Drug Class Review
on
Drugs for Neuropathic Pain

Final Report

October 2007

The Agency for Healthcare Research and Quality has not yet seen or approved this report

A literature scan of the topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date.

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INTRODUCTION

Neuropathic pain (NP) is defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system."[1] NP can occur because of dysfunction or disease of the nervous system at the peripheral and/or central level.[2] NP can be very severe and disabling, with significant functional, psychological, and social consequences. Regardless of the underlying cause of NP, common treatment goals are to decrease pain and/or improve function.

NP is often classified by etiology or by the presumed site of neurologic involvement (central or peripheral). However, both peripheral and central nervous system lesions may contribute to most types of chronic NP.[3] More complex classification systems based on symptoms, signs, anatomical distribution, or hypotheses regarding etiologies have been proposed, but it is not clear if such classifications are accurate or reproducible. A mechanistic classification may be the preferred approach, but current knowledge of the pathophysiology of NP is incomplete, and multiple mechanisms may be involved.[4]

NP is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching, or shooting. The pain may be provoked by normally innocuous stimuli (allodynia). NP is also commonly associated with hyperalgesia (increased pain intensity evoked by normally painful stimuli), paresthesia, and dysesthesia.[4]

Up to 3% of the general population reports NP at some time.[5] The prevalence of different types of NP varies widely.[6] NP is most commonly associated with painful diabetic neuropathy, post-herpetic neuralgia (PHN), or lumbar nerve root compression.[6] Diabetic neuropathy occurs in approximately 10% of persons with diabetes.[7] Prevalence of diabetic neuropathy increases with age, worsening glycemic control, and duration of diabetes. The most common form of diabetic peripheral neuropathy is a distal symmetric polyneuropathy.[8] PHN is defined as pain persisting or recurring at the site of acute herpes zoster 3 or more months after the acute episode.[9] It occurs in up to 25% of patients following an episode of shingles.[10] Symptomatic spinal stenosis and lumbar disc herniation with nerve root compression occur in approximately 3% and 4% of patients with low back pain, respectively.[11] Other causes of NP include cancer-related pain, spinal cord injury, post-stroke pain, HIV-associated neuropathy, and phantom limb pain. Uncommon but potentially debilitating NP conditions include trigeminal neuralgia (incidence 4/100,000 population).[12] In the U.S., health care and disability-related costs associated with NP are estimated at almost $40 billion annually.[13]

A number of medications (oral or topical) are available for treating NP (Table 1, Included Drugs). Some medications may act by decreasing nerve excitability and conduction in sensory axons. Others may have effects on neural damage-related synaptic changes (particularly for central pain). However, the mechanism of action for various drugs varies substantially and in some cases is not well understood. For example, antiepileptic drugs may target peripheral and/or central sensitization mechanisms involved in NP, but the exact mechanisms of action are uncertain.[12] Topical lidocaine, on the other hand, blocks sodium channels, which may stabilize nerve membranes.[14]

Choosing therapy for NP is challenging because of the large number of medications available to treat this condition and potential differences between medications in effectiveness or harms (Table 1). The objective of this study is to review evidence on comparative effectiveness of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or gel), including the comparative effectiveness of these medications compared to other medications for NP (defined in this review as tricyclic antidepressants, other antiepileptic medications [carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid and derivatives], selective serotonin reuptake inhibitors, and dextromethorphan). The medications gabapentin, pregabalin, duloxetine, and lidocaine patch were chosen as the main focus of this review because they have been approved by the US Food and Drug Administration (FDA) for treatment of diabetic neuropathy or PHN. Venlafaxine was chosen because it is similar in structure and mechanism of action to duloxetine and lidocaine gel chosen because of its similarities to the lidocaine patch. The other drugs included in this review have been used but are not FDA-approved for treatment of neuropathic pain, with the exception of carbamazepine, which was approved for trigeminal neuralgia based on trials published in the 1960's. Simple analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids were not included in this review. However, NSAIDs and opioids for chronic pain, including neuropathic pain, are addressed in separate Drug Effectiveness Review Project[15] reviews available at http://www.ohsu.edu/drugeffectiveness/reports/final.cfm.

Table 1. Included drugs

Drug	Trade Name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain	Range of daily doses used in RCTs of neuropathic pain (median)	FDA warnings/cautions*
Gabapentin, pregabalin, SNRIs, and topical lidocaine patch or gel					
Antiepileptics					
Gabapentin	Neurontin®	Postherpetic neuralgia	Start at 300 mg, titrate to 900 mg, increase up to 1800 mg (divided TID)	900-3600 mg (1800 mg)	Central nervous system adverse events in pediatric patients with epilepsy.
Pregabalin	Lyrica®	Diabetic neuropathy Postherpetic neuralgia	Diabetic neuropathy: Start at 150 mg, increase up to 300 mg (divided TID) Postherpetic neuralgia: Start at 150 mg, increase up to 75 to 150 mg BID, or 50 to 100 mg TID in patients with creatinine clearance of at least 60 mL/min	75-600 mg (300 mg)	Angioedema, hypersensitivity reactions
SNRI antidepressants					
Duloxetine	Cymbalta®	Diabetic neuropathy	60 mg once daily; consider lower starting dose and gradual increase in patients with renal impairment	20-120 mg (90 mg)	Increased suicidality in children, adolescents, and young adults with major depressive disorder and other psychiatric conditions. Risk of serotonin syndrome when SNRIs and triptans are used together.
Venlafaxine	Effexor® Effexor XR®	None	NA	37.5-225 mg (75 mg)	
Topical analgesic					
Lidocaine patch 5%	Lidoderm®	Postherpetic neuralgia	Up to 3 patches for up to 12 hours within a 24-hour period	5%, up to 3 patches	Accidental exposure in children Excessive dosing by applying patch longer than or to a larger area than recommended
Lidocaine topical gel 5%	Anestacon® Xylocaine®	None	NA	5%	
Other medications for neuropathic pain					

Drug	Trade Name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain	Range of daily doses used in RCTs of neuropathic pain (median)	FDA warnings/cautions*
Antiepileptics					
Carbamazepine	Tegretol® Tegretol XR®	Trigeminal neuralgia	Start at 100 mg BID, increase up to a maximum of 1200 mg daily (divided BID). Most patients are maintained on 400-800 mg daily. Attempt to reduce dose to minimum effective level, or discontinue, at least every 3 months.	500-2400 mg (1000 mg)	
Lamotrigine	Lamictal®	None	NA	200-600 mg (350 mg)	Teratogenicity: Possible risk of cleft lip or palate
Topiramate	Topamax®	None	NA	75-600 mg (258 mg)	Use is associated with metabolic acidosis
Oxcarbazepine	Trileptal®	None	NA	600-1800 mg (900 mg)	Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN
Valproic acid/divalproex	Depakote® Depakene®	None	NA	600-2400 mg (1000 mg)	BOXED WARNING: Teratogenicity
Tricyclic antidepressants					
Amitriptyline	Elavil®	None	NA	10-150 mg (70 mg)	Increased suicidality in patients with depression
Desipramine	Norpramin®	None	NA	50-200 mg (184 mg)	
Nortriptyline	Pamelor®	None	NA	25-100 mg	
Imipramine	Tofranil®	None	NA	50-150 mg (75 mg)	
Doxepin	Sinequan®	None	NA	No trials	
SSRI antidepressants					
Citalopram	Celexa®	None	NA	40 mg	Increased suicidality in patients with depression
Fluoxetine	Prozac®	None	NA	40 mg	
Paroxetine	Paxil®	None	NA	No trials	
Sertraline	Zoloft®	None	NA	No trials	
Escitalopram	Lexapro®	None	NA	No trials	
NMDA receptor antagonist					
Dextromethorphan	Several	None	NA	40.5-439 mg (270 mg)	BOXED WARNING: Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events.

Drug	Trade Name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain	Range of daily doses used in RCTs of neuropathic pain (median)	FDA warnings/cautions*
					FDA notification: There have been five recently reported deaths of teenagers that may be associated with the abuse/ over-consumption of powdered dextromethorphan sold in capsules

*Please see package inserts and FDA labeling information for more detailed and specific cautions and black box warnings for medications included in this review.

Scope and Key Questions

The purpose of this review is to compare the effectiveness and harms of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or gel) for neuropathic pain. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in DERP. The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine (patch or gel) versus each other for neuropathic pain?

2. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, or topical lidocaine (patch or gel) versus other drugs (other antiepileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

3. What are the comparative harms of pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel) for neuropathic pain?

4. What are the comparative harms of pregabalin, gabapentin, SNRIs, or topical lidocaine (patch or gel) versus other drugs (other antiepileptics, tricyclic antidepressants (including tertiary versus secondary amines), selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

5. What are the comparative effectiveness and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine (patch or gel) plus a tricyclic antidepressant or another antiepileptic versus monotherapy with a tricyclic antidepressant or another antiepileptic?

6. Are there differences in effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions?

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® (1966 to November Week 3 2006), the Cochrane Database of Systematic Reviews® (4th Quarter 2006), the Cochrane Central Register of Controlled Trials® (4th Quarter 2006), and the Database of Abstracts of Reviews of Effects (4th Quarter 2006), using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). Electronic database searches were supplemented by hand searches of reference lists of included studies and reviews. In addition, we searched the FDA's Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technology in Health, the National Institute for Health and Clinical Excellence web sites for

medical or statistical reviews and technology assessments. Finally, we searched dossiers of published and unpublished studies submitted by pharmaceutical companies. All citations were imported into an electronic database (Endnote® v.9.0).

Study Selection

All citations were reviewed for inclusion using the criteria shown in Table 2. Two reviewers independently assessed titles and abstracts of citations identified from literature searches. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by two reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form (e.g. as a conference proceeding) were not included because they typically provide insufficient detail to perform adequate quality assessment. In addition, results of studies can change substantially between initial presentation at a conference and final journal publication.[16]

Table 2. Study inclusion criteria

Populations
Adults with neuropathic pain, including:
• Painful diabetic neuropathy
• Post herpetic neuralgia
• Trigeminal neuralgia
• Cancer related neuropathic pain
• HIV related neuropathic pain
• Central/post-stroke neuropathic pain
• Neuropathy associated with low back pain
• Peripheral nerve injury pain
• Phantom limb pain
• Guillain Barre syndrome
• Polyneuropathy
• Spinal cord injury related pain
Effectiveness outcomes
• Response (including patient reported pain relief, patient reported global impression of clinical change, pain on movement, pain on rest, any other pain related measure)
• Use of rescue analgesics
• Functional capacity (quality of life, work productivity)
• Speed and duration of response
• Relapse
Harms outcomes
• Overall adverse events
• Withdrawals
• Withdrawals due to adverse events
• Serious adverse events (including mortality, arrhythmias, seizures, overdose)

• Specific adverse events or withdrawals due to specific adverse events (including, but not limited to, hepatic, renal, hematologic, dermatologic, sedation/drowsiness, and other neurologic side effects)
Study designs
1. For effectiveness, controlled clinical trials, good or fair quality systematic reviews, comparative observational studies.
2. For harms, in addition to controlled trials and systematic reviews, controlled or long-term observational studies.
Additional criteria for systematic reviews
Literature searches performed in or after 2003.

