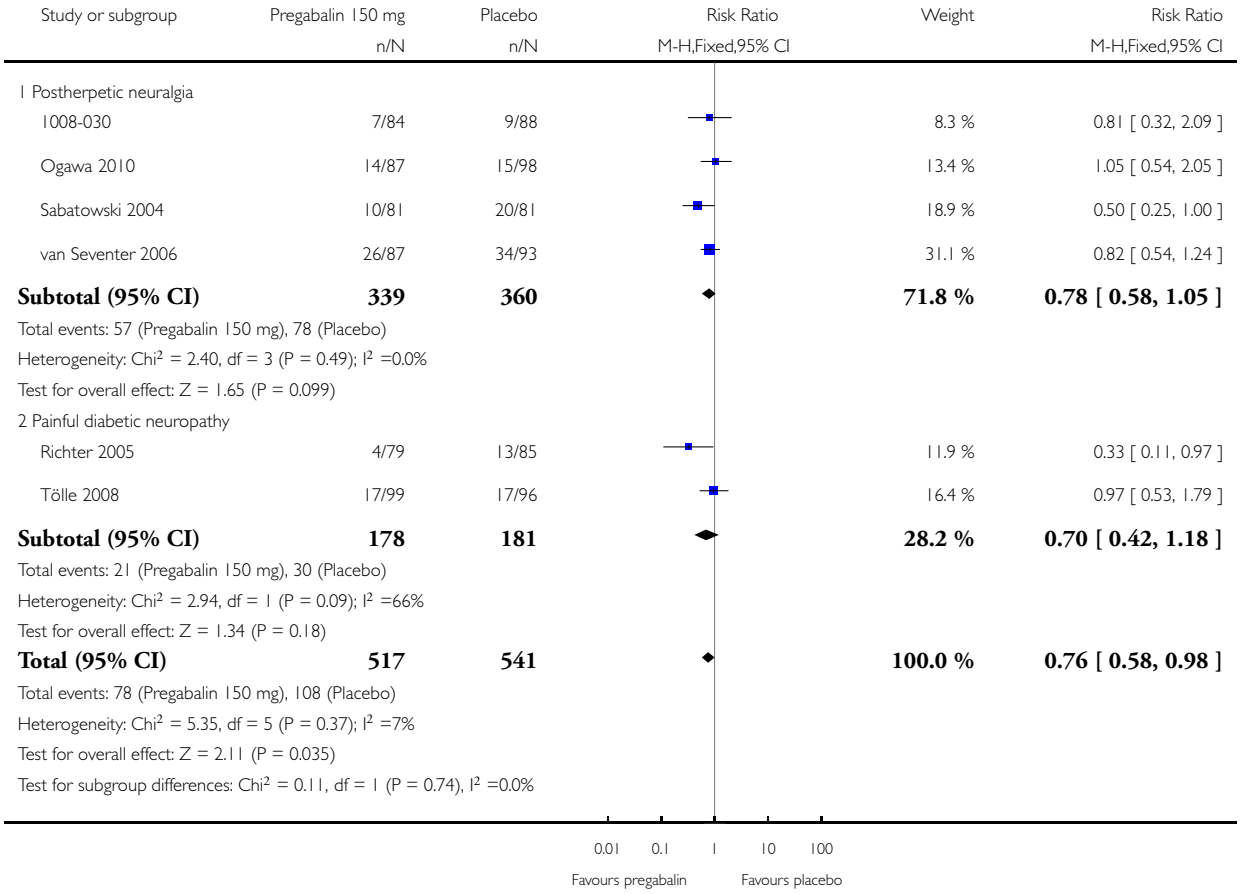


Analysis 1.6. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 6 Withdrawal - all cause.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 6 Withdrawal - all cause

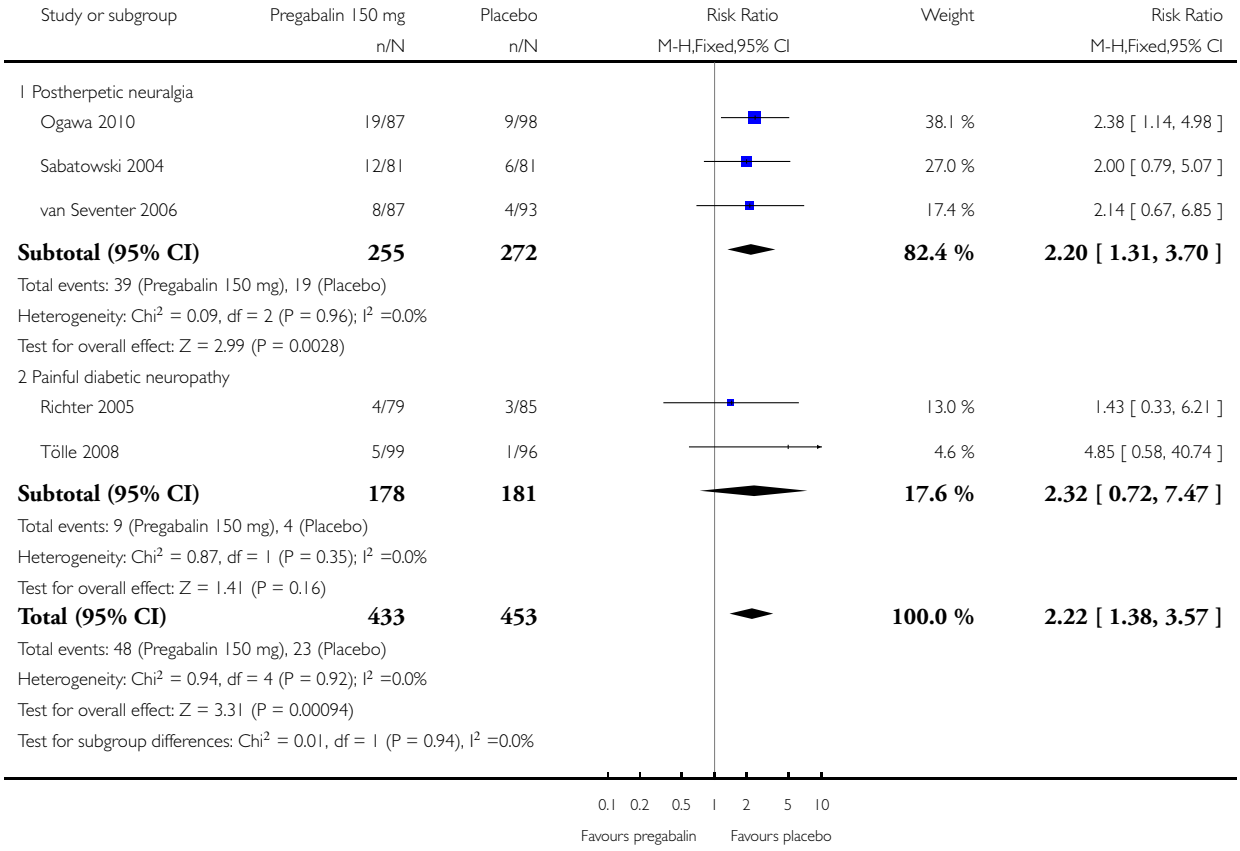


Analysis 1.7. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 7 Somnolence.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 7 Somnolence

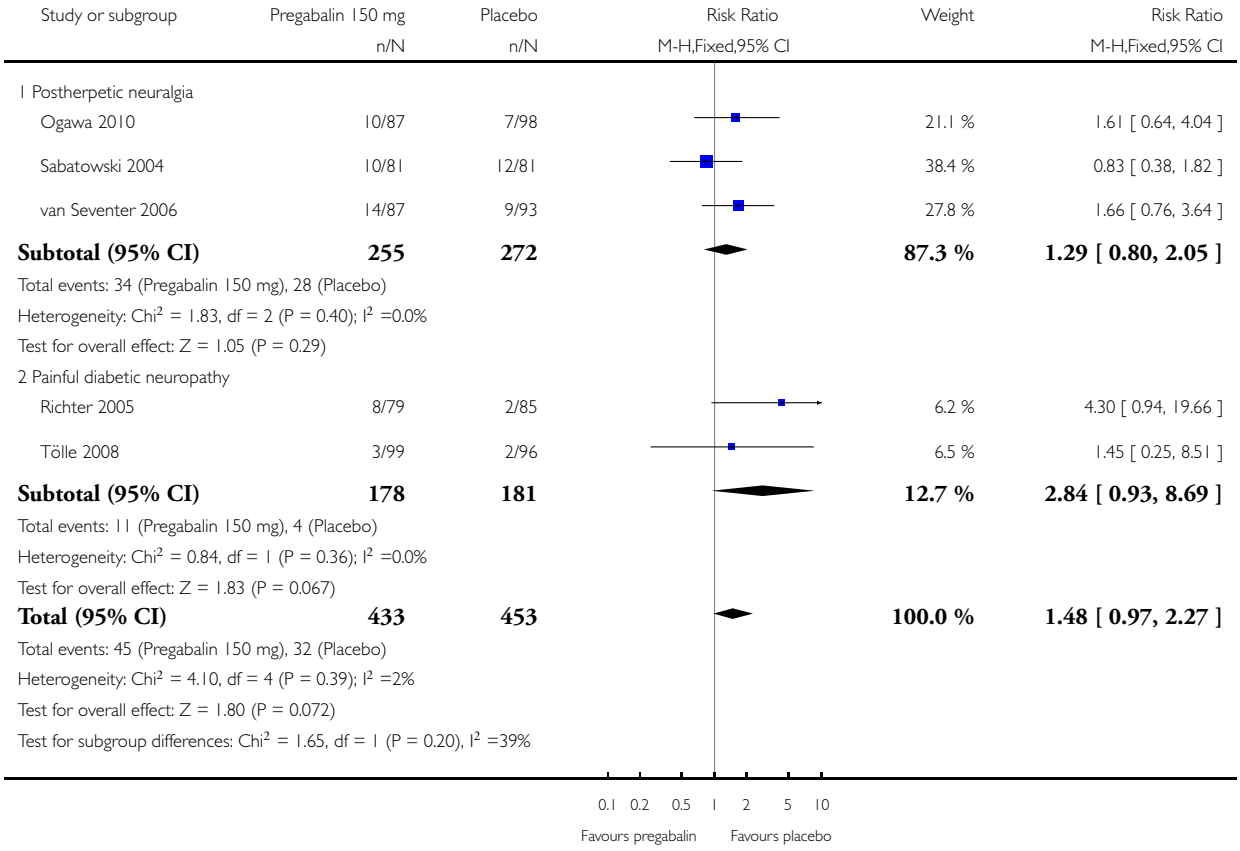


Analysis 1.8. Comparison 1 Pregabalin 150 mg daily versus placebo, Outcome 8 Dizziness.

Review: Pregabalin for neuropathic pain in adults

Comparison: 1 Pregabalin 150 mg daily versus placebo

Outcome: 8 Dizziness

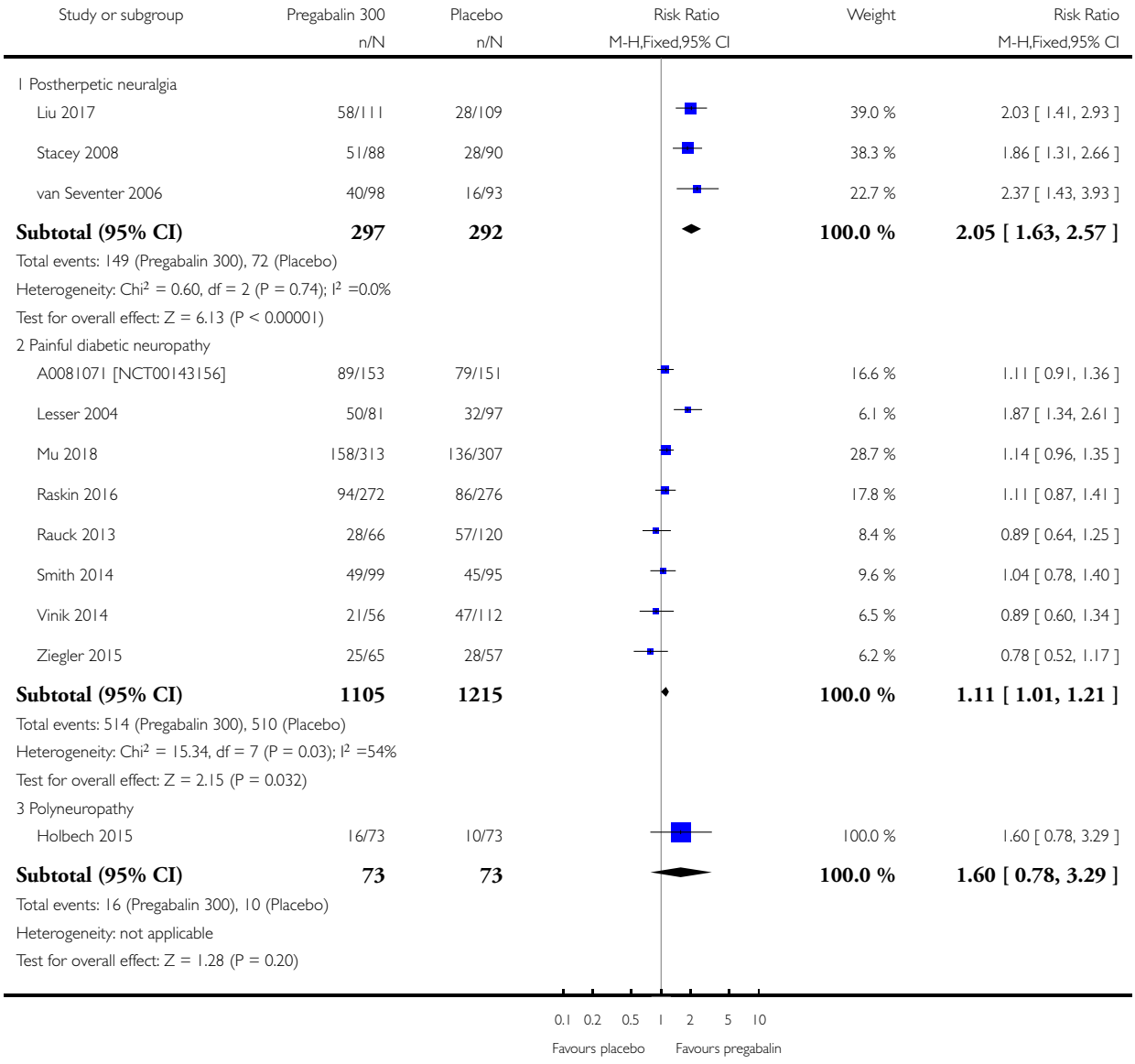


Analysis 2.1. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 1 At least 30% pain intensity reduction.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 1 At least 30% pain intensity reduction