Data Abstraction

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. The following data were abstracted by two independent reviewers from included trials: study design; setting; population characteristics (including gender, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. We considered methods to meet criteria for intention-to-treat analysis if outcomes for at least 95% of participants were analyzed according to the group to which they were originally assigned. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data to perform these calculations were available. For crossover trials, we abstracted results from both crossover periods.[17] If this data was not available, we abstracted results from the first intervention period.

For included systematic reviews, we abstracted the databases searched, study eligibility criteria, number of studies and patients represented, characteristics of included studies, data synthesis methods, main efficacy and safety results, and any subgroup analyses.

Validity Assessment

We assessed the internal validity (quality) of trials using the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[18, 19] We rated the internal validity of each trial based on use of adequate methods for randomization, allocation concealment, and blinding; similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; absence of high or differential loss to follow-up; and use of intention-to-treat analysis. We also rated whether trials adequately described methods and criteria for identifying and classifying adverse events. Trials that had a "fatal flaw" were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the

results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. We defined a "fatal flaw" as a very serious methodological shortcoming or a combination of methodological shortcomings that is highly likely to lead to biased or uninterpretable results. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source. Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive two different ratings: one for effectiveness and another for adverse events.

We assessed the internal validity of systematic reviews using pre-defined criteria developed by Oxman and Guyatt (See Appendix C).[20] These included adequacy of literature search and study selection methods, methods of assessing validity of included trials, methods used to combine studies, and validity of conclusions. Systematic reviews of pain interventions scoring four or lower (maximum score seven) using the Oxman criteria have been shown to be more likely to report positive conclusions.[21, 22] We classified systematic reviews scoring less than or equal to four lower-quality and systematic reviews scoring more than four higher-quality.

Data Synthesis

We assigned an overall strength of evidence (good, fair or poor) for a particular body of evidence based on the quality, consistency, and power of the set of studies. A body of evidence consisting of multiple good-quality, consistent, head-to-head trials with at least some studies evaluating larger sample sizes would generally be rated good-quality. A body of evidence consisting of a few poor-quality, small trials with inconsistent results would be rated poor-quality. Such evidence is unreliable for drawing conclusions about benefits or harms. Other factors that could result in downgrading of a body of evidence from good to fair (or poor) include high likelihood of publication bias or selective outcomes reporting bias, unexplained statistical heterogeneity, or primarily relying on indirect evidence (i.e. lack of head-to-head trials).

In addition to qualitative synthesis, we also performed meta-analyses when two or more trials of a medication (or medication class) reported an outcome related to pain relief, functional status, or adverse events. We pooled results for each individual medication included in this review except in the case of SSRIs, tricyclic antidepressants and the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, valproic acid, and topiramate, unless stratified analyses suggested differences between tertiary versus secondary amine tricyclics or for individual antiepileptic drugs. We used this strategy in order to help limit the number of comparisons in this review and because relatively few trials were available for individual antiepileptic drugs and SSRIs.

Our main outcome was the proportion of patients reporting significant pain relief. We defined significant pain relief as at least 50% improvement in pain score compared to baseline (preferred outcome) or the proportion reporting at least moderate improvement in pain or global efficacy on a categorical scale. We also analyzed mean improvement or mean difference in pain scores using various scales (standardized to a 0 to 10 scale) and mean improvement in the Short-Form

McGill Pain Questionnaire, Total Score (0 to 45 scale). For functional status, we pooled data on SF-36 scores, Bodily Pain Index Interference scores, and Euro QoL scores. For adverse events, we pooled data on overall withdrawals, withdrawals due to adverse events, somnolence (including sedation, tiredness, fatigue, or lethargy), gait disturbances (including ataxia and incoordination), dizziness or vertigo, dry mouth, and "serious" adverse events. There was insufficient data to analyze hepatic, renal, hematologic, and dermatologic adverse events.

We estimated pooled relative risks (for categorical outcomes) or weighted mean differences (for continuous outcomes) and 95% confidence intervals using the DerSimonian-Laird method in a random effects model.[23] We chose the random effects model because trials differed in patient populations, dosing of drugs, and other factors. Statistical heterogeneity was assessed by calculating the Q-statistic and the percent of the total variance due to between study variability (I^2 statistic).[24] Relative risks, weighted mean differences, and confidence intervals were calculated using the meta package in R.[25] Forest plots were generated using RevMan 4.2.8 (Review Manager 4.2 for Windows, The Nordic Cochrane Centre, Copenhagen, Denmark). When six of more trials were available for a particular analysis, we produced funnel plots showing estimates of treatment effect versus standard errors (a measure of sample size) from individual trials and performed the Egger test to assess for funnel plot asymmetry.[26] Funnel plot asymmetry, which occurs when trials with smaller sample sizes report larger estimates of treatment effect than trials with larger sample sizes, can be due to publication bias, though it can also occur when statistical heterogeneity, clinical diversity, or poor-quality trials are present.[27]

Because head-to-head data were sparse, we also performed adjusted indirect comparisons using the method described by Bucher et al.[28] With this method, we calculated indirect relative risks (RR_{Ind}) for one drug (drug A) versus a second drug (drug B) for each of the outcomes, adjusted by the results of the direct-meta-analyses where each drug was compared against placebo:

$$RR_{Ind} = RR_{Drug\ A\ vs\ Placebo} / RR_{Drug\ B\ vs\ Placebo}.$$

The variance was estimated as:

$$Var\ (\ln RR_{Ind}) = Var\ (\ln RR_{Drug\ A\ vs\ Placebo}) + Var\ (\ln RR_{Drug\ B\ vs\ Placebo}).$$

We performed adjusted indirect comparisons for gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or gel) versus one another, as well as each of these medications versus other medications (tricyclic antidepressants, other antiepileptic medications, SSRIs, and dextromethorphan) for neuropathic pain. In theory, trials that compare two or more included drugs to a common comparator (usually placebo) can provide indirect evidence about comparative effectiveness while preserving some of the benefits of randomization.[28, 29] "Adjusted" indirect methods also incorporate the uncertainty that occurs when combining different sets of trials by adding together the variance from both sets of trials, resulting in less precise estimates of treatment effects compared to analyses based on the same number of similarly sized head-to-head trials.[28, 29] Although indirect comparisons usually agree with direct comparisons, large discrepancies have been reported in some cases.[30, 31] The validity of indirect analyses depends on how well the critical assumption of similarity of treatment effects across all studies is met. This assumption can be violated when there are methodological shortcomings in

some or all of the trials or when there is clinical diversity in trial populations, interventions (e.g., different durations of therapy or non-equivalent dosing), or assessment of outcomes. As one method for testing assumptions regarding similarity of treatment effects, we compared rates of response to placebo across different sets of trials included in indirect analyses.

To assess stability of estimates and conclusions and to evaluate for sources of heterogeneity (when detected), we performed several subgroup and sensitivity analyses. To evaluate potential effects of study design factors, we re-analyzed results after excluding trials rated poor quality. We also compared results of trials using a crossover design versus those using a parallel-group design. To evaluate whether response to medications varies depending on the specific type of neuropathic pain, we analyzed results after excluding trials of patients with trigeminal neuralgia and HIV-associated neuropathy (neuropathic pain conditions which may be more difficult to treat), and we performed subgroup analyses on trials evaluating patients with diabetic neuropathy or post-herpetic neuralgia (conditions evaluated in the largest number of trials, see Key Question 6). To assess effects of differential dosing, we analyzed results after excluding gabapentin trials that titrated patients to less than 2400 mg/day, pregabalin trials evaluating less than 300 mg/day, venlafaxine trials evaluating less than 150 mg/day, and duloxetine trials evaluating less than 60 mg/day. For trials of pregabalin and gabapentin, we also re-analyzed results after excluding trials that did not enroll previous non-responders to gabapentin. To assess effects of active placebo (such as benztropine) versus inert placebo on assessments of adverse events, we performed an analysis stratified by type of placebo. When funnel plot asymmetry was detected, we performed sensitivity analyses by adjusting estimates using the trim and fill method.[32]