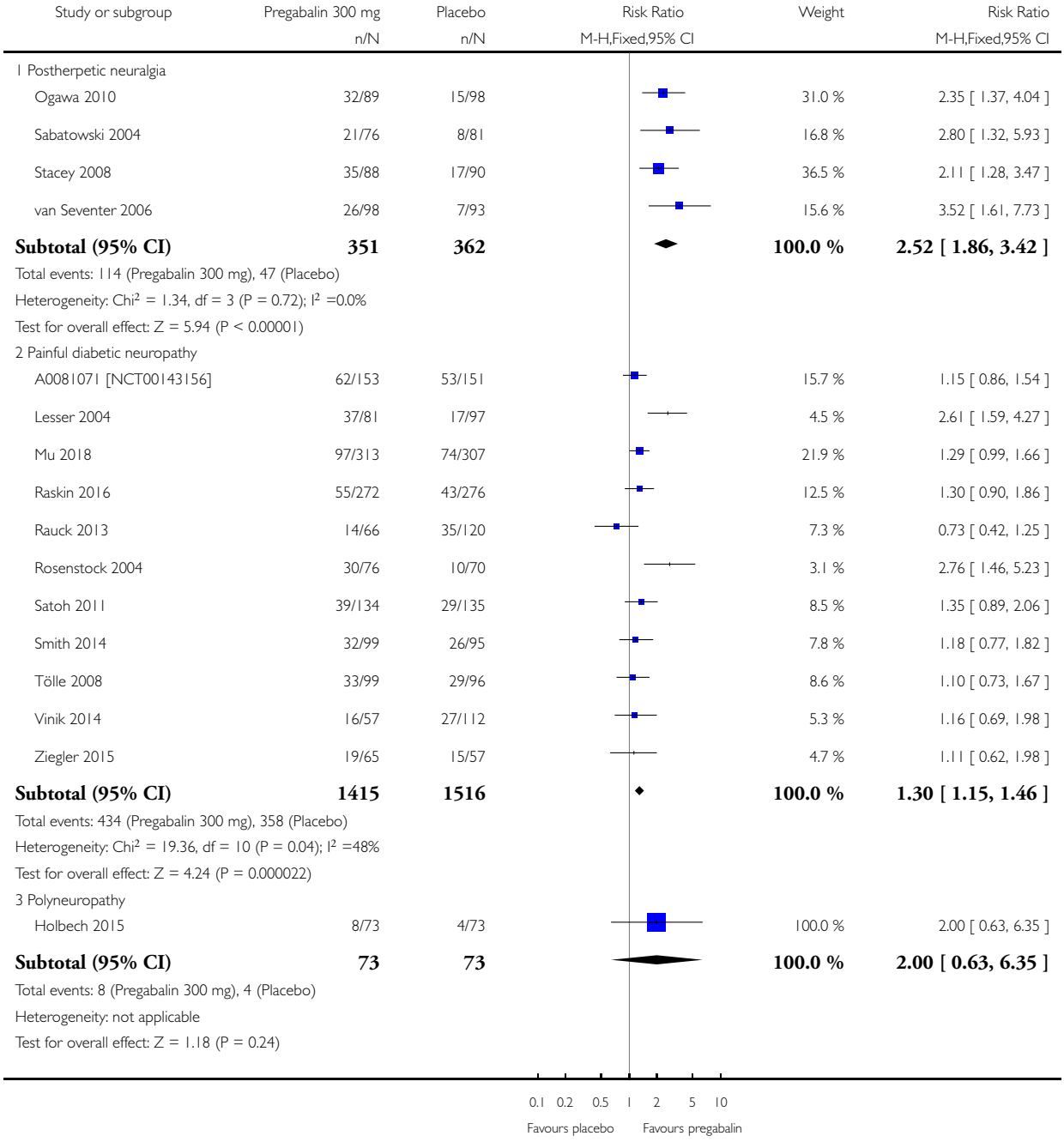


Analysis 2.2. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 2 At least 50% pain intensity reduction.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 2 At least 50% pain intensity reduction

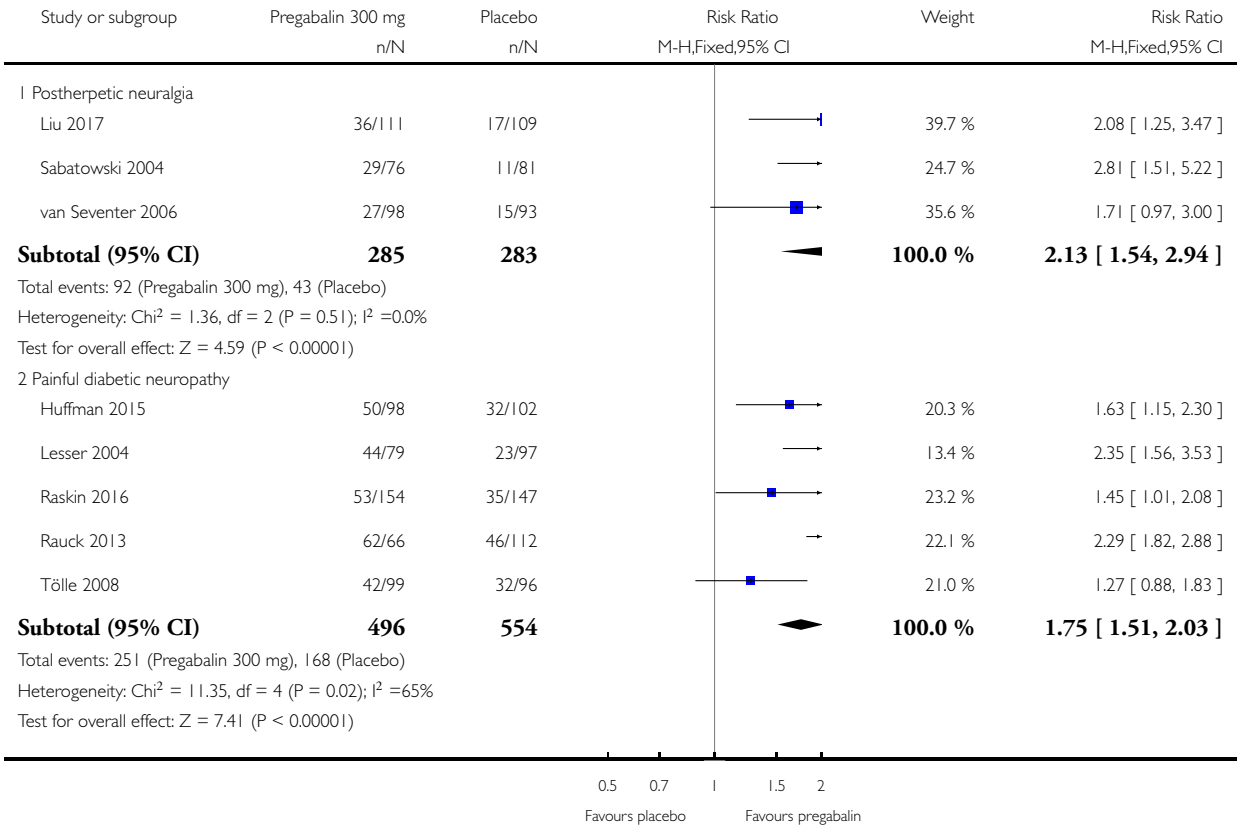


Analysis 2.3. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 3 PGIC much or very much improved.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 3 PGIC much or very much improved

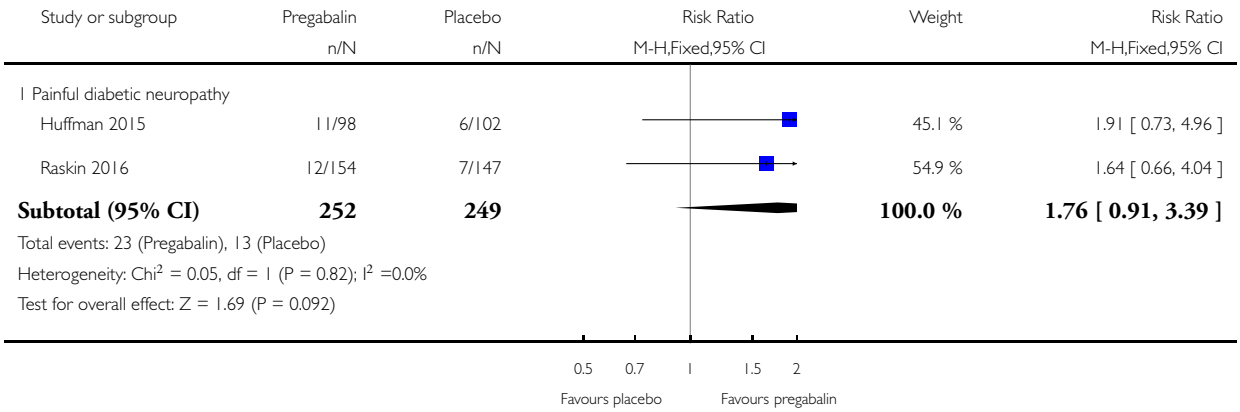


Analysis 2.4. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 4 Very much improved.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 4 Very much improved

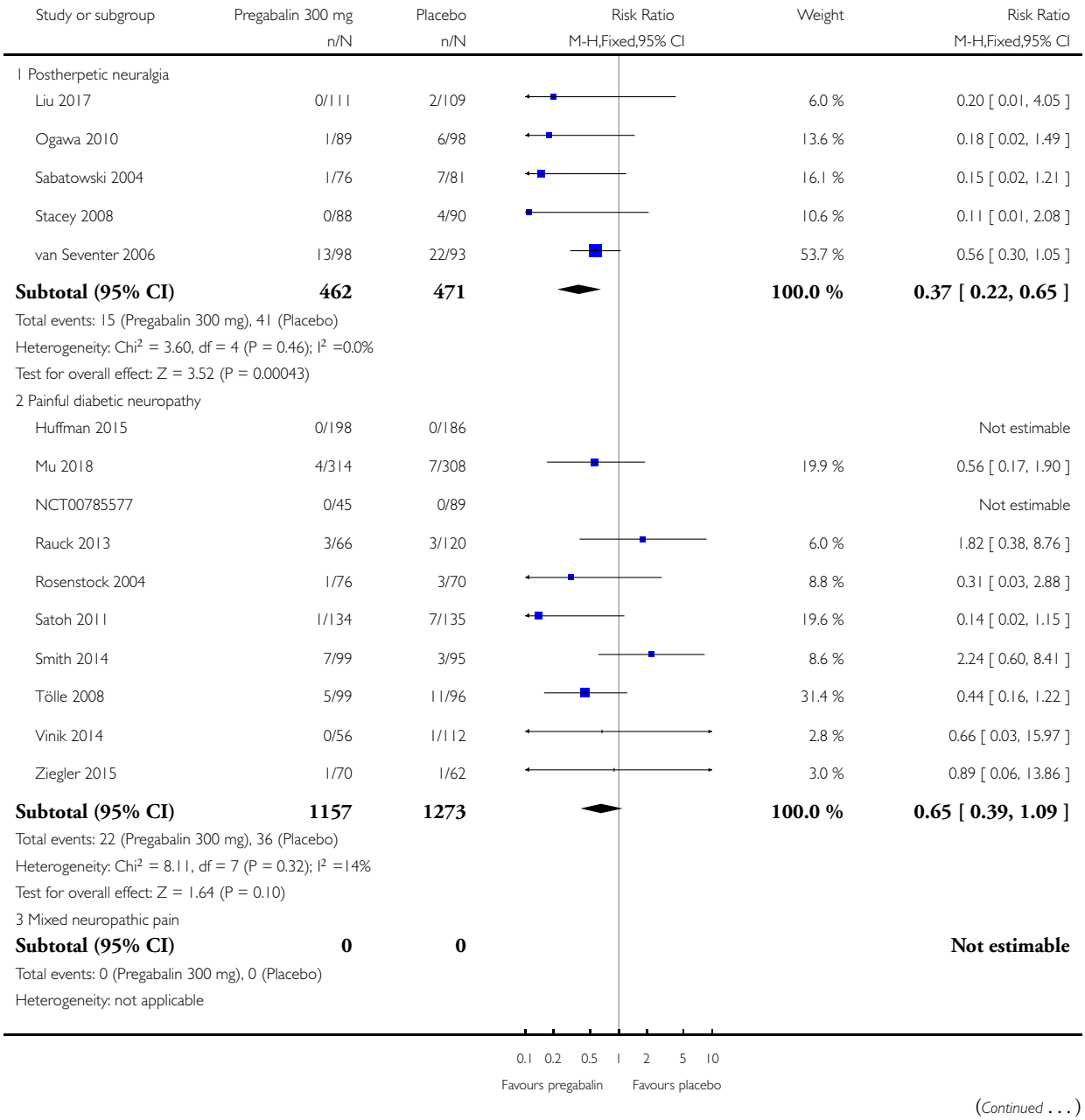


Analysis 2.5. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 5 Withdrawal - lack of efficacy.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 5 Withdrawal - lack of efficacy