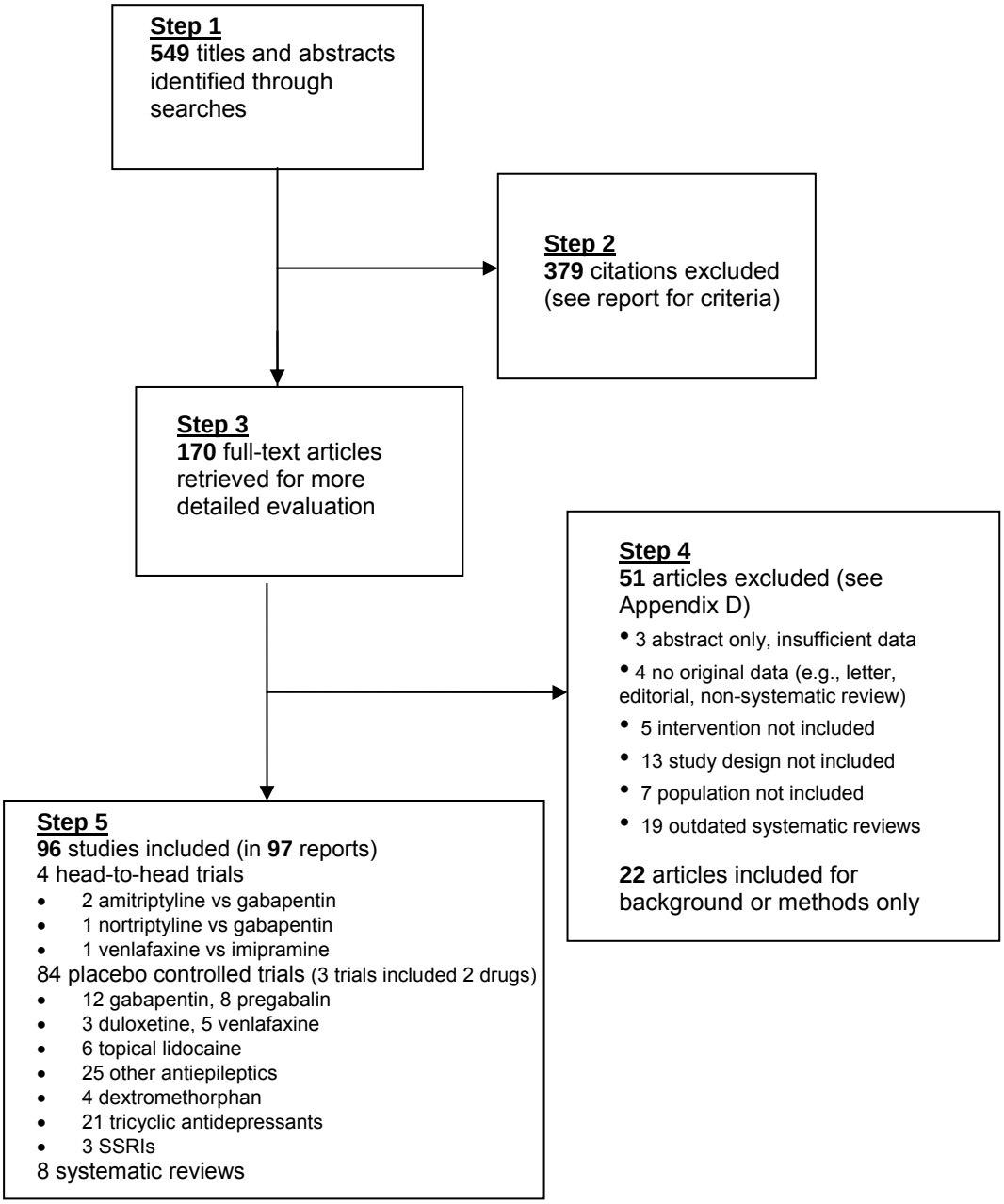
When results from direct and indirect estimates were available for a particular comparison and outcome, we measured the discrepancy between estimates by calculating the difference in log relative risks, and we deemed a p value of less than 0.05 statistically significant (as described by Song and colleagues[31]).

RESULTS

Overview

Figure 1 shows the flow of studies from initial results of literature searches to final inclusion or exclusion. Literature searches identified 545 citations, and 169 of these appeared potentially relevant. After review of the full text of these169, we included 96 studies: 88 reports of randomized controlled trials (in 90 articles), and 8 systematic reviews. We identified no controlled observational studies provided information on long-term benefits or harms. Excluded systematic reviews and trials are listed in Appendix D.

Figure 1. Literature search results



Results of Search: Systematic Reviews

We identified eight systematic reviews of medications for neuropathic pain that met inclusion criteria (Table 3 and Evidence Table 1).[2, 12, 33-38] Three reviews were rated higher-quality (score 5 or higher) and 5 reviews lower-quality (score 4 or below) using the Oxman criteria (Evidence Table 2). The systematic reviews varied considerably in scope. Four reviews focused on one drug (gabapentin, lidocaine, carbamazepine, or lamotrigine),[12, 35-37] one focused on antidepressants,[2] and three covered various classes of drugs.[33, 34, 38] Two reviews only included studies of patients with postherpetic neuralgia[34, 35], one review only included studies of patients with diabetic neuropathy,[38] and the remainder included studies of patients with any type of neuropathic pain. Per our inclusion criteria, all of the reviews conducted literature searches through 2003 or later.

Table 3. Overview of recent systematic reviews of drugs for neuropathic pain

Study (Quality score using Oxman criteria)	Populations/ Drugs included	Range of sample sizes (median)	Range of durations (median)	Literature search dates	Main conclusions
Finnerup, 2005[33] (5)	Any neuropathic pain Tricyclics, SSRIs, older antiepileptics, venlafaxine, gabapentin, pregabalin, topical lidocaine, dextromethorphan, others	9 to 1259 (31)	Not reported	1966-April 2005	For pain relief: TCAs> opioids>tramadol> gabapentin/pregabalin For both pain relief and quality of life measures, no data for older drugs (TCA, carbamazepine, phenytoin): gabapentin/pregabalin>tramadol>opioids>TCAs For lidocaine patch, efficacy in postherpetic neuralgia and allodynia. High-dose dextromethorphan effective in diabetic neuropathy, but not postherpetic neuralgia.
Hempenstall, 2005[34] (7)	Postherpetic neuralgia Gabapentin, pregabalin, lidocaine patch, dextromethorphan	18 to 334 (45)	Single session to 9 weeks (6 weeks)	1966-October 2004	Evidence of efficacy (i.e., NNT<5.00) for all.
Khaliq, 2007[35] (6)	Postherpetic neuralgia Lidocaine	35-150 (47)	24 hours (2 trials) to 4 weeks (1 trial)	1966-November 2006	Insufficient evidence to recommend.
Saarto, 2005[2] (4)	Any neuropathic pain Anti-depressants (tricyclics, SSRIs, venlafaxine, others)	10-235 (35)	2 weeks to 14 weeks (6 weeks)	1966-Dec 2003	Tricyclic antidepressants are effective for a variety of neuropathic pains; best evidence is for amitriptyline; limited data of effectiveness of SSRIs, for venlafaxine, studies too small for any firm conclusions to be made.
Wiffen, 2005[12] (4)	Any neuropathic pain Gabapentin	14-334 (40)	1 week to 12 weeks (6 weeks)	1966-November 2004	Effective in neuropathic pain.
Wiffen, 2005[36] (4)	Any neuropathic pain Carbamazepine	9-77 (29)	3 days to 8 weeks (4 weeks)	1966-November 2004	Evidence of efficacy but trials are small.
Wiffen, 2005[37]	Any neuropathic pain	14-227 (42)	2 weeks-14 weeks	1966- August 2006	Limited evidence suggests that lamotrigine is unlikely to be of benefit.

Study (Quality score using Oxman criteria)	Populations/ Drugs included	Range of sample sizes (median)	Range of durations (median)	Literature search dates	Main conclusions
(6)	Lamotrigine		(8 weeks)		
Wong, 2007[38] (5)	Painful diabetic neuropathy Antidepressants, antiepileptics, others	14-457 (59)	2 weeks to 16 weeks (6 weeks)	1966-October 2006	Oral tricyclic antidepressants and traditional antiepileptics are better for short term pain relief than newer generation antiepileptics. Evidence of long term effects of oral antidepressants and antiepileptics is lacking.

SSRI=selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant

Results of Search: Randomized Trials

We identified no head-to-head trials comparing gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or gel) versus each other for NP. Four small (sample sizes 25 to 70), fair-quality head-to-head trials compared one of these drugs versus a tricyclic antidepressant.[39-42] Two trials compared gabapentin to amitriptyline in patients with diabetic neuropathy,[40, 41] one trial compared gabapentin to nortriptyline for post-herpetic neuralgia,[39] and one trial compared venlafaxine to imipramine or placebo in patients with polyneuropathy due to a variety of conditions.[42] Two trials used a crossover design.[41, 42] Duration of therapy ranged from four to twelve weeks.

We identified a total of 34 placebo-controlled trials of gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) for neuropathic pain (Evidence Tables 3-7) and 52 placebo-controlled trials of other medications (tricyclic antidepressants, other antiepileptic medications, SSRI's, or dextromethorphan) for neuropathic pain (Evidence Tables 8-10). Fifty-five percent were crossover trials and the remainder parallel-group. Thirty trials (35%) evaluated patients with diabetic neuropathy, 16% postherpetic neuralgia, 17% central neuropathic pain, 1% radiculopathy, 12% unspecified or mixed neuropathic pain, and 19% other specific NP conditions (including 7% HIV-associated neuropathy and 7% trigeminal neuralgia). Sample sizes of placebo-controlled trials of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine ranged from 7 to 457 (median 80), and for other medications for NP ranged from 3 to 1269 (median 30). Most trials were short-term, with a median duration of therapy of 6 weeks (range 24 hours to 18 weeks).

Overview of methodological quality of included trials

Details of our quality assessment of included randomized controlled trials are shown in Evidence Table 11. No trial was rated good quality. The four head-to-head trials were rated fair quality, as were 68 of 84 placebo-controlled trials (81.0%). Sixteen placebo-controlled trials were rated poor quality (Table 4).

Table 4. Overview of included placebo-controlled trials

Drug Class	Diabetic neuropathy	Post-herpetic neuralgia	Other neuropathic pain	Totals	Quality
Gabapentin, pregabalin, SNRIs, and topical lidocaine (patch or gel)					
Gabapentin	3	2	7	12	11 Fair 1 Poor
Pregabalin	3	3	2	8	8 Fair
Duloxetine	3	0	0	3	3 Fair
Venlafaxine	2	0	3	5*	3 Fair 2 Poor
Lidocaine patch	0	3	1	3	2 Fair 2 Poor
Lidocaine gel	0	1	1	2	2 Fair
Totals (gabapentin, pregabalin, SNRIs, lidocaine patch or gel)	**11**	**9**	**14**	**34**	**29 Fair** **5 Poor**
Other medications for neuropathic pain					
Tricyclic antidepressants	8	4	9	21*	17 Fair 4 Poor
SSRIs	3	0	0	3	2 Fair 1 Poor
Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	9	0	16	25	17 Fair 8 Poor
Dextromethorphan	1	1	2	4	4 Fair
Totals (tricyclic antidepressants, SSRIs, carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid, and dextromethorphan)	**21**	**5**	**27**	**53***	**40 Fair** **13 Poor**

*Includes one head-to-head trial of imipramine vs venlafaxine with a placebo arm[42]

Effectiveness versus efficacy and funding source

We considered all of the trials included in this report efficacy studies, as none met all criteria for effectiveness studies.[43] The trials generally applied numerous inclusion criteria, were conducted in specialty settings, used rigid dosing regimens, and evaluated relatively short-term and poorly standardized outcomes. Sixty-four of 87 trials reported a funding source. Nearly all of the trials that reported funding information were sponsored by a pharmaceutical company.

Key Question 1. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel) to each other for neuropathic pain?