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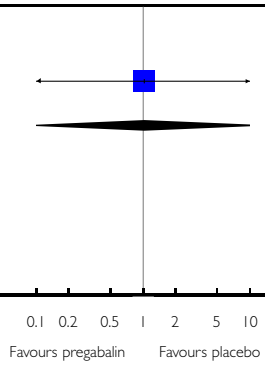
Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: not applicable					
4 Polyneuropathy					
Holbech 2015	1/61	1/62		100.0 %	1.02 [0.07, 15.89]
Subtotal (95% CI)	**61**	**62**		**100.0 %**	**1.02 [0.07, 15.89]**
Total events: 1 (Pregabalin 300 mg), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
Test for subgroup differences: Chi^2 = 2.34, df = 2 (P = 0.31), I^2 =15%					



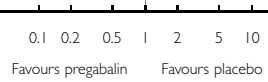
Analysis 2.6. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 6 Withdrawal - adverse event.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 6 Withdrawal - adverse event

Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Liu 2017	6/111	2/109		1.9 %	2.95 [0.61, 14.28]
Ogawa 2010	16/89	5/98		4.4 %	3.52 [1.35, 9.22]
Sabatowski 2004	12/76	8/81		7.2 %	1.60 [0.69, 3.70]
Stacey 2008	17/88	5/90		4.6 %	3.48 [1.34, 9.02]
van Seventer 2006	15/98	5/93		4.8 %	2.85 [1.08, 7.52]
Subtotal (95% CI)	**462**	**471**		**22.9 %**	**2.72 [1.75, 4.22]**
Total events: 66 (Pregabalin 300 mg), 25 (Placebo)					
Heterogeneity: Chi^2 = 2.10, df = 4 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 4.45 (P < 0.00001)					
2 Painful diabetic neuropathy					
A0081071 [NCT00143156]	24/153	12/151		11.2 %	1.97 [1.02, 3.80]



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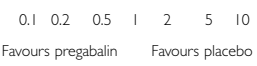
Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Huffman 2015	11/206	4/102		5.0 %	1.36 [0.44, 4.17]
Lesser 2004	3/81	3/97		2.5 %	1.20 [0.25, 5.77]
Mu 2018	11/314	9/308		8.4 %	1.20 [0.50, 2.85]
NCT00785577	7/45	5/89		3.1 %	2.77 [0.93, 8.24]
Raskin 2016	18/272	19/276		17.5 %	0.96 [0.52, 1.79]
Rauck 2013	6/66	11/120		7.3 %	0.99 [0.38, 2.56]
Rosenstock 2004	8/76	2/70		1.9 %	3.68 [0.81, 16.76]
Satoh 2011	17/134	7/135		6.5 %	2.45 [1.05, 5.71]
Smith 2014	10/99	8/95		7.6 %	1.20 [0.49, 2.91]
Tölle 2008	11/99	3/96		2.8 %	3.56 [1.02, 12.35]
Vinik 2014	3/56	2/112		1.2 %	3.00 [0.52, 17.44]
Ziegler 2015	4/70	2/62		2.0 %	1.77 [0.34, 9.34]
Subtotal (95% CI)	**1671**	**1713**		**77.1 %**	**1.61 [1.24, 2.09]**
Total events: 133 (Pregabalin 300 mg), 87 (Placebo)					
Heterogeneity: Chi^2 = 10.18, df = 12 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 3.54 (P = 0.00039)					
Total (95% CI)	**2133**	**2184**		**100.0 %**	**1.86 [1.49, 2.33]**
Total events: 199 (Pregabalin 300 mg), 112 (Placebo)					
Heterogeneity: Chi^2 = 16.13, df = 17 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 5.43 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 4.02, df = 1 (P = 0.05), I^2 =75%					



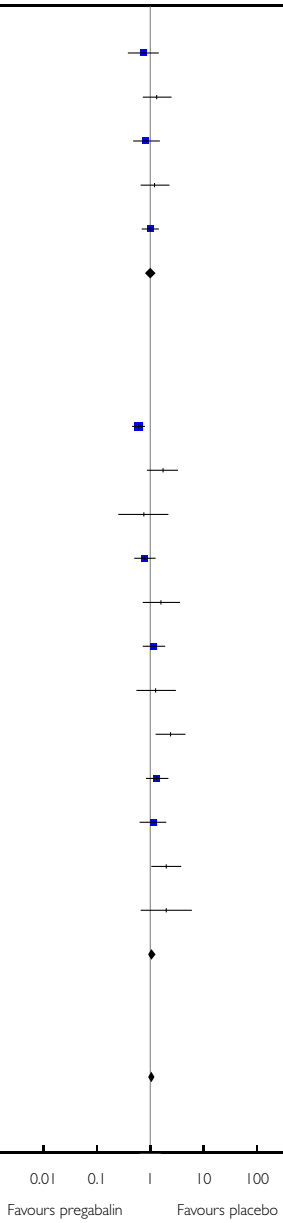
Analysis 2.7. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 7 Withdrawal - all cause.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 7 Withdrawal - all cause

Study or subgroup	Pregabalin 300 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Liu 2017	13/111	17/109		5.1 %	0.75 [0.38, 1.47]
Ogawa 2010	18/89	15/98		4.3 %	1.32 [0.71, 2.46]
Sabatowski 2004	16/76	20/81		5.8 %	0.85 [0.48, 1.52]
Stacey 2008	18/88	15/90		4.4 %	1.23 [0.66, 2.28]
van Seventer 2006	36/98	34/93		10.4 %	1.00 [0.69, 1.46]
Subtotal (95% CI)	**462**	**471**		**30.1 %**	**1.01 [0.79, 1.28]**
Total events: 101 (Pregabalin 300), 101 (Placebo)					
Heterogeneity: Chi^2 = 2.17, df = 4 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 0.08 (P = 0.94)					
2 Painful diabetic neuropathy					
A0081071 [NCT00143156]	49/153	79/151		23.8 %	0.61 [0.46, 0.81]
Huffman 2015	22/198	12/186		3.7 %	1.72 [0.88, 3.38]
Lesser 2004	5/81	8/97		2.2 %	0.75 [0.25, 2.20]
Mu 2018	29/314	36/308		10.9 %	0.79 [0.50, 1.26]
NCT00785577	9/45	11/89		2.2 %	1.62 [0.72, 3.62]
Rauck 2013	19/66	30/120		6.4 %	1.15 [0.71, 1.88]
Rosenstock 2004	11/76	8/70		2.5 %	1.27 [0.54, 2.97]
Satoh 2011	13/45	16/135		2.4 %	2.44 [1.27, 4.67]
Smith 2014	29/99	21/95		6.4 %	1.33 [0.82, 2.15]
Tölle 2008	20/99	17/96		5.2 %	1.14 [0.64, 2.04]
Vinik 2014	15/56	15/112		3.0 %	2.00 [1.05, 3.79]
Ziegler 2015	9/70	4/62		1.3 %	1.99 [0.65, 6.15]
Subtotal (95% CI)	**1302**	**1521**		**69.9 %**	**1.06 [0.91, 1.24]**
Total events: 230 (Pregabalin 300), 257 (Placebo)					
Heterogeneity: Chi^2 = 32.58, df = 11 (P = 0.00061); I^2 =66%					
Test for overall effect: Z = 0.72 (P = 0.47)					
Total (95% CI)	**1764**	**1992**		**100.0 %**	**1.04 [0.92, 1.19]**
Total events: 331 (Pregabalin 300), 358 (Placebo)					



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Study or subgroup	Pregabalin 300 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 34.72, df = 16 (P = 0.004); I² =54%					
Test for overall effect: Z = 0.65 (P = 0.51)					
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² =0.0%					

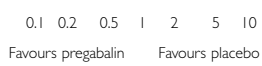
Analysis 2.8. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 8 Somnolence.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 8 Somnolence

Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Liu 2017	6/111	5/109		6.6 %	1.18 [0.37, 3.75]
Ogawa 2010	22/89	9/98		11.3 %	2.69 [1.31, 5.53]
Sabatowski 2004	18/76	6/81		7.7 %	3.20 [1.34, 7.63]
Stacey 2008	17/88	2/90		2.6 %	8.69 [2.07, 36.52]
van Seventer 2006	11/98	4/93		5.4 %	2.61 [0.86, 7.91]
Subtotal (95% CI)	**462**	**471**		**33.6 %**	**2.96 [1.93, 4.53]**
Total events: 74 (Pregabalin 300 mg), 26 (Placebo)					
Heterogeneity: Chi² = 4.74, df = 4 (P = 0.31); I² =16%					
Test for overall effect: Z = 5.00 (P < 0.00001)					
2 Painful diabetic neuropathy					
A0081071 [NCT00143156]	29/153	8/151		10.6 %	3.58 [1.69, 7.57]
Huffman 2015	12/198	4/186		5.4 %	2.82 [0.93, 8.58]
Lesser 2004	19/81	4/97		4.8 %	5.69 [2.02, 16.05]
Mu 2018	18/314	6/308		8.0 %	2.94 [1.18, 7.31]
NCT00785577	9/45	2/89		1.8 %	8.90 [2.01, 39.48]



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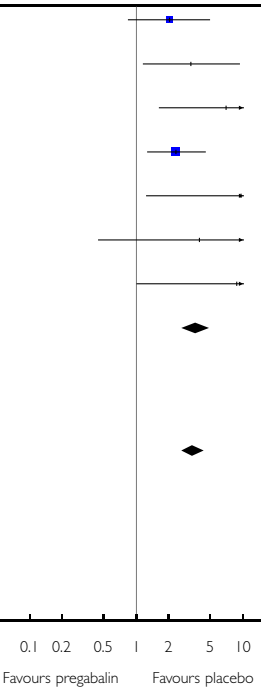
Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Raskin 2016	14/272	7/276		9.2 %	2.03 [0.83, 4.95]
Rauck 2013	9/66	5/120		4.7 %	3.27 [1.14, 9.36]
Rosenstock 2004	15/76	2/70		2.7 %	6.91 [1.64, 29.13]
Satoh 2011	28/134	12/135		15.7 %	2.35 [1.25, 4.43]
Smith 2014	10/98	1/93		1.4 %	9.49 [1.24, 72.69]
Tölle 2008	4/99	1/96		1.3 %	3.88 [0.44, 34.08]
Vinik 2014	4/50	1/108		0.8 %	8.64 [0.99, 75.33]
Subtotal (95% CI)	**1586**	**1729**		**66.4 %**	**3.54 [2.63, 4.76]**
Total events: 171 (Pregabalin 300 mg), 53 (Placebo)					
Heterogeneity: Chi^2 = 8.10, df = 11 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 8.34 (P < 0.00001)					
Total (95% CI)	**2048**	**2200**		**100.0 %**	**3.34 [2.62, 4.26]**
Total events: 245 (Pregabalin 300 mg), 79 (Placebo)					
Heterogeneity: Chi^2 = 13.37, df = 16 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 9.72 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%					



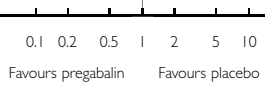
Analysis 2.9. Comparison 2 Pregabalin 300 mg daily versus placebo, Outcome 9 Dizziness.

Review: Pregabalin for neuropathic pain in adults

Comparison: 2 Pregabalin 300 mg daily versus placebo

Outcome: 9 Dizziness

Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Liu 2017	27/111	4/109		4.0 %	6.63 [2.40, 18.31]
Ogawa 2010	27/89	7/98		6.6 %	4.25 [1.95, 9.27]
Sabatowski 2004	21/76	12/81		11.6 %	1.87 [0.99, 3.52]
Stacey 2008	27/88	6/90		5.9 %	4.60 [2.00, 10.60]
van Seventer 2006	32/98	9/93		9.2 %	3.37 [1.70, 6.68]
Subtotal (95% CI)	**462**	**471**		**37.4 %**	**3.61 [2.57, 5.05]**
Total events: 134 (Pregabalin 300 mg), 38 (Placebo)					
Heterogeneity: Chi^2 = 6.03, df = 4 (P = 0.20); I^2 =34%					
Test for overall effect: Z = 7.46 (P < 0.00001)					
2 Painful diabetic neuropathy					
A0081071 [NCT00143156]	36/153	5/151		5.0 %	7.11 [2.87, 17.62]
Huffman 2015	11/198	6/186		6.2 %	1.72 [0.65, 4.56]
Lesser 2004	22/81	5/97		4.5 %	5.27 [2.09, 13.29]
Mu 2018	30/314	12/308		12.1 %	2.45 [1.28, 4.70]
NCT00785577	4/45	2/89		1.3 %	3.96 [0.75, 20.78]
Raskin 2016	28/272	4/276		4.0 %	7.10 [2.53, 19.98]
Rauck 2013	9/66	7/120		5.0 %	2.34 [0.91, 5.99]
Rosenstock 2004	27/76	8/70		8.3 %	3.11 [1.51, 6.38]
Satoh 2011	26/134	9/135		8.9 %	2.91 [1.42, 5.98]
Smith 2014	9/98	4/93		4.1 %	2.14 [0.68, 6.70]
Tölle 2008	9/99	2/96		2.0 %	4.36 [0.97, 19.68]
Vinik 2014	3/50	2/108		1.3 %	3.24 [0.56, 18.79]
Subtotal (95% CI)	**1586**	**1729**		**62.6 %**	**3.48 [2.67, 4.55]**
Total events: 214 (Pregabalin 300 mg), 66 (Placebo)					
Heterogeneity: Chi^2 = 9.93, df = 11 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 9.15 (P < 0.00001)					
Total (95% CI)	**2048**	**2200**		**100.0 %**	**3.53 [2.86, 4.35]**
Total events: 348 (Pregabalin 300 mg), 104 (Placebo)					



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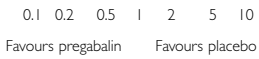
Study or subgroup	Pregabalin 300 mg n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 15.98, df = 16 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 11.80 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² =0.0%					



Analysis 3.1. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 1 At least 30% pain intensity reduction.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 1 At least 30% pain intensity reduction

Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Dworkin 2003	56/89	21/84		33.0 %	2.52 [1.68, 3.77]
Stacey 2008	64/91	28/90		43.0 %	2.26 [1.62, 3.16]
van Seventer 2006	47/90	16/93		24.0 %	3.04 [1.86, 4.94]
Subtotal (95% CI)	**270**	**267**		**100.0 %**	**2.53 [2.01, 3.18]**
Total events: 167 (Pregabalin 600), 65 (Placebo)					
Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² =0.0%					
Test for overall effect: Z = 7.94 (P < 0.00001)					
2 Painful diabetic neuropathy					
A0081071 [NCT00143156]	94/152	79/151		44.2 %	1.18 [0.97, 1.44]
Guan 2011	130/206	53/102		39.5 %	1.21 [0.98, 1.50]
Lesser 2004	53/81	32/97		16.2 %	1.98 [1.43, 2.74]
Subtotal (95% CI)	**439**	**350**		**100.0 %**	**1.33 [1.16, 1.51]**
Total events: 277 (Pregabalin 600), 164 (Placebo)					
Heterogeneity: Chi² = 7.85, df = 2 (P = 0.02); I² =75%					
Test for overall effect: Z = 4.17 (P = 0.000030)					

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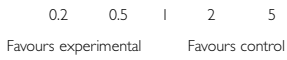
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Mixed neuropathic pain					
A0081279 [NCT01701362]	113/274	109/265		50.8 %	1.00 [0.82, 1.23]
Freynhagen 2005	171/273	24/65		17.8 %	1.70 [1.22, 2.36]
Moon 2010	68/161	27/77		16.7 %	1.20 [0.85, 1.72]
van Seventer 2010	50/126	32/126		14.7 %	1.56 [1.08, 2.26]
Subtotal (95% CI)	**834**	**533**		**100.0 %**	**1.24 [1.08, 1.43]**
Total events: 402 (Pregabalin 600), 192 (Placebo)					
Heterogeneity: Chi^2 = 9.26, df = 3 (P = 0.03); I^2 =68%					
Test for overall effect: Z = 2.98 (P = 0.0029)					
4 Central neuropathic pain					
Cardenas 2013	48/105	33/105		42.8 %	1.45 [1.02, 2.07]
Kim 2011	48/108	35/108		45.4 %	1.37 [0.97, 1.94]
Siddall 2006	29/69	9/67		11.8 %	3.13 [1.60, 6.10]
Subtotal (95% CI)	**282**	**280**		**100.0 %**	**1.62 [1.28, 2.03]**
Total events: 125 (Pregabalin 600), 77 (Placebo)					
Heterogeneity: Chi^2 = 4.97, df = 2 (P = 0.08); I^2 =60%					
Test for overall effect: Z = 4.07 (P = 0.000046)					
5 HIV neuropathy					
A0081244 [NCT01049217]	88/183	98/192		54.2 %	0.94 [0.77, 1.16]
Simpson 2010	84/139	84/150		45.8 %	1.08 [0.89, 1.31]
Subtotal (95% CI)	**322**	**342**		**100.0 %**	**1.00 [0.87, 1.16]**
Total events: 172 (Pregabalin 600), 182 (Placebo)					
Heterogeneity: Chi^2 = 0.89, df = 1 (P = 0.34); I^2 =0.0%					
Test for overall effect: Z = 0.07 (P = 0.95)					

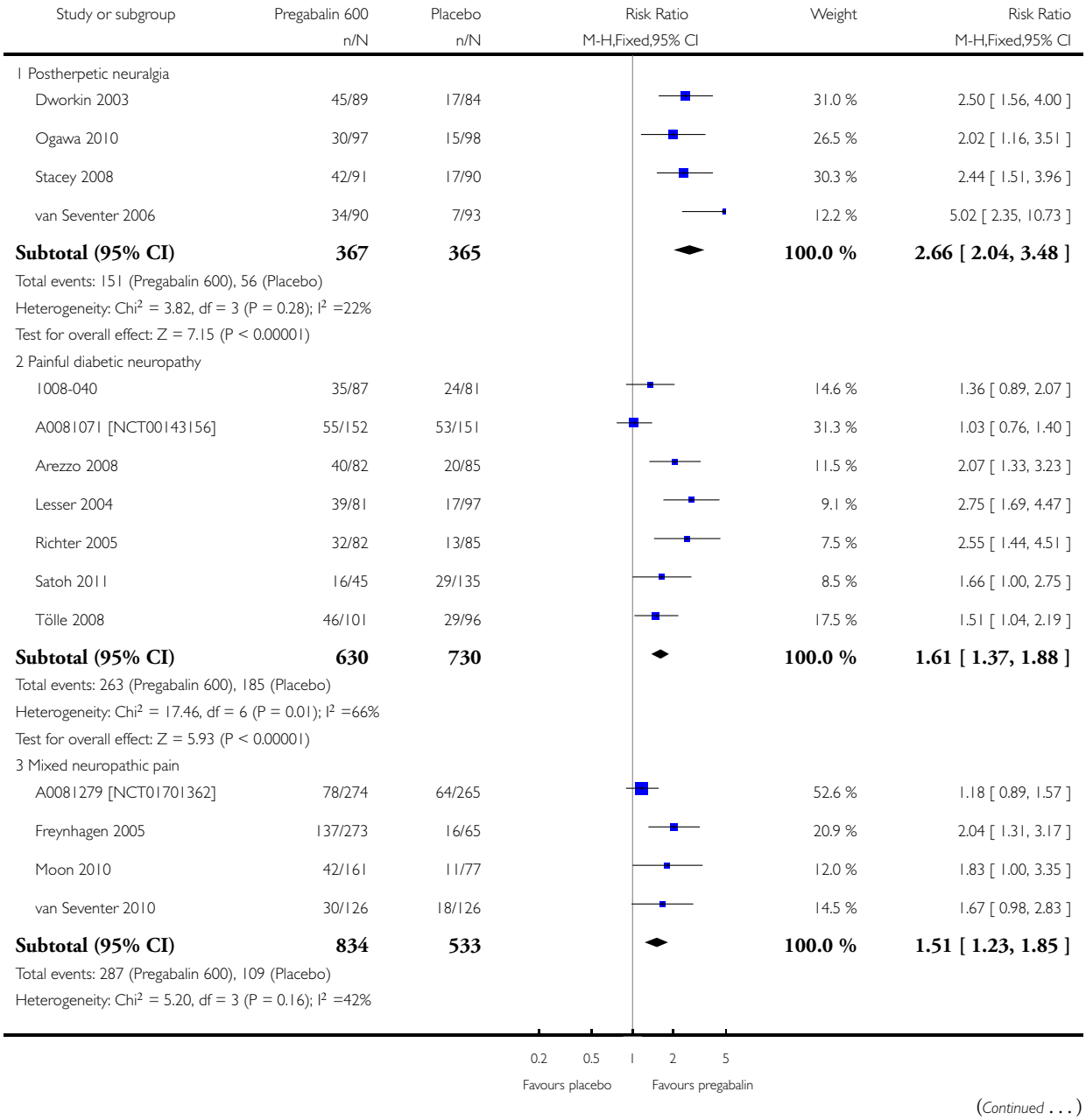


Analysis 3.2. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 2 At least 50% pain intensity reduction.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 2 At least 50% pain intensity reduction



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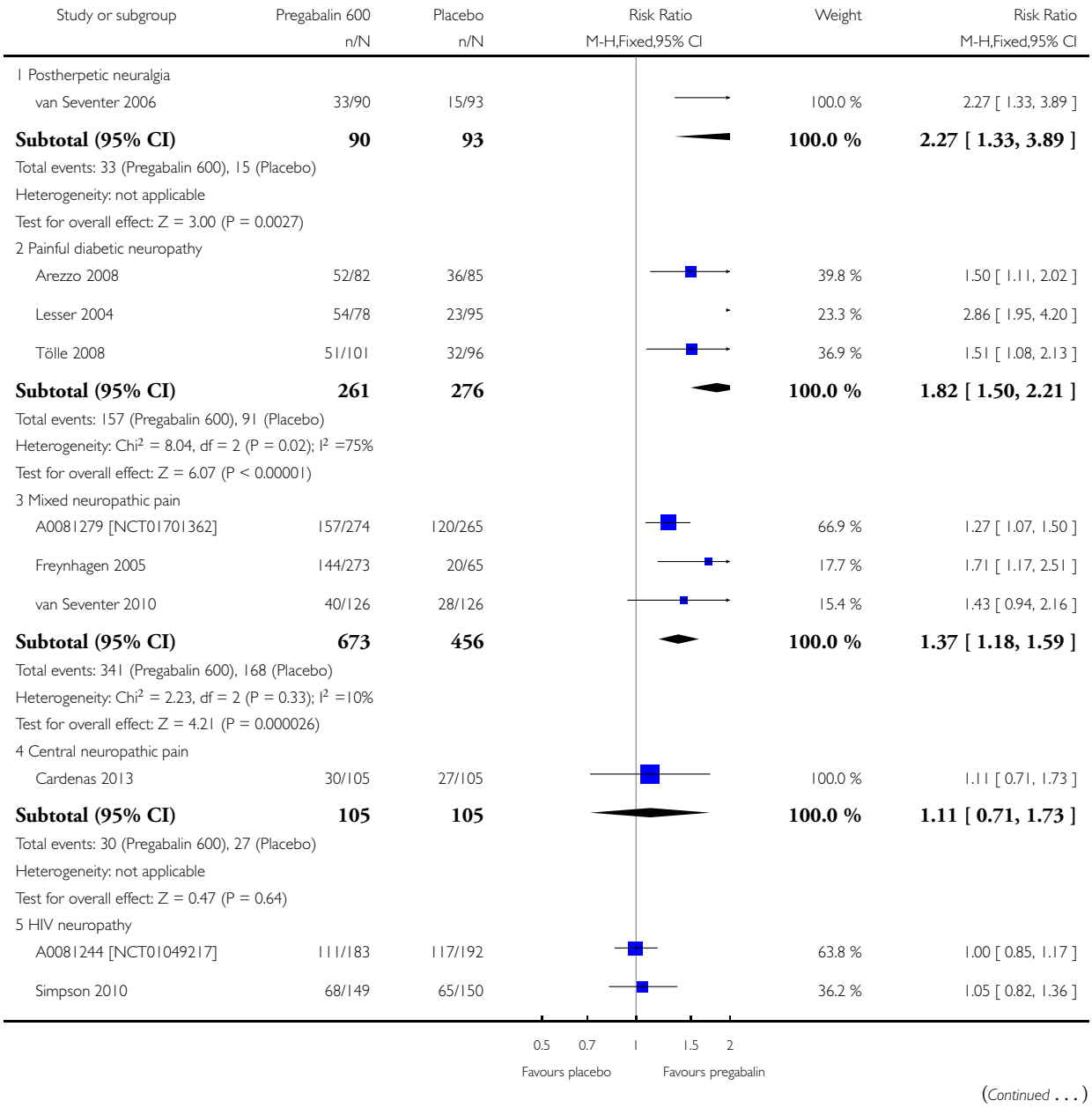
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 3.93 (P = 0.000086)					
4 Central neuropathic pain					
Cardenas 2013	31/105	16/105		37.1 %	1.94 [1.13, 3.32]
Kim 2011	26/108	22/108		51.1 %	1.18 [0.72, 1.95]
Siddall 2006	15/69	5/67		11.8 %	2.91 [1.12, 7.57]
Subtotal (95% CI)	**282**	**280**		**100.0 %**	**1.67 [1.19, 2.34]**
Total events: 72 (Pregabalin 600), 43 (Placebo)					
Heterogeneity: Chi^2 = 3.42, df = 2 (P = 0.18); I^2 =42%					
Test for overall effect: Z = 2.95 (P = 0.0032)					
5 HIV neuropathy					
A0081244 [NCT01049217]	51/183	66/192		50.2 %	0.81 [0.60, 1.10]
Simpson 2010	58/149	64/150		49.8 %	0.91 [0.69, 1.20]
Subtotal (95% CI)	**332**	**342**		**100.0 %**	**0.86 [0.70, 1.06]**
Total events: 109 (Pregabalin 600), 130 (Placebo)					
Heterogeneity: Chi^2 = 0.32, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 1.43 (P = 0.15)					