Summary of findings

We identified no head-to-head trials comparing gabapentin, pregabalin, an SNRI, or topical lidocaine (patch or gel) to each other. Gabapentin was consistently more effective than placebo for pain relief or improvement in function in 12 placebo-controlled trials. Pregabalin (eight trials) and duloxetine (three trials) were also consistently more effective than placebo. Trials of topical lidocaine (patch and gel) and venlafaxine versus placebo were inconsistent or showed no clear benefit. Adjusted indirect analyses of placebo-controlled trials found gabapentin, duloxetine, and venlafaxine similarly effective for pain relief and improvement in function compared to one another. Pregabalin was moderately superior to duloxetine for the proportion of patients experiencing significant pain relief, but there were no differences between pregabalin and gabapentin or venlafaxine. Stratified and subgroup analyses of trials according to use of crossover versus parallel-group design, dose, or exclusion of previous non-responders to gabapentin (for trials of gabapentin or pregabalin) did not affect conclusions. Trials were characterized by different methods for assessing and reporting outcomes, which limited the number of trials that could be pooled for some comparisons. There were no suitable data from placebo-controlled trials of topical lidocaine (patch or gel) to perform indirect analyses.

Detailed assessment

Systematic reviews

Six systematic reviews evaluated benefits of gabapentin, pregabalin, SNRIs, or topical lidocaine for NP, but differed in how they selected trials for inclusion and in how they analyzed and synthesized data (Table 5 (overview of SR's section).[2, 12, 33-35, 38] None of the systematic reviews included any head-to-head trial of one of these drugs versus another. The systematic reviews included a total of 17 unique placebo-controlled trials of gabapentin, 5 trials of pregabalin, 3 trials of venlafaxine, 6 trials of topical lidocaine, and 2 trials of duloxetine. All of the newer medications for NP were superior to placebo in at least one systematic review. In general, however, the usefulness of published systematic reviews for assessing comparative benefits of newer medications for NP is limited because they all primarily focused on placebo-controlled trials and did not attempt formal indirect analyses. In addition, estimates of treatment benefit were fairly imprecise (relatively wide confidence intervals) for some medications included in the reviews because of small numbers of trials (frequently with small sample sizes).

In reviews in which data were pooled, the most frequently calculated estimate of effect was the NNT to achieve a minimum threshold of pain or symptom relief. Because trials varied substantially in how they reported pain outcomes, three reviews calculated pooled estimates for clinically relevant pain relief based on a composite 'hierarchy' of outcomes.[12, 33, 34] For example, one systematic review of gabapentin calculated NNT using the following hierarchy of outcomes: proportion reporting pain relief 50% or greater (preferred outcome), followed by proportion reporting global impression of clinical change, pain on movement, pain on rest, or any other pain related measure.[12] Another used the following hierarchy: proportion reporting pain relief 50% or greater, or proportion reporting at least good pain relief or reporting improvement.[33]

Table 5. Summary of results of recent systematic reviews of gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) for neuropathic pain

Drug	Total # of unique trials	Review	# of included trials	# of trials not included in any other relevant systematic review	Outcome	Benefit vs placebo NNT (95% CI) (unless other outcome specified)	# of trials for pooled estimates
Gabapentin or pregabalin studies (results pooled for both medications)	22	Finnerup, 2005[33]	Gaba: 17 Pregab: 5	Gaba: 0 Pregab: 1	>50% pain relief, or proportion reporting at least good pain relief or reporting improvement (hierarchy of outcomes)	Any NP: 4.7 (4.0-5.6) DN: 3.9 (3.2–5.1) PHN: 4.6 (3.7–6.0)	Any NP: 12 DN: 6 PHN: 4
Gabapentin	17	Hempenstall; 2005[34]	2	0	Top two values on a five-point scale for pain relief, effectiveness, or improvement, top three values on a six-point scale, top value on a three-point scale, top two values on a four-point scale, 50% or greater reduction on a visual analogue or 11-point scale (hierarchy of outcomes)	PHN: 4.4 (3.3-6.1)	2
		Wiffen, 2005[12]	13	0	>50% pain relief, global impression of clinical change, pain on movement, pain on rest, any other pain related measure (hierarchy of outcomes)	DN: 2.9 (2.2-4.3) PHN: 3.9 (3.0-5.7)	DN:4 PHN: 2
Pregabalin	5	Hempenstall; 2005[34]	2	0	See Hempenstall above	PHN: 4.9 (3.7-7.6)	2
Duloxetine	2	Wong, 2007[38]	2	2	>50% pain relief (defined as number of patients with ‘moderate,’ ‘good,’ or ‘notable’ improvement in global	DN: OR=2.6 (1.7-3.8)	2

Drug	Total # of unique trials	Review	# of included trials	# of trials not included in any other relevant systematic review	Outcome	Benefit vs placebo NNT (95% CI) (unless other outcome specified)	# of trials for pooled estimates
					assessment of treatment or at least moderate pain relief on a categorical scale)		
Venlafaxine	3	Finnerup, 2005[33]	3	1	See Finnerup above	Any NP: 5.5 (3.4-14)	3
		Saarto, 2005[2]	2	0	Moderate pain relief or better	No pooling of data; studies too small for any firm conclusions to be made	NA
Topical lidocaine	6	Finnerup, 2005[33]	4	2	See Finnerup above	Any NP: 4.4 (2.5-17)	4
		Hempenstall, 2005[34]	3	1	See Hempenstall above	PHN: 2.00 (1.4-3.3)	1
		Khalig, 2007[35]	3	1	Improvement in pain relief on a 6-point scale.	Any NP: WMD=0.42 (95% CI 0.14 to 0.69)	2

DN=diabetic neuropathy, PHN=post-herpetic neuralgia, NP=neuropathic pain, WMD=weighted mean difference, OR=odds ratio

Three systematic reviews (two rated higher-quality[33, 34]) found gabapentin or pregabalin more effective than placebo for pain relief.[12] In general, confidence intervals for estimates of benefits for the two drugs overlapped in all of the systematic reviews. The NNTs for pain relief in short-term follow-up ranged from 2.9 to 3.9 for gabapentin in diabetic nephropathy and 3.9 to 4.6 for gabapentin in postherpetic neuralgia, and was 4.9 for pregabalin in postherpetic neuralgia. One systematic review pooled data for gabapentin and pregabalin together.[33] We calculated separate relative risks for pregabalin and gabapentin from individual trial data as reported in this systematic review. Relative risk for 50% pain relief was 2.07 (95% CI 1.70 to 2.52) for gabapentin and 2.60 (95% CI 2.04 to 3.32) for pregabalin (NNTs about 4.2 and 5, respectively).

Two systematic reviews (one higher-quality[33]) evaluated the SNRI venlafaxine.[2] The pooled NNT for the composite outcome pain relief was 5.5 (95% CI 3.4 to 14.0) for venlafaxine versus placebo in the higher-quality review.[33] The other, qualitative systematic review found insufficient data (small studies with imprecise estimates) to reach conclusions about efficacy of venlafaxine.[2] One higher-quality systematic review found duloxetine superior to placebo for achieving 50% pain relief (two trials, OR=2.6, 95% CI 1.7 to 3.8).[38]

Topical lidocaine gel or patch was evaluated in 3 higher-quality reviews.[33-35] A Cochrane review found the topical lidocaine patch more effective than placebo as measured by mean improvement on a 6-point scale, but the pooled difference (2 trials) was small (WMD=0.42; 95% CI, 0.14 to 0.69, or roughly the equivalent of 7 points on a 100 point pain scale). There was no difference between patch and placebo in mean VAS score or reduction in VAS score.[35] Two other systematic reviews found topical lidocaine patch superior to placebo for achieving pain relief in patients with postherpetic neuralgia (NNT=2.0, 95% CI, 1.4 to 3.3, 1 trial[44])[34] or for any NP condition (NNT=4.4, 95% CI, 2.5 to17, 1 trial[45]).[33]

Randomized trials: Direct evidence

We identified no head-to-head trials comparing gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) to one another. We excluded one randomized trial that evaluated duloxetine versus routine care (the most frequently prescribed medications were gabapentin, amitriptyline, or venlafaxine) in patients with diabetic neuropathic pain in patients who had completed a 12-week trial of duloxetine versus placebo.[46]

Randomized trials: Indirect evidence

Gabapentin

We identified 12 placebo-controlled trials of gabapentin (reported in 13 articles[47-59]). One trial was not included in any previously published systematic review.[59] (Table 6) All were short-term trials, with duration of therapy ranging from 4 to 8 weeks. Most trials (11 of 12) were rated fair quality (Evidence Table 11). Dose of gabapentin ranged from 900 to 3600 mg daily. Sample sizes ranged from seven[58] to 334,[54] with a median of 57. Three trials evaluated patients with diabetic neuropathy, two evaluated gabapentin for post-herpetic neuralgia, one evaluated gabapentin for HIV-associated neuropathy,[52] and the remainder evaluated patients with mixed or other neuropathic pain. Two trials excluded previous non-responders to gabapentin.[54, 56] All trials evaluated some type of pain outcome and seven trials evaluated some type of functional outcome. However, there was substantial variation in how trials assessed pain or function. For example, pain outcomes were assessed in different trials using a 0-10 Likert Scale, 0-10 or 0-100

visual analogue scales, 0-4 categorical scale, 0-3 categorical scale, the Short-Form McGill Pain Questionnaire, the Neuropathic Pain Scale, and various categorical scales for global or overall improvement.

Table 6. Placebo-controlled trials of gabapentin for neuropathic pain

Study, year	Dose	N	Duration	Design	Results: Gabapentin versus placebo for pain relief	Results: Gabapentin versus placebo for improvement in function	Quality
Painful diabetic neuropathy							
Backonja, 1998 & 1999[47, 48]	3600 mg	165	8 weeks	Parallel	Benefit	Benefit	Fair
Gorson, 1999[51]	900 mg	40	6 weeks	Crossover	No benefit on 3 of 4 outcomes	Not measured	Fair
Simpson, 2001[57]	900-2700 mg	60	8 weeks	Parallel	Benefit	Benefit	Fair
Postherpetic neuralgia							
Rice, 2001[54]	1800-2400 mg	334	7 weeks	Parallel	Mixed: benefit on 4 of 6 outcomes	Mixed: benefit on some subscales (reported graphically only)	Fair
Rowbotham, 1998[55]	3600 mg	225	8 weeks	Parallel	Benefit	Benefit	Fair
Other or mixed neuropathic pain							
Hahn, 2004[52] (HIV-associated neuropathy)	1200-2400 mg	26	4 weeks	Parallel	Mixed: benefit on one of 2 outcomes.	Not measured	Fair
Gilron, 2005[50]	3200 mg	57	5 weeks	Crossover	Benefit	Benefit	Fair
Serpell, 2002[56]	900-2400 mg	305	8 weeks	Parallel	Mixed: benefit on 2 of 3 outcomes	Mixed; benefit on some domains (reported graphically only)	Fair
Bone, 2002[49]	2400 mg	19	6 weeks	Crossover	Mixed: benefit on 1 of 2 outcomes	No benefit	Fair
Yildirim, 2003[59]	900-3600 mg	50	8 weeks	Parallel	Benefit	Not measured	Fair

Study, year	Dose	N	Duration	Design	Results: Gabapentin versus placebo for pain relief	Results: Gabapentin versus placebo for improvement in function	Quality
Levendoglu, 2004[53]	3600 mg	20	8 weeks	Crossover	Mixed: benefit for pain intensity, mixed for different pain descriptors	Not measured	Fair
Tai, 2002[58]	up to 1800	7	4 weeks	Crossover	No benefit	Not measured	Poor

Qualitatively, 10 of 12 trials found gabapentin superior to placebo on at least one measure of pain relief or improvement in pain. The three largest trials (N=229, 305, and 334) consistently found gabapentin at doses of 1800 mg to 3600 mg/day superior to placebo on at least some measures of pain relief and at least some domains (as measured by the SF-36) of quality of life.[54-56] On a 10-point pain scale, differences in pain relief ranged from 0.5 to 2.2 points in favor of gabapentin. The two trials that found no differences between gabapentin and placebo for pain outcomes appeared underpowered to detect differences (N=7[58] and N=40[51]). One also evaluated low doses (900 mg) of gabapentin.[51] Gabapentin was superior to placebo on at least some measures of function in six of seven trials.