Analysis 3.3. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 3 PGIC much or very much improved.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 3 PGIC much or very much improved



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Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**332**	**342**		**100.0 %**	**1.02 [0.88, 1.17]**
Total events: 179 (Pregabalin 600), 182 (Placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					

Analysis 3.4. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 4 PGIC very much improved.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 4 PGIC very much improved

Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Mixed neuropathic pain					
A0081279 [NCT01701362]	52/274	41/265		87.4 %	1.23 [0.84, 1.78]
van Seventer 2010	13/126	6/126		12.6 %	2.17 [0.85, 5.52]
Subtotal (95% CI)	**400**	**391**		**100.0 %**	**1.34 [0.95, 1.90]**
Total events: 65 (Pregabalin 600), 47 (Placebo)					
Heterogeneity: Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =19%					
Test for overall effect: Z = 1.68 (P = 0.093)					
2 Central neuropathic pain					
Cardenas 2013	7/105	2/105		100.0 %	3.50 [0.74, 16.46]
Subtotal (95% CI)	**105**	**105**		**100.0 %**	**3.50 [0.74, 16.46]**
Total events: 7 (Pregabalin 600), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
3 HIV neuropathy					
A0081244 [NCT01049217]	42/183	51/192		64.9 %	0.86 [0.61, 1.23]
Simpson 2010	27/149	27/150		35.1 %	1.01 [0.62, 1.63]
Subtotal (95% CI)	**332**	**342**		**100.0 %**	**0.91 [0.69, 1.22]**

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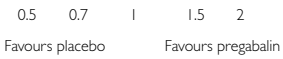
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 69 (Pregabalin 600), 78 (Placebo)					
Heterogeneity: Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 0.62 (P = 0.54)					



Analysis 3.5. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 5 Withdrawal - lack of efficacy.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 5 Withdrawal - lack of efficacy

Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Dworkin 2003	0/89	6/84		17.4 %	0.07 [0.00, 1.27]
Ogawa 2010	3/97	6/98		15.6 %	0.51 [0.13, 1.96]
Stacey 2008	1/91	4/90		10.5 %	0.25 [0.03, 2.17]
van Seventer 2006	6/90	22/93		56.5 %	0.28 [0.12, 0.66]
Subtotal (95% CI)	**367**	**365**		**100.0 %**	**0.28 [0.14, 0.53]**
Total events: 10 (Pregabalin 600), 38 (Placebo)					
Heterogeneity: Chi^2 = 1.61, df = 3 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 3.84 (P = 0.00012)					
2 Painful diabetic neuropathy					
1008-040	7/87	9/81		30.8 %	0.72 [0.28, 1.85]
Arezzo 2008	4/82	5/85		16.2 %	0.83 [0.23, 2.98]
Richter 2005	1/82	1/85		3.2 %	1.04 [0.07, 16.30]
Satoh 2011	0/45	7/135		12.5 %	0.20 [0.01, 3.38]
Tölle 2008	3/101	11/96		37.2 %	0.26 [0.07, 0.90]

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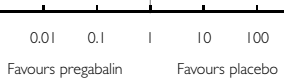
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**397**	**482**		**100.0 %**	**0.51 [0.28, 0.93]**
Total events: 15 (Pregabalin 600), 33 (Placebo)					
Heterogeneity: Chi^2 = 2.90, df = 4 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					
3 Mixed neuropathic pain					
A0081279 [NCT01701362]	6/274	6/265		11.3 %	0.97 [0.32, 2.96]
Freynhagen 2005	23/273	19/65		56.6 %	0.29 [0.17, 0.50]
Moon 2010	5/162	4/78		10.0 %	0.60 [0.17, 2.18]
van Seventer 2010	2/127	12/127		22.1 %	0.17 [0.04, 0.73]
Subtotal (95% CI)	**836**	**535**		**100.0 %**	**0.37 [0.24, 0.57]**
Total events: 36 (Pregabalin 600), 41 (Placebo)					
Heterogeneity: Chi^2 = 5.31, df = 3 (P = 0.15); I^2 =43%					
Test for overall effect: Z = 4.47 (P < 0.00001)					
4 Central neuropathic pain					
Cardenas 2013	1/112	2/107		8.5 %	0.48 [0.04, 5.19]
Kim 2011	0/110	1/109		6.3 %	0.33 [0.01, 8.02]
Siddall 2006	5/70	20/67		85.2 %	0.24 [0.10, 0.60]
Subtotal (95% CI)	**292**	**283**		**100.0 %**	**0.27 [0.12, 0.61]**
Total events: 6 (Pregabalin 600), 23 (Placebo)					
Heterogeneity: Chi^2 = 0.30, df = 2 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 3.15 (P = 0.0016)					
5 HIV neuropathy					
A0081244 [NCT01049217]	1/183	1/192		21.8 %	1.05 [0.07, 16.65]
Simpson 2010	0/151	3/151		78.2 %	0.14 [0.01, 2.74]
Subtotal (95% CI)	**334**	**343**		**100.0 %**	**0.34 [0.05, 2.13]**
Total events: 1 (Pregabalin 600), 4 (Placebo)					
Heterogeneity: Chi^2 = 0.97, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 1.15 (P = 0.25)					
Test for subgroup differences: Chi^2 = 2.48, df = 4 (P = 0.65), I^2 =0.0%					

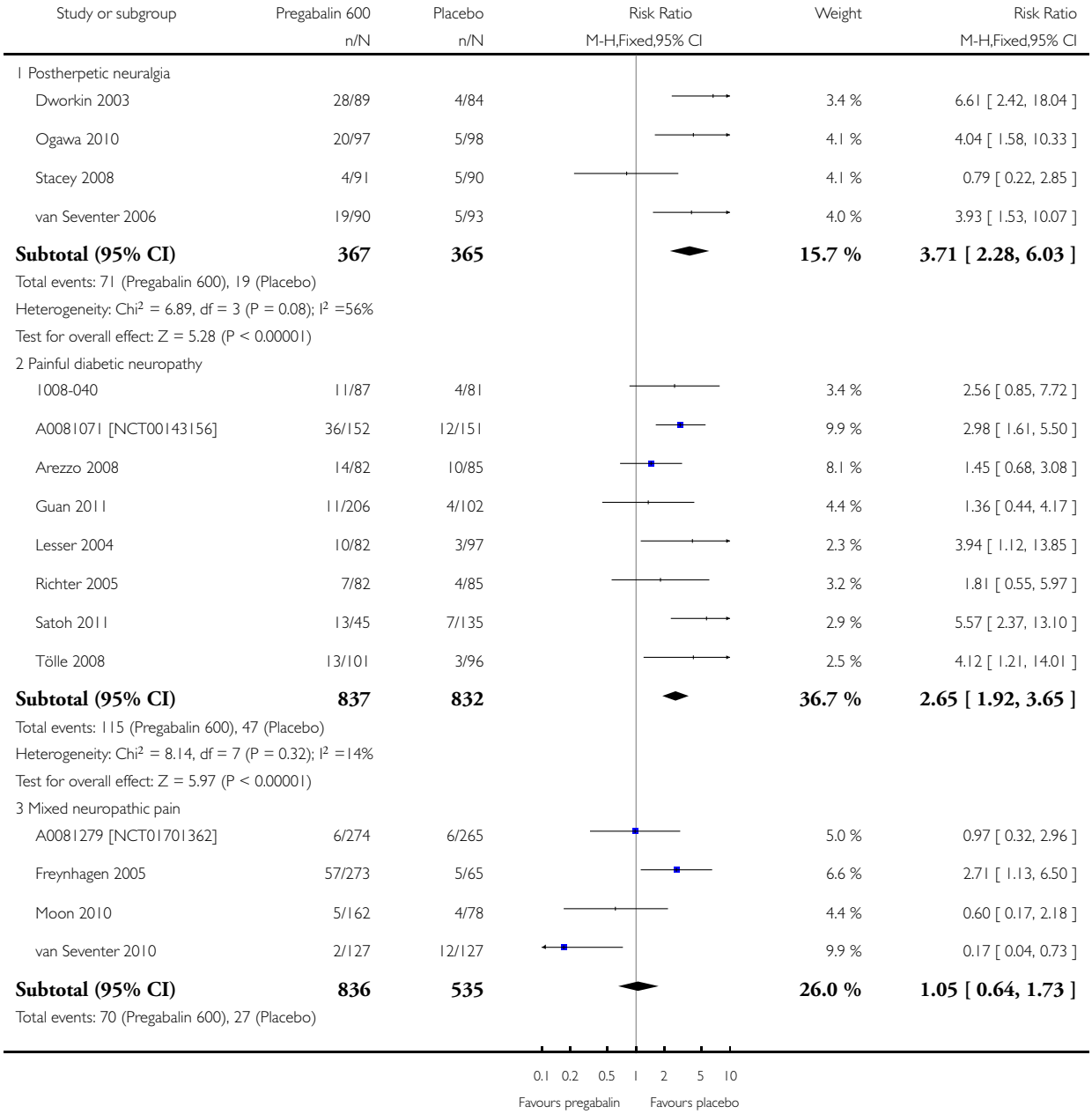


Analysis 3.6. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 6 Withdrawal - adverse event.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 6 Withdrawal - adverse event



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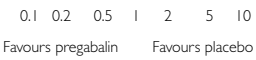
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 11.25, df = 3 (P = 0.01); I² =73%					
Test for overall effect: Z = 0.18 (P = 0.86)					
4 Central neuropathic pain					
Cardenas 2013	8/112	8/107		6.7 %	0.96 [0.37, 2.45]
Kim 2011	9/110	4/109		3.3 %	2.23 [0.71, 7.02]
Siddall 2006	15/70	9/67		7.6 %	1.60 [0.75, 3.40]
Subtotal (95% CI)	**292**	**283**		**17.6 %**	**1.47 [0.87, 2.47]**
Total events: 32 (Pregabalin 600), 21 (Placebo)					
Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 1.45 (P = 0.15)					
5 HIV neuropathy					
A0081244 [NCT01049217]	3/183	1/192		0.8 %	3.15 [0.33, 29.99]
Simpson 2010	9/151	4/151		3.3 %	2.25 [0.71, 7.15]
Subtotal (95% CI)	**334**	**343**		**4.1 %**	**2.43 [0.87, 6.77]**
Total events: 12 (Pregabalin 600), 5 (Placebo)					
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 1.69 (P = 0.091)					
Total (95% CI)	**2666**	**2358**		**100.0 %**	**2.18 [1.78, 2.68]**
Total events: 300 (Pregabalin 600), 119 (Placebo)					
Heterogeneity: Chi² = 41.20, df = 20 (P = 0.004); I² =51%					
Test for overall effect: Z = 7.44 (P < 0.00001)					
Test for subgroup differences: Chi² = 16.50, df = 4 (P = 0.00), I² =76%					



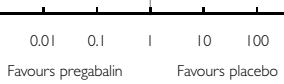
Analysis 3.7. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 7 Withdrawal - all cause.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 7 Withdrawal - all cause

Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Postherpetic neuralgia					
Dworkin 2003	31/89	10/84		2.0 %	2.93 [1.53, 5.59]
Ogawa 2010	27/97	15/98		2.9 %	1.82 [1.03, 3.20]
Stacey 2008	5/91	15/90		2.9 %	0.33 [0.13, 0.87]
van Seventer 2006	34/90	34/93		6.5 %	1.03 [0.71, 1.51]
Subtotal (95% CI)	**367**	**365**		**14.4 %**	**1.31 [1.01, 1.71]**
Total events: 97 (Pregabalin 600), 74 (Placebo)					
Heterogeneity: Chi^2 = 16.52, df = 3 (P = 0.00089); I^2 =82%					
Test for overall effect: Z = 2.03 (P = 0.043)					
2 Painful diabetic neuropathy					
1008-040	24/87	19/81		3.8 %	1.18 [0.70, 1.98]
A0081071 [NCT00143156]	64/152	79/151		15.4 %	0.80 [0.63, 1.02]
Arezzo 2008	28/82	24/85		4.6 %	1.21 [0.77, 1.90]
Guan 2011	24/206	17/102		4.4 %	0.70 [0.39, 1.24]
Lesser 2004	12/82	8/97		1.4 %	1.77 [0.76, 4.13]
Richter 2005	10/82	13/85		2.5 %	0.80 [0.37, 1.72]
Satoh 2011	13/45	16/135		1.6 %	2.44 [1.27, 4.67]
Tölle 2008	23/101	17/96		3.4 %	1.29 [0.73, 2.25]
Subtotal (95% CI)	**837**	**832**		**37.1 %**	**1.03 [0.87, 1.21]**
Total events: 198 (Pregabalin 600), 193 (Placebo)					
Heterogeneity: Chi^2 = 15.90, df = 7 (P = 0.03); I^2 =56%					
Test for overall effect: Z = 0.35 (P = 0.73)					
3 Mixed neuropathic pain					
A0081279 [NCT01701362]	41/274	54/265		10.7 %	0.73 [0.51, 1.06]
Freynhagen 2005	99/273	30/65		9.4 %	0.79 [0.58, 1.07]
Moon 2010	24/162	16/78		4.2 %	0.72 [0.41, 1.28]
van Seventer 2010	31/127	29/127		5.6 %	1.07 [0.69, 1.66]
Subtotal (95% CI)	**836**	**535**		**30.0 %**	**0.81 [0.67, 0.99]**
Total events: 195 (Pregabalin 600), 129 (Placebo)					



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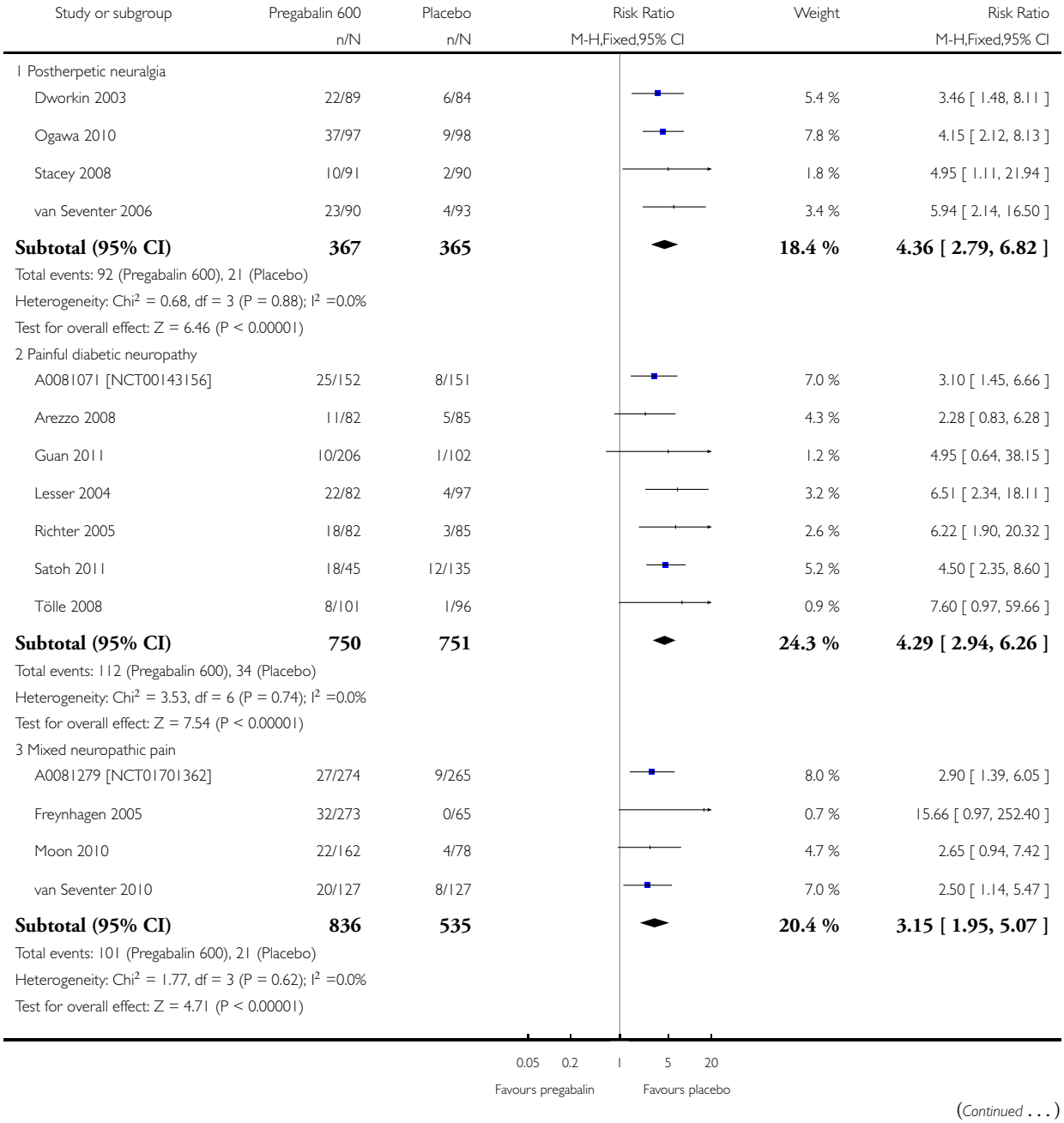
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 1.97, df = 3 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 2.05 (P = 0.040)					
4 Central neuropathic pain					
Cardenas 2013	19/112	16/107		3.2 %	1.13 [0.62, 2.09]
Kim 2011	17/110	19/109		3.7 %	0.89 [0.49, 1.61]
Siddall 2006	21/70	30/67		6.0 %	0.67 [0.43, 1.05]
Subtotal (95% CI)	**292**	**283**		**12.9 %**	**0.85 [0.62, 1.15]**
Total events: 57 (Pregabalin 600), 65 (Placebo)					
Heterogeneity: Chi² = 1.97, df = 2 (P = 0.37); I² =0.0%					
Test for overall effect: Z = 1.05 (P = 0.29)					
5 HIV neuropathy					
Simpson 2010	32/151	29/151		5.6 %	1.10 [0.70, 1.73]
Subtotal (95% CI)	**151**	**151**		**5.6 %**	**1.10 [0.70, 1.73]**
Total events: 32 (Pregabalin 600), 29 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
Total (95% CI)	**2483**	**2166**		**100.0 %**	**0.99 [0.89, 1.09]**
Total events: 579 (Pregabalin 600), 490 (Placebo)					
Heterogeneity: Chi² = 45.39, df = 19 (P = 0.00060); I² =58%					
Test for overall effect: Z = 0.27 (P = 0.79)					
Test for subgroup differences: Chi² = 9.64, df = 4 (P = 0.05), I² =58%					

Analysis 3.8. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 8 Somnolence.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 8 Somnolence



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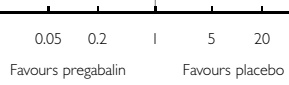
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
4 Central neuropathic pain					
Cardenas 2013	37/112	14/107		12.5 %	2.52 [1.45, 4.40]
Kim 2011	24/110	5/109		4.4 %	4.76 [1.88, 12.01]
Siddall 2006	29/70	6/67		5.3 %	4.63 [2.05, 10.43]
Subtotal (95% CI)	**292**	**283**		**22.2 %**	**3.47 [2.30, 5.23]**
Total events: 90 (Pregabalin 600), 25 (Placebo)					
Heterogeneity: Chi^2 = 2.19, df = 2 (P = 0.33); I^2 =9%					
Test for overall effect: Z = 5.96 (P < 0.00001)					
5 HIV neuropathy					
A0081244 [NCT01049217]	13/183	4/192		3.4 %	3.41 [1.13, 10.27]
Simpson 2010	35/151	13/151		11.3 %	2.69 [1.48, 4.88]
Subtotal (95% CI)	**334**	**343**		**14.7 %**	**2.86 [1.69, 4.83]**
Total events: 48 (Pregabalin 600), 17 (Placebo)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 3.93 (P = 0.000086)					
Total (95% CI)	**2579**	**2277**		**100.0 %**	**3.68 [3.02, 4.47]**
Total events: 443 (Pregabalin 600), 118 (Placebo)					
Heterogeneity: Chi^2 = 11.27, df = 19 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 13.02 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.57, df = 4 (P = 0.63), I^2 =0.0%					

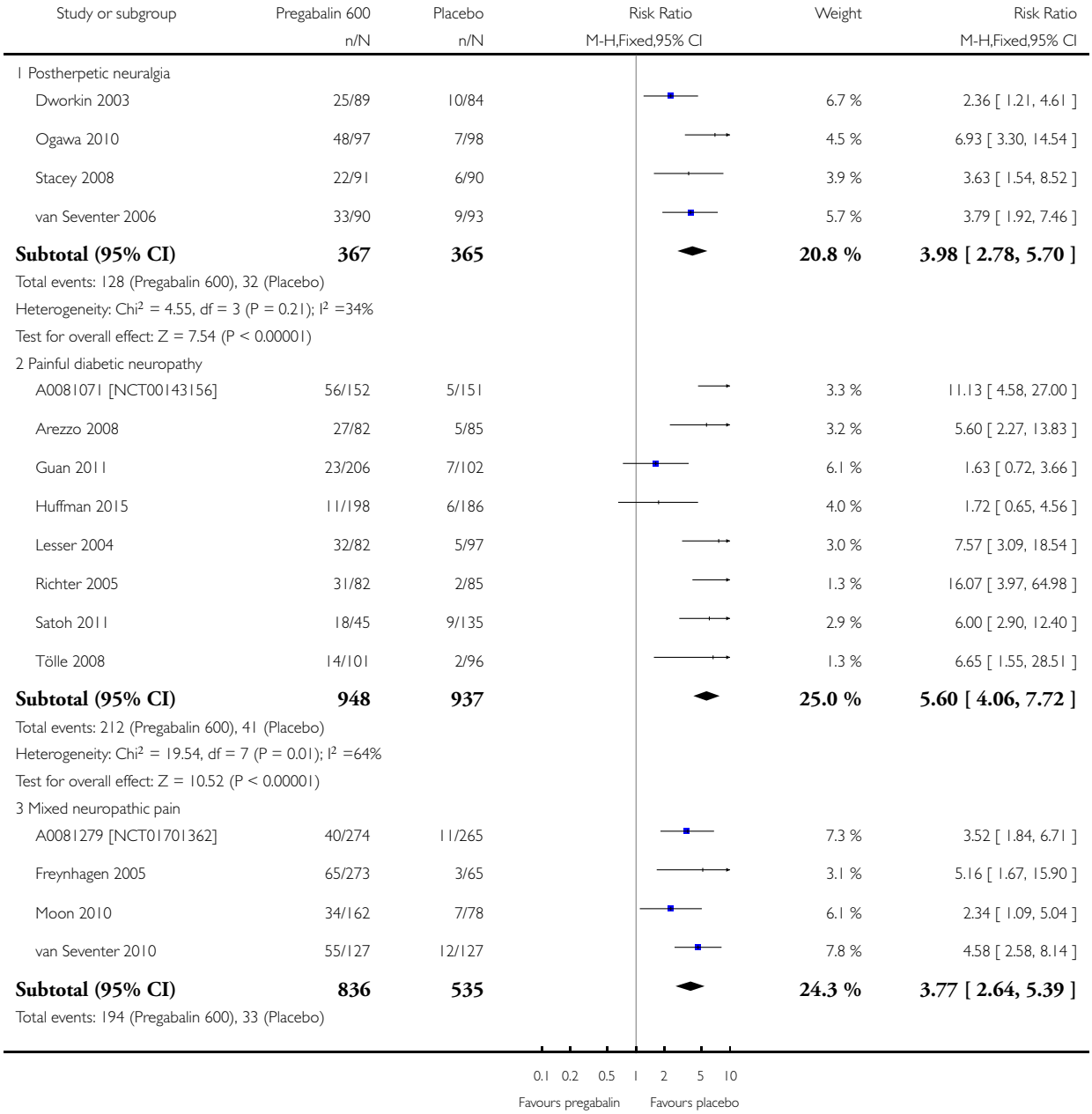


Analysis 3.9. Comparison 3 Pregabalin 600 mg daily versus placebo, Outcome 9 Dizziness.