Quantitative analyses were limited by differential reporting of outcomes across trials (Table 7). For example, only three[49, 53, 55] of 12 trials reported mean improvements in patient-reported pain using some form of visual analogue scale, and only seven trials[48, 50, 51, 54-57] reported the proportion of patients experiencing >50% or at least moderate pain relief.

Table 7. Pooled results, placebo-controlled trials of gabapentin versus placebo

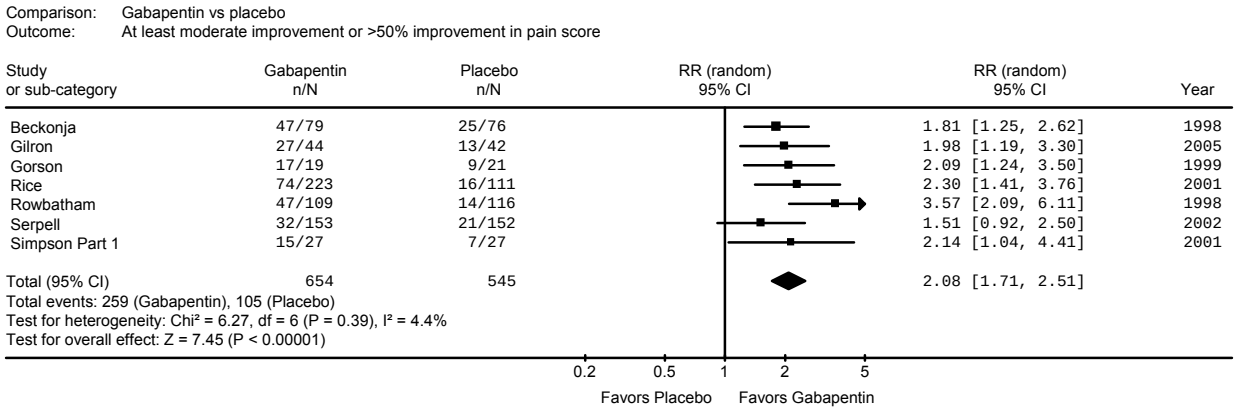
Outcome type	Scale	Outcome		Effect	N	Effect size vs. Placebo	95% CI	Heterogeneity I^2	Heterogeneity Q	Heterogeneity p(Q)
Patient-reported pain	Average pain, 0-10 Likert scale, 10 cm VAS, or 0-100 VAS (rescaled)	Mean score*		WMD	3	-2.06	[-4.46; 0.33]	98.7%	159.9	0.000
	SF-McGill Pain Questionnaire, Total score	Mean score*		WMD	2	-3.56	[-7.09; -0.03]		3.97	0.046
	Pain relief/response	% at least moderate improvement or >50% improvement in pain score	Gabapentin 900 to 3600 mg/day	RR	7	2.08	[1.71; 2.51]	4.4%	6.27	0.394
			Gabapentin 2400 to 3600 mg/day	RR	6	2.09	[1.66; 2.62]	20%	6.28	0.28
Functional capacity	SF-36 Bodily Pain**	Mean score		WMD	1	10.10	[4.92; 15.28]	NA		
	SF-36 Mental Health**	Mean score		WMD	1	4.70	[-0.14; 9.54]	NA		
	SF-36 Vitality**	Mean score		WMD	1	11.40	[5.95; 16.85]	NA		

*Higher scores mean worse pain
**Higher scores mean better function
VAS=visual analogue scale, SF-MPQ=Short-Form McGill Pain Questionnaire; CGI=Clinical Global Impression; SF-36= Medical Outcomes Study 36-item short-form health survey; BPI=Brief Pain Inventory, WMD=weighted mean difference, RR=relative risk

Patients randomized to gabapentin were more likely to report at least moderate pain relief or >50% improvement in pain scores than those randomized to placebo (RR=2.08, 95% CI 1.71 to 2.51, 7 trials, Figure 2).[48, 50, 51, 54-57] Statistical heterogeneity was not detected (I^2=4%), and no funnel plot asymmetry was apparent. In the two trials reporting the proportion of patients experiencing at least 50% pain relief, response to gabapentin ranged from 24% to 36%.[54, 56] In

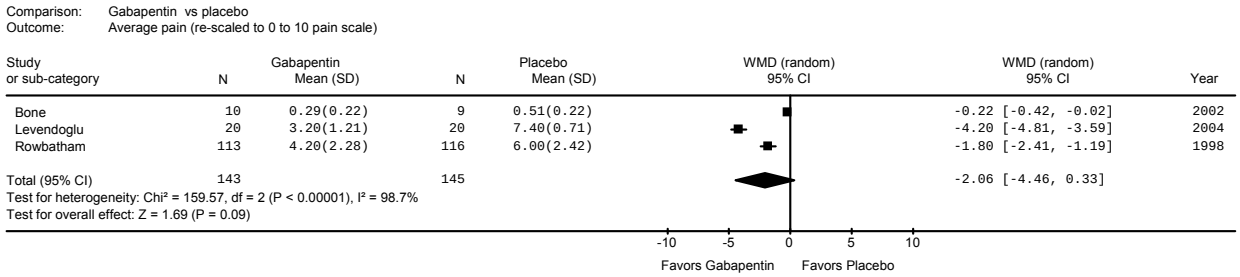
the five trials reporting pain relief on a categorical scale, the proportion reporting at least moderate improvement ranged from 27% to 60%.[48, 50, 51, 54, 55, 57] All of the trials included in the pooled estimate were rated fair-quality. Excluding the trial of gabapentin dosed at 900 mg/day[51] had little impact on estimates (RR 2.09, 95% CI 1.66 to 2.62, I^2=20%). All of the other trials attempted to titrate patients to at least 2400 mg/day. Stratifying trials by use of a parallel-group (RR 2.12, 95% CI 1.61 to 2.81, I^2=36%, 5 trials[48, 54-57]) versus crossover design (RR 2.03, 95% CI 1.41 to 2.92, 2 trials[50, 51]) and exclusion of trials[54, 56] that did not enroll previous non-responders to gabapentin (RR 2.17, 95% CI 1.72 to 2.74, I^2=13%, 5 trials) also did not affect estimates.

Figure 2. Relative risk for at least moderate improvement or >50% improvement in pain score from placebo-controlled trials of gabapentin



In three trials, gabapentin was consistently superior to placebo for mean improvement in pain scores as standardized to a 0 to 10 scale (Figure 3).[49, 53, 55] However, there was no statistically significant difference in the pooled estimate for this outcome (WMD=-2.06, 95% CI, -4.46 – +0.33, 3 trials). This finding is most likely due to the large statistical heterogeneity observed (I^2=99%), which results in a wide confidence intervals using a random effects model (Figure 3). However, the source of heterogeneity is not clear. No trial evaluated doses lower than 2400 mg/day, all trials were rated fair-quality, and none excluded previous non-responders to gabapentin. Although two trials evaluated patients with mixed neuropathic pain conditions and one trial evaluated patients with post-herpetic neuralgia,[55] the estimate from the latter trial fell between the estimates from the other two trials.

Figure 3. Mean improvement in pain score from placebo-controlled trials of gabapentin (re-scaled to 0 to 10 pain scale)



Gabapentin was statistically superior to placebo on the short-form McGill Pain Questionnaire Total Score (0 to 45 scale), but differences were small (WMD=-3.56, 95% CI, -7.09 to -0.03), there was evidence of statistical heterogeneity (p=0.046), and data were poolable from only two trials.[54, 55] Several other trials reported various measures of functional capacity or quality of life. However, no single measure was reported in more than one trial (Table 7).

Pregabalin

We identified a total of eight placebo-controlled trials of pregabalin (Table 8).[60-67] Three trials were not included in any previously published systematic review.[61, 66, 67] All trials were rated fair-quality (Evidence Table 11) and used a parallel-group design. Sample size ranged from 137 to 368 (median 238). Three trials evaluated patients with post-herpetic neuralgia,[62-64] three trials patients with diabetic neuropathy,[60, 65, 67] one trial patients with either post-herpetic neuralgia or diabetic neuropathy,[61] and one trial patients with spinal cord injury.[66] Three trials excluded previous non-responders to gabapentin.[60, 64, 65] The trials evaluated doses of pregabalin ranging from 75 to 600 mg daily, and ranged from 5 to 13 weeks in duration.

Table 8. Placebo-controlled trials of pregabalin for neuropathic pain

Study, year	Dose	N	Duration	Design	Results: Pregabalin versus placebo for pain relief	Results: Pregabalin versus placebo for improvement in function	Quality
Painful diabetic neuropathy							
Lesser, 2004[62]	75 mg 300 mg 600 mg	337	5 weeks	Parallel	No benefit at 75 mg (data not reported) Benefit at 300 and 600 mg	Mixed: benefit on some subscales at 300 and 600 mg; limited reporting of outcomes.	Fair
Richter, 2005[63]	150 mg 600 mg	246	6 weeks	Parallel	No benefit at 150 mg Benefit at 600 mg	Mixed: benefit on some subscales; limited reporting of outcomes.	Fair
Rosenstock, 2004[64]	300 mg	146	8 weeks	Parallel	Benefit	Mixed: benefit on one of 3 subscales	Fair
Postherpetic neuralgia							
Dworkin, 2003[60]	300 mg 600 mg	173	8 weeks	Parallel	Mixed: benefit on 2 of 4 outcomes	Mixed: benefit on 2 of 5 subscales	Fair
Sabatowski, 2004[65]	150 mg 300 mg	238	8 weeks	Parallel	Benefit	Mixed: benefit on 1 of 4 subscales (others not reported)	Fair
Van Seventer 2006[67]	150 mg 300 mg	368	13 weeks	Parallel	Benefit at all doses	Not measured	Fair
Other or mixed neuropathic pain							
Freynhagen, 2005[61]	150-600 mg (flexible dosing) 600 mg (fixed dosed)	338	12 weeks	Parallel	Benefit at both dosing schedules	Not measured	Fair
Siddall, 2006[66]	150-600 mg (flexible dosing) mean 460 mg	137	12 weeks	Parallel	Benefit	Not measured	Fair

Qualitatively, in trials that evaluated higher and lower doses of pregabalin, the higher doses of pregabalin (300-600 mg/day) were more effective than placebo, but lower doses (75-150 mg/day) were not consistently more effective than placebo.[62, 63, 65, 67] Patients randomized to higher-doses of pregabalin experienced greater pain relief compared to placebo on at least one outcome (by between 1.0 and 1.8 points on a 10 point pain scale) in all eight trials. Pregabalin was also superior to placebo on at least some subscales of the SF-36 or on measures of sleep quality in the six trials reporting these outcomes.[60, 62-66]

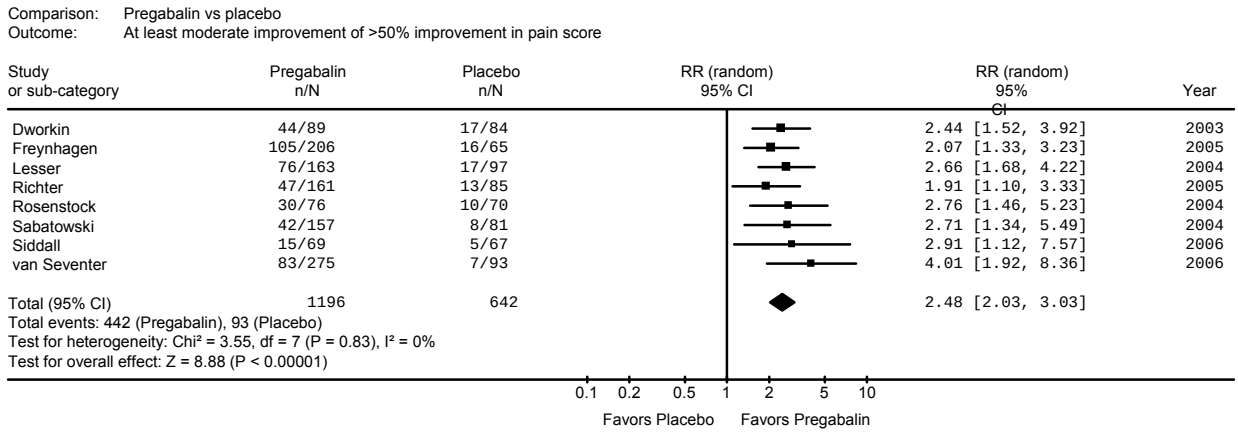
Quantitatively, pregabalin at any dose was superior to placebo for achieving pain relief in eight trials (RR=2.48, 95% CI 2.03 to 3.03, I^2=0%; Table 9, Figure 4).[60-67] All trials reported the proportion of patients experiencing at least 50% pain relief, which ranged from 22%[66] to 50%[61] in patients randomized to pregabalin. When results were stratified by pregabalin dose, estimates were somewhat higher at doses of 300 to 600 mg/day (RR 2.59, 95% CI 2.12 to 3.17, I^2=0%, 8 trials[60-67]) compared to 150 mg/day (RR 2.19, 95% CI 1.18 to 4.09, I^2=54%, 3 trials[63, 65, 67]), but the difference between stratified estimates was not significant (p=0.44). Exclusion of trials that did not enroll previous non-responders to gabapentin[60, 64, 65] did not significantly affect estimates (RR 2.59, 95% CI 2.01 to 3.33).

Table 9. Pooled results, placebo-controlled trials of pregabalin for neuropathic pain

Outcome type	Scale	Outcome		Effect	N	Effect size vs Placebo	95% CI	Heterogeneity I^2	Heterogeneity Q	Heterogeneity p(Q)
Patient-reported pain	Average pain, 0-10 Likert scale, 10 cm VAS, or 0-100 VAS (rescaled)	Mean score*		WMD	7	-1.56	[-1.81; -1.31]	0.0%	1.6	0.953
	SF-McGill Pain Questionnaire, Total score	Mean score*		WMD	5	-5.21	[-6.45; -3.96]	0.0%	0.65	0.957
	Pain relief/response	% at least moderate improvement or >50% improvement in pain score	Pregabalin 150 to 600 mg/day	RR	8	2.48	[2.03; 3.03]	0.0%	3.55	0.830
			Pregabalin 300 or 600 mg/day	RR	8	2.59	[2.12; 3.17]	0.0%	2.92	0.89
			Pregabalin 150 mg/day	RR	3	2.19	[1.18; 4.09]	54%	4.3	0.12
Functional capacity	SF-36 Bodily Pain	Mean score**		WMD	2	8.02	[3.69; 12.36]		0.23	0.632
	SF-36 Mental Health	Mean score**		WMD	2	3.67	[0.33; 7.01]		0.01	0.920
	SF-36 Vitality	Mean score**		WMD	2	2.08	[-1.72; 5.89]		0.32	0.572

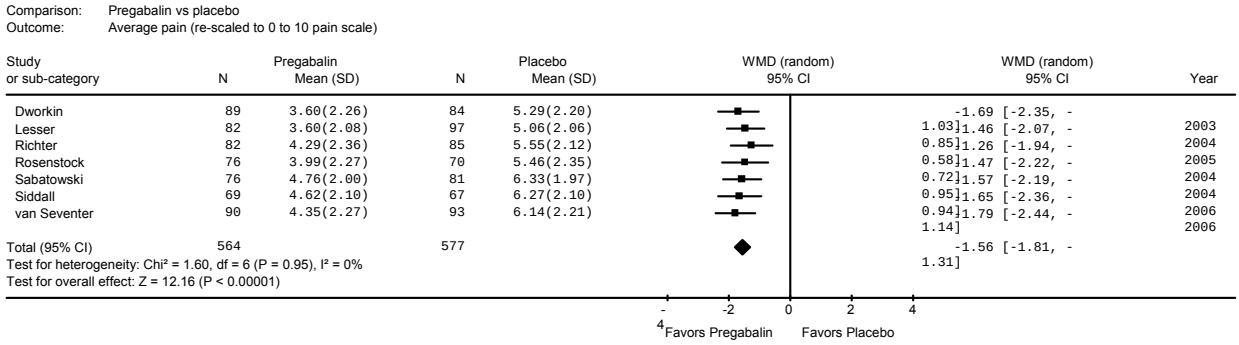
*Higher scores mean worse pain
**Higher scores mean better function
VAS=visual analogue scale, SF-MPQ=Short-Form McGill Pain Questionnaire; CGI=Clinical Global Impression; SF-36= Medical Outcomes Study 36-item short-form health survey; BPI=Brief Pain Inventory, WMD=weighted mean difference, RR=relative risk

Figure 4. Relative risk for at least moderate improvement or >50% improvement in pain score from placebo-controlled trials of pregabalin



Pregabalin was also superior to placebo for mean improvement in average pain scores (standardized to a 0 to 10 scale, WMD=-1.6, 95% CI, -1.8 to -1.3, 7 trials, I^2=0%; Figure 5),[60, 62-67] mean improvement in the SF-McGill Pain Questionnaire, Total (0 to 45 scale) score (WMD=-5.2, 95% CI -6.4 to -4.0, 5 trials, I^2=0%),[60, 62-64, 66], and on the SF-36 bodily pain (less than 10 points) and mental health (less than 5 points) subscales (2 trials each[60, 64]). For outcomes reported by at least six trials, no funnel plot asymmetry was present.

Figure 5. Mean improvement in pain score from placebo-controlled trials of pregabalin (on 0 to 10 pain scale)



Duloxetine

We identified three parallel-group randomized trials of duloxetine for painful diabetic neuropathy (Table 10).[68-70] One trial was not included in any previously published systematic review.[70] All were rated fair quality (Evidence Table 11). Sample sizes ranged from 334 to 457 subjects. All trials were twelve weeks in duration.

Table 10. Placebo-controlled trials of duloxetine for neuropathic pain

Study, year	Dose	N	Duration	Design	Results: Duloxetine versus placebo for pain relief	Results: Duloxetine versus placebo for improvement in function	Quality
Painful diabetic neuropathy							
Goldstein, 2005[68]	20 mg 60 mg 120 mg	457	12 weeks	Parallel	20 mg: no benefit 60 mg and 120 mg: mixed, benefit on most scales	20 mg: no benefit 60 mg and 120 mg: mixed, benefit on most scales	Fair
Raskin, 2005[69]	60 mg 120 mg	348	12 weeks	Parallel	Benefit	Benefit	Fair
Wernicke, 2006[70]	60 mg 120 mg	334	12 weeks	Parallel	Benefit	Benefit	Fair

Qualitatively, all three trials found duloxetine at doses of 60 to 120 mg/daily superior to placebo for patient-reported pain.[68-70] Differences on average pain scores as measured using a 0 to 10 scale ranged from 0.9 to 1.45 in the three trials. Two trials also found duloxetine superior to placebo by less than 10 points on SF-36 subscales for mental health and bodily pain.[68, 70]

Quantitatively, the proportion of patients experiencing at least 50% pain relief or moderate improvement in pain was reported by all three trials and superior with duloxetine 60 mg once daily or 60 mg twice daily versus placebo (RR=1.71, 95% CI 1.46 to 2.01, Figure 6, I^2=17%).[68-70] Results for doses of 60 mg/day and 120 mg/day were pooled together because estimates were very similar (Table 11). Rates of response in patients randomized to duloxetine ranged from 39% to 57%. Duloxetine was also superior to placebo for mean improvement in patient-reported pain by a little over one point on a 10 point scale and similar for doses of 60 mg once daily (Table 11) and 60 mg twice daily (Figure 7).[68-70] On the SF-36, duloxetine 60 mg twice daily was superior to placebo on the bodily pain subscale by an average of 8.2 points (95% CI 4.3 to 12.0, 2 trials) and on the mental health subscale by 5.8 points (95% CI 2.3 to 9.4, 2 trials), but there was no difference on the physical functioning subscale (weighted mean difference 4.21, 95% CI -1.23 to 9.65, 2 trials).[68, 70]