Review: Pregabalin for neuropathic pain in adults

Comparison: 3 Pregabalin 600 mg daily versus placebo

Outcome: 9 Dizziness



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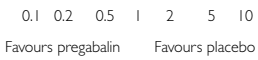
Study or subgroup	Pregabalin 600 n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 2.28, df = 3 (P = 0.52); I² =0.0%					
Test for overall effect: Z = 7.28 (P < 0.00001)					
4 Central neuropathic pain					
Cardenas 2013	22/112	6/107		4.0 %	3.50 [1.48, 8.30]
Kim 2011	32/110	8/109		5.2 %	3.96 [1.91, 8.21]
Siddall 2006	17/70	6/67		4.0 %	2.71 [1.14, 6.46]
Subtotal (95% CI)	**292**	**283**		**13.2 %**	**3.45 [2.16, 5.50]**
Total events: 71 (Pregabalin 600), 20 (Placebo)					
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² =0.0%					
Test for overall effect: Z = 5.19 (P < 0.00001)					
5 HIV neuropathy					
A0081244 [NCT01049217]	25/183	10/192		6.3 %	2.62 [1.30, 5.31]
Simpson 2010	29/151	16/151		10.4 %	1.81 [1.03, 3.20]
Subtotal (95% CI)	**334**	**343**		**16.7 %**	**2.12 [1.36, 3.29]**
Total events: 54 (Pregabalin 600), 26 (Placebo)					
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² =0.0%					
Test for overall effect: Z = 3.34 (P = 0.00084)					
Total (95% CI)	**2777**	**2463**		**100.0 %**	**3.95 [3.34, 4.68]**
Total events: 659 (Pregabalin 600), 152 (Placebo)					
Heterogeneity: Chi² = 37.13, df = 20 (P = 0.01); I² =46%					
Test for overall effect: Z = 16.06 (P < 0.00001)					
Test for subgroup differences: Chi² = 12.54, df = 4 (P = 0.01), I² =68%					



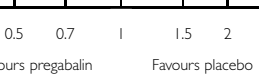
Analysis 4.1. Comparison 4 Participants with at least one adverse event, Outcome 1 At least one adverse event.

Review: Pregabalin for neuropathic pain in adults

Comparison: 4 Participants with at least one adverse event

Outcome: 1 At least one adverse event

Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pregabalin 600 mg					
A0081071 [NCT00143156]	123/152	98/151		9.7 %	1.25 [1.08, 1.43]
A0081244 [NCT01049217]	126/183	117/192		11.2 %	1.13 [0.97, 1.31]
A0081279 [NCT01701362]	138/274	106/265		10.6 %	1.26 [1.04, 1.52]
Cardenas 2013	95/112	84/107		8.4 %	1.08 [0.95, 1.23]
Dworkin 2003	77/89	53/84		5.4 %	1.37 [1.14, 1.65]
Freynhagen 2005	169/273	18/65		2.9 %	2.24 [1.49, 3.35]
Guan 2011	103/206	41/102		5.4 %	1.24 [0.95, 1.63]
Kim 2011	77/110	60/109		5.9 %	1.27 [1.03, 1.57]
Moon 2010	70/162	24/78		3.2 %	1.40 [0.96, 2.05]
Ogawa 2010	90/97	62/98		6.1 %	1.47 [1.25, 1.72]
Satoh 2011	42/45	99/135		4.9 %	1.27 [1.12, 1.45]
Siddall 2006	67/70	50/67		5.0 %	1.28 [1.11, 1.49]
Simpson 2010	123/151	106/151		10.4 %	1.16 [1.02, 1.32]
Stacey 2008	66/91	39/90		3.9 %	1.67 [1.28, 2.19]
van Seventer 2010	109/127	73/127		7.2 %	1.49 [1.27, 1.76]
Subtotal (95% CI)	**2142**	**1821**		**100.0 %**	**1.30 [1.24, 1.37]**
Total events: 1475 (Pregabalin), 1030 (Placebo)					
Heterogeneity: Chi^2 = 31.30, df = 14 (P = 0.01); I^2 =55%					
Test for overall effect: Z = 10.62 (P < 0.00001)					
2 Pregabalin 300 mg					
A0081071 [NCT00143156]	124/153	98/151		10.8 %	1.25 [1.09, 1.44]
A9011015 [NCT01117766]	20/28	15/30		1.6 %	1.43 [0.93, 2.19]
Holbech 2015	37/69	30/69		3.3 %	1.23 [0.87, 1.75]
Huffman 2015	94/198	78/186		8.8 %	1.13 [0.91, 1.42]
Liu 2017	71/111	48/109		5.3 %	1.45 [1.13, 1.87]
Mu 2018	113/314	98/308		10.8 %	1.13 [0.91, 1.41]



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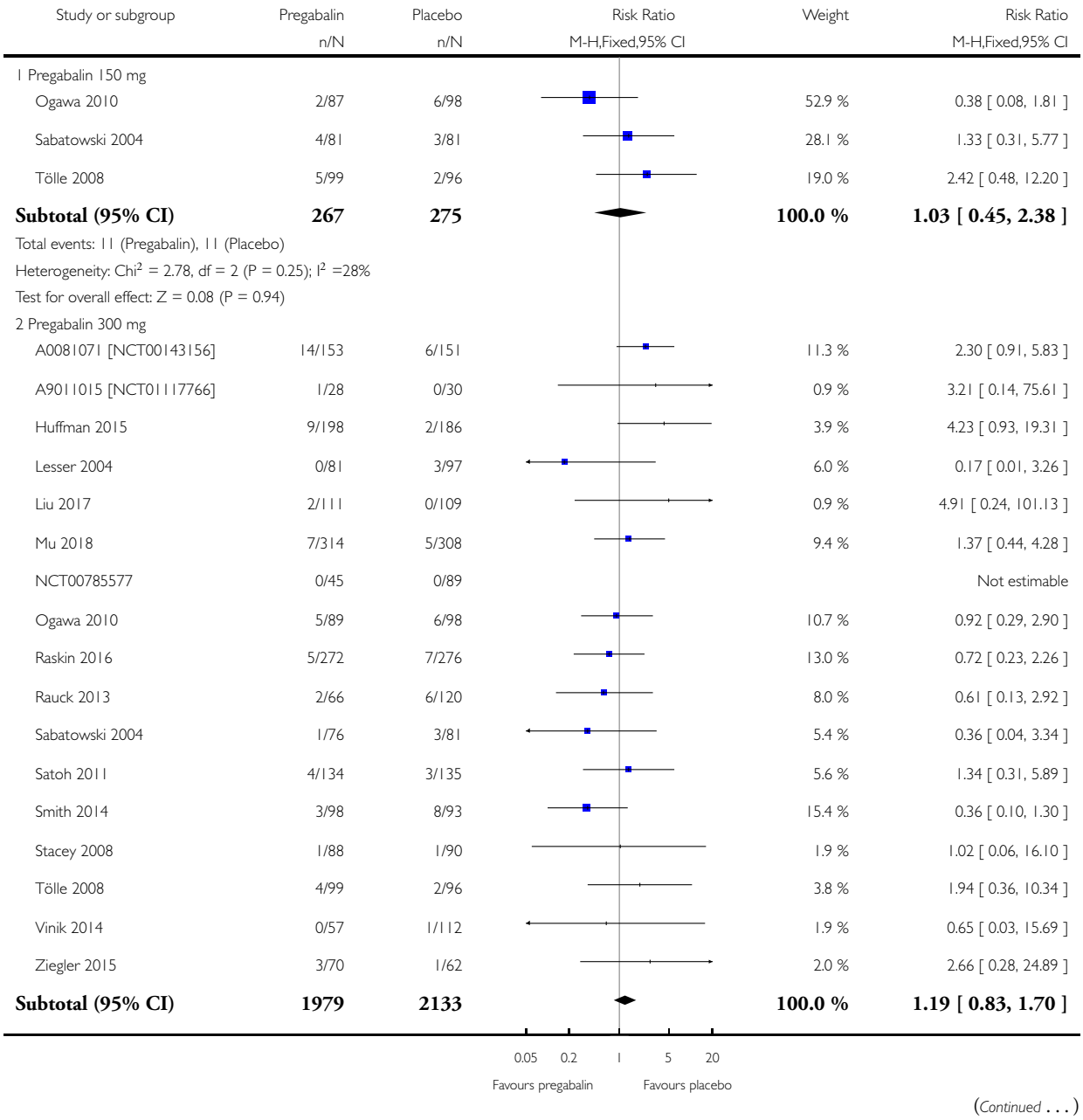
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
NCT00785577	37/45	68/89		5.0 %	1.08 [0.90, 1.29]
Ogawa 2010	78/89	62/98		6.5 %	1.39 [1.17, 1.64]
Raskin 2016	152/272	126/276		13.7 %	1.22 [1.04, 1.45]
Rauck 2013	47/66	79/120		6.1 %	1.08 [0.89, 1.32]
Rosenstock 2004	47/76	20/70		2.3 %	2.16 [1.44, 3.26]
Satoh 2011	111/134	99/135		10.8 %	1.13 [0.99, 1.28]
Smith 2014	61/98	60/93		6.7 %	0.96 [0.78, 1.20]
Stacey 2008	55/88	39/90		4.2 %	1.44 [1.08, 1.92]
Ziegler 2015	38/70	34/62		4.0 %	0.99 [0.72, 1.35]
Subtotal (95% CI)	**1811**	**1886**		**100.0 %**	**1.21 [1.15, 1.28]**
Total events: 1085 (Pregabalin), 954 (Placebo)					
Heterogeneity: Chi^2 = 24.97, df = 14 (P = 0.03); I^2 =44%					
Test for overall effect: Z = 6.66 (P < 0.00001)					
3 Pregabalin 150 mg					
Ogawa 2010	65/87	62/98		100.0 %	1.18 [0.97, 1.43]
Subtotal (95% CI)	**87**	**98**		**100.0 %**	**1.18 [0.97, 1.43]**
Total events: 65 (Pregabalin), 62 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.093)					

Analysis 5.1. Comparison 5 Participants with at least one serious adverse event, Outcome 1 At least one serious adverse event.

Review: Pregabalin for neuropathic pain in adults

Comparison: 5 Participants with at least one serious adverse event

Outcome: 1 At least one serious adverse event



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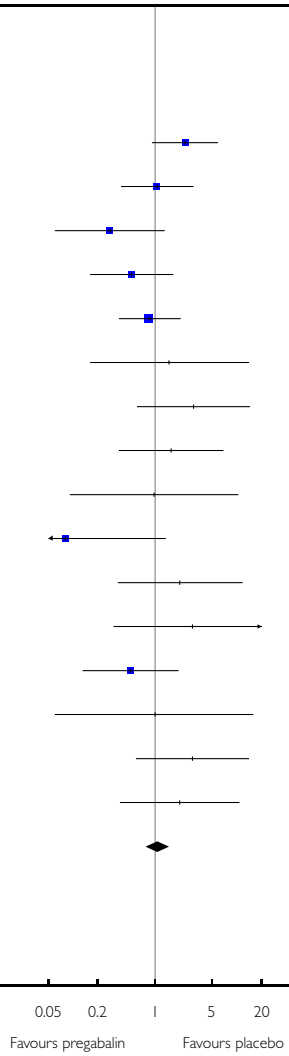
Study or subgroup	Pregabalin n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 61 (Pregabalin), 54 (Placebo)					
Heterogeneity: Chi^2 = 14.64, df = 15 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 0.93 (P = 0.35)					
3 Pregabalin 600 mg					
A0081071 [NCT00143156]	14/152	6/151		9.2 %	2.32 [0.92, 5.87]
A0081244 [NCT01049217]	7/183	7/192		10.4 %	1.05 [0.38, 2.93]
A0081279 [NCT01701362]	2/274	7/265		10.9 %	0.28 [0.06, 1.32]
Arezzo 2008	4/82	8/85		12.0 %	0.52 [0.16, 1.66]
Cardenas 2013	9/112	10/107		15.6 %	0.86 [0.36, 2.03]
Guan 2011	3/206	1/102		2.0 %	1.49 [0.16, 14.10]
Kim 2011	6/110	2/109		3.1 %	2.97 [0.61, 14.41]
Lesser 2004	4/82	3/97		4.2 %	1.58 [0.36, 6.84]
Moon 2010	2/162	1/78		2.1 %	0.96 [0.09, 10.46]
Ogawa 2010	0/97	6/98		9.9 %	0.08 [0.00, 1.36]
Satoh 2011	2/45	3/135		2.3 %	2.00 [0.35, 11.59]
Siddall 2006	3/70	1/67		1.6 %	2.87 [0.31, 26.92]
Simpson 2010	3/151	6/151		9.2 %	0.50 [0.13, 1.96]
Stacey 2008	1/91	1/90		1.5 %	0.99 [0.06, 15.57]
Tölle 2008	6/101	2/96		3.1 %	2.85 [0.59, 13.78]
van Seventer 2010	4/127	2/127		3.1 %	2.00 [0.37, 10.73]
Subtotal (95% CI)	**2045**	**1950**		**100.0 %**	**1.07 [0.77, 1.48]**
Total events: 70 (Pregabalin), 66 (Placebo)					
Heterogeneity: Chi^2 = 16.94, df = 15 (P = 0.32); I^2 =11%					
Test for overall effect: Z = 0.38 (P = 0.71)					



APPENDICES

Appendix 1. Methodological considerations for chronic pain

There have been several changes in how the efficacy of conventional and unconventional treatments is assessed in chronic painful conditions. The outcomes are now better defined, particularly with new criteria for what constitutes moderate or substantial benefit (Dworkin 2008); older trials may report only participants with 'any improvement'. Newer trials tend to be larger, avoiding problems from the random play of chance. Newer trials also tend to be of longer duration, 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 we are more aware of problems that may affect our overall assessment. Here we summarise some of the recent insights that must be considered in this new review.

- Pain results tend to have a U-shaped distribution rather than a bell-shaped distribution. This is true in acute pain (Moore 2011b), back pain (Moore 2010d), and arthritis (Moore 2010e), as well as in fibromyalgia (Straube 2010); 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.
- 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 of less than 12 weeks' duration, and especially those shorter than eight weeks, overestimate the effect of treatment (Moore 2010d); the effect is particularly strong for less effective analgesics, and this may also be relevant in neuropathic-type pain.
- The proportion of people 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 2010d; Moore 2010e; Moore 2013b; Moore 2014b; Straube 2008; Sultan 2008). The earlier Cochrane Review on 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.
- Individual patient analyses indicate that people who get good pain relief (moderate or better) derive major benefits in many other outcomes, affecting quality of life in a significant way (Moore 2010c; Moore 2014b).
- Imputation methods such as 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 2012a).

Appendix 2. CENTRAL search strategy (via CRSO)

Line	Search for	Hits
#1	pregabalin:TI,AB,KY	995
#2	lyrica:TI,AB,KY	24
#3	#1 OR #2	996
#4	MESH DESCRIPTOR Neuralgia EXPLODE ALL TREES	842
#5	MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL TREES	3290
#6	MESH DESCRIPTOR Somatosensory Disorders EXPLODE ALL TREES	872

(*Continued*)

#7	((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)):TI,AB,KY	4873
#8	((neur* or nerv*) adj6 (compress* or damag*)):TI,AB,KY	897
#9	#4 OR #5 OR #6 OR #7 OR #8	8725
#10	**#3 AND #9**	**288**

Appendix 3. MEDLINE search strategy (via Ovid)

1	pregabalin.mp.	2389
2	lyrica.mp.	80
3	1 or 2	2392
4	exp PAIN/	356863
5	exp PERIPHERAL NERVOUS SYSTEM DISEASES/	135728
6	exp SOMATOSENSORY DISORDERS/	19709
7	exp NEURALGIA/	172807
8	((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp	79025
9	((neur* or nerv*) adj6 (compress* or damag*)).mp.	56685
10	4 or 5 or 6 or 7 or 8 or 9	537225
11	randomized controlled trial.pt.	458970
12	controlled clinical trial.pt.	92322
13	randomized.ab.	358446
14	placebo.ab.	172075
15	drug therapy.fs.	2011207
16	randomly.ab.	248387

(*Continued*)

17	trial.ab.	371627
18	groups.ab.	1552778
19	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	3874260
20	3 and 10 and 19	1174
21	limit 20 to yr="2009 -Current"	952

Appendix 4. Embase search strategy (via Ovid)

1	pregabalin.mp.	11842
2	lyrica.mp.	1016
3	1 or 2	11847
4	exp PAIN/	1142952
5	exp PERIPHERAL NERVOUS SYSTEM DISEASES/	64021
6	exp SOMATOSENSORY DISORDERS/	86852
7	exp NEURALGIA/	94129
8	((pain* or discomfort*) adj10 (central or complex or rheumat* or muscl* or muscul* or myofasci* or nerv* or neuralg* or neuropath*)).mp	158407
9	((neur* or nerv*) adj6 (compress* or damag*)).mp.	86680
10	4 or 5 or 6 or 7 or 8 or 9	1319290
11	crossover-procedure/	55297
12	double-blind procedure/	149255
13	Randomized Controlled Trial/	500144
14	(random* or factorial* or crossover* or cross over* or cross-over* or placebo* or (doubl* adj blind*) or assign* or allocat*) .tw	1717434
15	11 or 12 or 13 or 14	1808859

(*Continued*)

16	3 and 10 and 15	1639
17	limit 16 to yr="2009 -Current"	1407

Appendix 5. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 12; Schünemann 2011b).

- **High:** randomised trials; or double-upgraded observational studies.
- **Moderate:** downgraded randomised trials; or upgraded observational studies.
- **Low:** double-downgraded randomised trials; or observational studies.
- **Very low:** triple-downgraded randomised trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence include the following.

- Limitations in the design and implementation of available studies, suggesting high likelihood of bias.
- Indirectness of evidence (indirect population, intervention, control, outcomes).
- Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
- Imprecision of results (wide confidence intervals).
- High probability of publication bias.

Factors that may increase the quality level of a body of evidence include the following.

- Large magnitude of effect.
- All plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect.
- Dose-response gradient.

Appendix 6. Risk of bias evaluations for EERW studies

This evaluation uses a proposed RoB assessment using additional criteria (Moore 2015c).

Baron 2010

Bias	Review authors' judgement	Support for judgement
Randomisation	Low risk	Central telephone system
Allocation concealment	Low risk	Central telephone system
Blinding	Low risk	Matching placebo
Duration	Unclear risk	5-Week double-blind phase
Outcome	Unclear risk	≥ 30% PIR to enter the DB phase. Any pain increase from randomisation deemed LOR
Incomplete outcome assessment	High risk	LOCF
Size	Unclear risk	50 to 199 participants per treatment arm

(*Continued*)

Tapering to placebo in double-blind phase	Low risk	1 week taper period after randomisation to placebo

Gilron 2011

Bias	**Review authors' judgement**	**Support for judgement**
Randomisation	Low risk	Computer generated
Allocation concealment	Low risk	Telerandomisation
Blinding	Low risk	Matching placebo
Duration	Unclear risk	Longer than 2-week double-blind phase
Outcome	Unclear risk	≥ 30% PIR to enter the DB phase, LOR judged by increased pain since randomisation, or discontinuation
Incomplete outcome assessment	High risk	LOCF
Size	Unclear risk	50 to 199 participants per treatment arm
Tapering to placebo in double-blind phase	Low risk	1-Week dose reduction period after randomisation to placebo

Hewitt 2011

Bias	**Review authors' judgement**	**Support for judgement**
Randomisation	Unclear risk	Method not described
Allocation concealment	Unclear risk	Method not described
Blinding	Unclear risk	Method not described
Duration	Unclear risk	5-Week double-blind phase
Outcome	Unclear risk	≥ 30% PIR to enter the DB phase, LOR judged by increased pain since randomisation, or discontinuation
Incomplete outcome assessment	High risk	LOCF for responder analysis; BOCF for loss of therapeutic response
Size	Unclear risk	50 to 199 participants per treatment arm

(*Continued*)

Tapering to placebo in double-blind phase	High risk	No obvious tapering

Huffman 2017

Bias	**Review authors' judgement**	**Support for judgement**
Randomisation	Low risk	Computer-generated code
Allocation concealment	Low risk	Interactive voice recognition
Blinding	Low risk	Matched placebo
Duration	Low risk	13-Week double-blind treatment
Outcome	Low risk	< 30% pain intensity compared with single-blind baseline, or discontinuation due to AE or LoE
Incomplete outcome assessment	Low risk	True responder for primary outcome of LTR; LOCF for mean data
Size	Low risk	> 200 participants per treatment arm
Tapering to placebo in double-blind phase	Low risk	1-Week blinded taper

Raskin 2014

Bias	**Review authors' judgement**	**Support for judgement**
Randomisation	Low risk	Computer-generated code
Allocation concealment	Unclear risk	Method not described
Blinding	Low risk	Matched placebo
Duration	Low risk	13-Week double-blind treatment
Outcome	Unclear risk	≥ 30% PIR to enter the DB phase, LOR judged as < 15% pain response relative to baseline
Incomplete outcome assessment	Unclear risk	LOCF for some outcomes, although sensitivity with BOCF and other imputations also used
Size	Unclear risk	50 to 199 participants per treatment arm

(*Continued*)

Tapering to placebo in double-blind phase	Low risk	1-Week blinded taper

WHAT'S NEW

Date	Event	Description
28 May 2019	Amended	Contact details updated.
25 January 2019	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 3, 2009

Date	Event	Description
30 April 2018	New search has been performed	Searches updated in April 2018. Thirty one new studies (8045 participants) added (45 studies and 11,906 participants included in total in the review); 17 studies excluded in total. Eight studies awaiting classification and 6 ongoing studies identified
30 April 2018	New citation required but conclusions have not changed	Background and Methods sections updated using a template for reviews of drugs for neuropathic pain, to reflect current thinking and current Cochrane standards. Risk of bias assessment expanded, GRADE used to judge the quality of the evidence, and 'Summary of findings' tables included
24 September 2010	Amended	Contact details updated
25 August 2009	Amended	Minor amendment to Analysis 2.2. Results and conclusions unchanged
10 November 2008	Amended	Published protocol converted to new review format

CONTRIBUTIONS OF AUTHORS

RAM and SD carried out searches, selected studies, and added new data to the review update; PW acted as adjudicator. All authors contributed to the final draft and approved the published version. RAM will be responsible for updates.

DECLARATIONS OF INTEREST

SD: none known.

RFB: none known. RFB is a retired specialist pain physician who has managed patients with neuropathic pain.

SS: none known. Sebastian Straube is a specialist occupational medicine physician.

PW: none known.

DA has received honoraria from Mundipharma and Grunenthal UK for presentations and expert opinion since 2015. DA is a pain physician who treats patients with neuropathic pain. He also works pro bono for various veterans charities in the UK.

RAM has received honoraria from Omega Pharma/Perrigo Pharma (2016, 2017), Futura Pharma (2015, 2016), RB (2015, 2017, 2018), and the Advertising Standards Authority (2016) for providing advice on trial and data analysis methods. He has received honoraria for lectures from Novartis (2016) and RB (2018).

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Funds, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2009 review

The main difference is that the review gave particular weight to efficacy criteria defined by the IMMPACT Study Group (Dworkin 2008), which were published after the protocol was prepared. We completed a risk of bias table. We carried out a post hoc sensitivity analysis for trials lasting eight weeks or longer based on increasing indications that trial duration affects efficacy estimates (Moore 2010e).

2018 update

We updated the Background and Methods sections using a template for reviews of drugs for neuropathic pain, to reflect current thinking and current Cochrane standards, and to comply with requirements of the current neuropathic pain template. In Types of studies, we accepted abstracted results with sufficient data to make judgements about studies - usually studies reported on the Internet. Neuropathic pain diagnostic criteria have been updated, and this review reflects that update. We did not use one secondary outcome - that of any pain-related outcome indicating some improvement - as this is not of importance to people with neuropathic pain (Moore 2013a; Moore 2013c).

We have expanded the Assessment of risk of bias in included studies, used GRADE to judge the quality of evidence, and included 'Summary of findings' tables. We have imposed a minimum of 25 participants per treatment arm, and two studies and 200 participants for analyses. These changes reflect several methodological improvements made since 2009, so this update uses similar methods as other reviews on neuropathic pain.

Because of the large number of individual neuropathic pain conditions, and because most evidence derives from PHN and PDN, we decided to use 'SoF' tables for these conditions only when analyses were performed for a given dose of pregabalin in that condition. This avoided a large number of SoF tables devoid of any information. We placed analyses for any adverse event and serious adverse event data in a separate 'SoF' table because these analyses used data from all studies and doses, across all conditions.

We included EERW studies, which had not been foreseen in the protocol. We provided additional methods describing how we dealt with them.

NOTES

No new studies likely to change the conclusions are expected in the next five years. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this time if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Analgesics [administration & dosage; adverse effects; *therapeutic use]; Chronic Disease; Diabetic Neuropathies [*drug therapy]; Dizziness [chemically induced]; Neuralgia [*drug therapy]; Neuralgia, Postherpetic [*drug therapy]; Pain [*drug therapy]; Pregabalin [administration & dosage; adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Sleepiness

MeSH check words

Adult; Humans