Table 11. Pooled results, placebo-controlled trials of duloxetine for neuropathic pain

Outcome type	Scale	Outcome	Dose	Effect	# o f studies	Effect size vs Placebo	95% CI	Heterogeneity I^2	Heterogeneity Q	Heterogeneity p(Q)
Patient-reported pain	Average pain, 0-10 Likert scale, 10cm VAS, or 0-100 VAS (rescaled)	Mean change from baseline*	Duloxetine 60 mg daily	WMD	3	-1.04	[-1.37; -0.71]	0.0%	1.18	0.554
			Duloxetine 60 mg BID	WMD	3	-1.17	[-1.53; -0.80]	16.80%	2.4	0.301
	SF-MPQ, Total score	Mean change from baseline*	Duloxetine 60 mg daily	WMD	2	-2.67	[-3.90; -1.44]		0.08	0.777
			Duloxetine 60 mg BID	WMD	2	-3.29	[-4.52; -2.07]		0.55	0.458
	Pain relief/response	% at least moderate improvement or >50% improvement in pain score	Duloxetine 60 mg daily or 60 mg bid	RR	3	1.71	[1.46; 2.01]	17.3%	2.42	0.298
			Duloxetine 60 mg daily	RR	3	1.71	[1.39; 2.11]	0.0%	0.59	0.745
			Duloxetine 60 mg bid	RR	3	1.71	[1.29; 2.26]	44.5%	3.6	0.165
Functional capacity	CGI severity	Mean change from baseline*	Duloxetine 60 mg daily	WMD	3	-0.49	[-0.66; -0.32]	0.0%	0.7	0.705
			Duloxetine 60 mg BID	WMD	3	-0.60	[-0.85; -0.35]	46.10%	3.71	0.156
	SF-36, Bodily Pain	Mean change from baseline**	Duloxetine 60 mg daily	WMD	2	5.54	[1.09; 9.99]		1.34	0.247
			Duloxetine 60 mg BID	WMD	2	8.19	[4.33; 12.05]		0.01	0.920
	SF-36, Mental Health Subscale	Mean change from baseline**	Duloxetine 60 mg daily	WMD	2	3.64	[0.04; 7.23]		1.34	0.247
			Duloxetine 60 mg BID	WMD	2	5.82	[2.26; 9.38]		1.32	0.251
	SF-36 Physical Functioning	Mean change from baseline**	Duloxetine 60 mg daily	WMD	2	4.68	[-1.54; 10.89]		5.08	0.024
			Duloxetine 60 mg BID	WMD	2	4.21	[-1.23; 9.65]		3.87	0.049
	BPI Interference	Mean change from baseline*	Duloxetine 60 mg daily	WMD	3	-0.70	[-0.99; -0.42]	0.0%	0.68	0.712
			Duloxetine 60 mg BID	WMD	3	-0.86	[-1.17; -0.56]	10.70%	2.24	0.326
	Euro QoL	Mean change from baseline**	Duloxetine 60 mg daily	WMD	2	0.06	[0.02; 0.10]		0.24	0.624
			Duloxetine 60 mg BID	WMD	2	0.06	[0.02; 0.10]		0.24	0.624

*Decrease in score means improvement; **Increase in score means improvement
VAS=visual analogue scale, SF-MPQ=Short-Form McGill Pain Questionnaire; CGI=Clinical Global Impression; SF-36= Medical Outcomes Study 36-item short-form health survey; BPI=Brief Pain Inventory

Figure 6. Relative risk for at least moderate improvement or >50% improvement in pain score from placebo-controlled trials of duloxetine

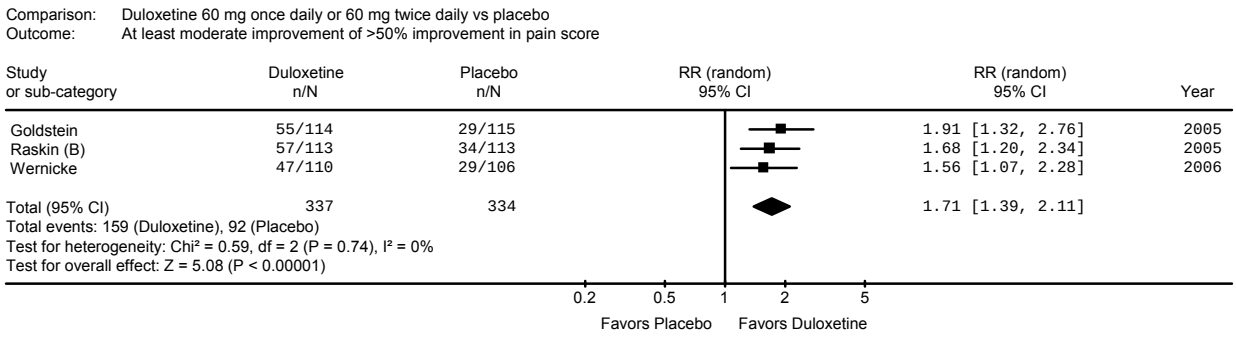
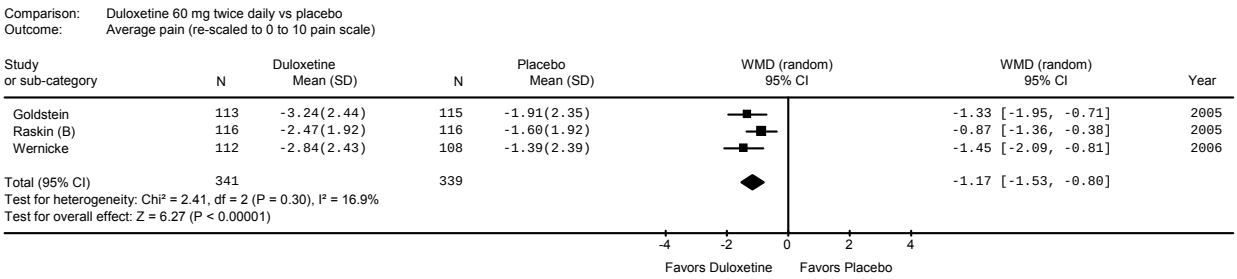


Figure 7. Mean improvement in pain score from placebo-controlled trials of duloxetine 60 mg twice daily (0 to 10 pain scale)



Venlafaxine

We identified four placebo-controlled trials of venlafaxine reporting efficacy outcomes at doses of 37.5 to 150 mg/day (N=13 to224) in patients with various NP syndromes (Table 12).[42, 71-73] Duration of therapy ranged from four to six weeks. One trial was not included in any previously published systematic review.[73] However, it was rated poor quality due to lack of reporting of baseline prognostic factors and no intention to treat analysis. The other three trials were rated fair-quality (Evidence Table 11). Two trials found no differences between venlafaxine and placebo for pain relief,[72, 73] and a third reported mixed results.[42] The fourth trial found venlafaxine at 150 or 225 mg/day superior to placebo by about 15 points on a 100 point visual analogue pain scale, but no significant differences between venlafaxine 75 mg/day and placebo.[71] The only trial to report functional outcomes found no benefits for venlafaxine over placebo.[73]

Quantitatively, only two trials reported poolable data for the proportion of patients experiencing pain relief.[42, 71] One trial[71] evaluated doses of 75 mg to 225 mg/day for diabetic neuropathy and the other[42] evaluated 225 mg/day for various neuropathic pain conditions. There was no difference between venlafaxine at any dose versus placebo in the proportion of patients experiencing at least moderate improvement or >50% improvement in pain scores (RR=1.79, 95% CI 0.75 to 4.27, 2 trials). Results were similar after limiting results to doses of venlafaxine 150 or 225 mg daily (RR 1.86, 95% CI 1.06 to 3.26, 2 trials). In one trial reporting mean improvement in pain scores, there was no difference between venlafaxine and placebo (WMD=-1.00 on a 0 to 10 scale, 95% CI -2.17 to 0.17).[42]

Table 12. Placebo-controlled trials of venlafaxine for neuropathic pain

Study, year	Dose	N	Duration	Design	Results: Venlafaxine versus placebo for pain relief	Results: Venlafaxine versus placebo for improvement in function	Quality
Painful diabetic neuropathy							
Rowbotham, 2004[71]	75 mg 150 mg 225 mg	244	6 weeks	Parallel	75 mg: no benefit 150 and 225 mg: benefit	Not measured	Fair
Other or mixed neuropathic pain							
Tasmuth, 2002[72]	37.5 mg 75 mg	13	4 weeks	Crossover	No benefit at any dose	Not measured	Fair
Yucel, 2005[73]	75 mg 150 mg	55	6 weeks	Parallel	No benefit at either dose	No benefit at either dose	Poor
Sindrup[42]	225 mg	32	4 weeks	Crossover	Mixed: benefit on 1 of 2 outcomes	Not measured	Fair

Topical lidocaine (patch or gel)

We identified four trials of topical lidocaine 5% patch and two trials of lidocaine 5% gel for NP (Table 13). One trial was rated poor-quality,[74] and the remainder rated fair-quality (Evidence Table 11).[44, 45, 74-77] Four trials evaluated patients with post-herpetic neuralgia,[44, 74, 76, 77] one trial evaluated patients with HIV-related polyneuropathy,[75] and one trial evaluated patients with various peripheral NP conditions.[45]. Sample sizes ranged from 35 to 96 subjects. Two trials evaluated patients at extremely short-term follow-up (8 to 12 hours following application of lidocaine gel or patch).[76, 77] The remainder evaluated one to three weeks of topical lidocaine therapy.

Table 13. Placebo-controlled trials of topical lidocaine for neuropathic pain

Study, year	Form	N	Duration	Design	Results: Topical lidocaine versus placebo for pain relief	Results: Topical lidocaine versus placebo for improvement in function	Quality
Postherpetic neuralgia							
Galer, 2002[74]	Patch, 5%	96	3 weeks	Parallel	Benefit on Neuropathic Pain Scale	Not measured	Poor
Galer, 1999[44]	Patch, 5%	32	Variable- 2 days to 2 weeks, depending on pain response	Crossover; all subjects were currently using lidocaine patch with at least moderate relief	Benefit on primary outcome (time to 2 consecutive days with 2-point decrease on 6-point pain relief scale) No difference in use of rescue analgesics Trend favoring lidocaine patch for patients experiencing pain relief (91% vs 41%, p-value not reported)	Not measured	Fair
Rowbotham, 1996[77]	Patch, 5%	35	Up to 12 hours	Crossover	Benefit	Not measured	Fair
Other neuropathic pain							
Estanislao, 2004[75] HIV-related neuropathy	Gel, 5%	64	2 weeks	Crossover	No benefit	Not measured	Fair
Rowbotham, 1995[76]	Gel, 5%	39	Up to 8 hours	Crossover	Benefit for pain relief	Not measured	Fair
Meier, 2003[45]	Patch, 5%	58	7 days	Crossover	Benefit (results reported graphically only)	Not measured	Poor

Qualitatively, the two short-term trials (up to 12 hours after application) both found topical lidocaine patch[77] or gel[76] superior to placebo for pain relief. Results from the four longer-term trials (up to three weeks) are mixed and difficult to interpret due to differences in methods for assessing pain outcomes or poor reporting of outcomes. One trial of the lidocaine patch did not report statistical significance for the proportion of patients experiencing pain relief, though the trend favored lidocaine (91% vs. 41%).[44] However, there was no difference in the proportion of patients using additional analgesics. The primary outcome in this study was "time to exit", with

the criterion for exit being 2 consecutive days with a 2-point decrease on a 6-point pain relief score. The median time to exit for the lidocaine patch group was14 days, compared with 3.8 days for the vehicle patch (P<0.001). Applicability of this trial may be limited, as all patients were already using the lidocaine patch with at least "moderate" relief of pain prior to enrollment.

A second trial found no differences between topical lidocaine gel and placebo in patients with HIV-related polyneuropathy.[75] Another trial found topical lidocaine patch superior to placebo for mixed NP conditions by about 10 points on a ten-point scale after one week of use.[45] The fourth trial found topical lidocaine patch superior to placebo on the Neuropathic Pain Scale (difference about 8 points on a 100 point composite scale, p=0.043), but was rated poor quality because the number of patients randomized was not reported and there was no information on withdrawals.[74] None of the trials evaluated outcomes related to quality of life or function. We found no data suitable for pooling because reported outcomes were different for each of the trials.

Indirect analyses

In adjusted indirect analyses (Table 14), pregabalin was moderately superior to duloxetine for the proportion of patients experiencing at least moderate improvement or >50% improvement in pain scores (RR=1.45, 95% CI 1.12 to 1.87). There was no significant difference between gabapentin and duloxetine (RR=1.22, 95% CI 0.95 to 1.56).

There were no significant differences between gabapentin and pregabalin in the likelihood of achieving pain relief (RR=0.84, 95% CI 0.64 to 1.11), average pain relief (WMD=-0.50 on a 0 to 10 scale, 95% CI -2.91 to +1.91), the SF-36 McGill Pain Questionnaire (Total score), or SF-36 Bodily Pain or Mental Health scores (Table 14). The only statistically significant difference between gabapentin versus pregabalin was observed on the SF-36 Vitality score. Gabapentin was superior to pregabalin by less than 10 points (WMD=+9.32, 95% CI, +2.67 to +15.97). However, this finding should be interpreted cautiously because it is based on an analysis that included only one trial of gabapentin[55] and two trials of pregabalin.[60, 64] Selective outcomes reporting bias may have occurred for some outcomes, as statistically significant SF-36 subscale scores appeared to be preferentially reported.

There were no differences between venlafaxine and either gabapentin, pregabalin, or duloxetine on average pain scores or the likelihood of achieving significant pain relief. However, analyses involving venlafaxine[42, 73] only included two trials of that medication. No data on topical lidocaine (patch or gel) were available for indirect analyses.

We performed several sensitivity analyses on our main outcome, the proportion of patients with at least moderate improvement or >50% improvement in pain scores. None resulted in clinically significant differences in estimates or in different conclusions. Excluding gabapentin crossover trials did not affect estimates. Excluding pregabalin trials that evaluated lower doses and trials that excluded previous non-responders to gabapentin also did not affect estimates. No trial included in the indirect analyses was rated poor-quality, or evaluated patients with HIV-associated neuropathic pain or trigeminal neuralgia.

Among trials included in the indirect analyses, pooled mean rates for at least moderate or >50% pain relief in patients randomized to placebo were somewhat higher in trials of gabapentin (22%,

95% CI 15% to 29%, 8 trials) compared to trials of pregabalin (14%, 95% CI 10% to 18%, 7 trials), but the difference was non-significant. Mean rate of response to placebo in trials of duloxetine was 28% (95% CI 23% to 32%, 3 trials) and in trials of venlafaxine was 20% (95% CI 0% to 46%, 2 trials).

Table 14. Indirect analyses of comparative effectiveness of gabapentin, pregabalin, duloxetine, and venlafaxine for neuropathic pain

Outcome domain	Scale	Outcome	Treatment comparison	Effect	Effect Size	Lower limit of 95% CI	Upper limit of 95% CI
Patient-reported pain	Average pain, 0-10 Likert scale, 10cm VAS, or 0-100 VAS (rescaled)	Mean score*	Gabapentin vs Pregabalin	WMD	-0.50	-2.91	1.91
			Gabapentin vs. Venlafaxine	WMD	-1.06	-3.73	1.61
			Pregabalin vs. Venlafaxine	WMD	-0.56	-1.76	0.64
	SF-McGill Pain Questionnaire, Total score	Mean score*	Gabapentin vs Pregabalin	WMD	1.65	-2.09	5.39
	% at least moderate improvement or >50% improvement in pain score	RR	Gabapentin vs. Pregabalin	RR	0.84	0.64	1.11
			Gabapentin vs. Duloxetine	RR	1.22	0.95	1.56
			Gabapentin vs. Venlafaxine	RR	1.16	0.48	2.83
			Pregabalin vs. Duloxetine	RR	1.45	1.12	1.87
			Pregabalin vs. Venlafaxine	RR	1.39	0.57	3.38
			Duloxetine vs. Venlafaxine	RR	0.96	0.39	2.31
Functional capacity	SF-36 Bodily Pain	Mean score**	Gabapentin vs Pregabalin	WMD	2.08	-4.67	8.83
			Gabapentin vs Duloxetine 60 mg daily	WMD	4.56	-2.27	11.39
			Gabapentin vs Duloxetine 60 mg BID	WMD	1.91	-4.55	8.37
			Pregabalin vs Duloxetine 60 mg daily	WMD	2.48	-3.73	8.69
			Pregabalin vs Duloxetine 60 mg BID	WMD	-0.17	-5.97	5.63
	SF-36 Mental Health	Mean score**	Gabapentin vs Pregabalin	WMD	1.03	-4.85	6.91
			Gabapentin vs Duloxetine 60 mg daily	WMD	1.06	-4.97	7.09
			Gabapentin vs Duloxetine 60 mg BID	WMD	-1.12	-7.13	4.89
			Pregabalin vs Duloxetine	WMD	0.03	-4.88	4.94

Outcome domain	Scale	Outcome	Treatment comparison	Effect	Effect Size	Lower limit of 95% CI	Upper limit of 95% CI
			60 mg daily				
			Pregabalin vs Duloxetine 60 mg BID	WMD	-2.15	-7.03	2.73
	SF-36 Vitality	Mean score**	Gabapentin vs Pregabalin	WMD	9.32	2.67	15.97

*Higher score means worse pain
**Higher score means improvement in function

Key Question 2. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, or topical lidocaine (patch or gel) versus other drugs (other antiepileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

Summary of findings

Direct analyses of three head-to-head trials found no difference between gabapentin and tricyclic antidepressants for pain relief. However, because estimates are relatively imprecise, they do not rule out a clinically significant difference between medications. One other small head-to-head trial found no difference in efficacy between venlafaxine and imipramine.

Adjusted indirect analyses of placebo-controlled trials found gabapentin and pregabalin each moderately superior to other antiepileptic medications (carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid) for achieving pain relief. Gabapentin and duloxetine were both moderately inferior to tricyclic antidepressants for achieving pain relief, and gabapentin and pregabalin were both moderately superior to SSRIs. There were no significant differences between either duloxetine or venlafaxine versus other medications for neuropathic pain or in comparisons involving dextromethorphan, but analyses were limited by small numbers of trials.

Results of indirect analyses should be interpreted cautiously. Conclusions about comparative efficacy of tricyclic antidepressants based on indirect analyses may be unreliable because of funnel plot asymmetry and heterogeneity among placebo-controlled trials. Although estimates were similar after adjusting for potential publication bias and after excluding trials of HIV-related neuropathic pain (which substantially reduced heterogeneity), there were statistically significant discrepancies between direct and indirect estimates of gabapentin versus tricyclic antidepressants for pain relief. Because there were no head-to-head trials of tricyclic antidepressants versus pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel), we could not contrast results of direct and indirect analyses for these comparisons.

Analyses involving pooled results for the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid should also be interpreted cautiously,

as these medications vary in pharmacologic structure and mechanism of action. However, stratified estimates suggest no clear differences in efficacy, and estimates for individual drugs were too imprecise to be informative in adjusted indirect analyses.

Detailed assessment

Systematic reviews

Two systematic reviews included head-to-head trials of gabapentin versus tricyclic antidepressants for NP (Table 3).[2, 12] One systematic review[2] found no difference between gabapentin versus tricyclic amitriptyline for the proportion of patients experiencing pain relief (RR=1.30, 95% CI 0.91 to 1.85, 2 trials[40, 41]). The other systematic review[12] analyzed the same two trials qualitatively, and found inconsistent results, with no difference between drugs in one trial[41] and gabapentin superior by about 0.6 points on a 0 to 4 pain scale in the other.[40] Both head-to-head trials were small (N=25) and relatively short-term (6 weeks and 12 weeks).

Six systematic reviews evaluated benefits of tricyclic antidepressants, SSRIs, dextromethorphan or the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid versus placebo for neuropathic pain (Table 3).[2, 33, 34, 36-38] They varied in how they selected trials for inclusion and in how they analyzed and synthesized data. One systematic review evaluated all medications for any type of neuropathic pain.[33] Other systematic reviews focused specifically on antidepressant medications,[2] carbamazepine,[36] patients with postherpetic neuralgia,[34] or patients with diabetic neuropathy.[38]

The systematic reviews included a total of 29 unique placebo-controlled trials of tricyclic antidepressants, 3 trials of SSRIs, 29 trials of other antiepileptic medications (13 trials of carbamazepine, 7 trials of lamotrigine, 2 trials of topiramate, 2 trials of oxcarbazepine, and 5 trials of valproic acid) and 3 trials of dextromethorphan (Table 15). In general, the systematic reviews consistently found tricyclic antidepressants, valproic acid, and carbamazepine more effective than placebo for achieving significant pain relief (variously defined). However, carbamazepine was primarily evaluated for treatment of trigeminal neuralgia (4 of 6 trials evaluated patients exclusively or primarily with trigeminal neuralgia). Data were sparse, with imprecise estimates (wide confidence intervals) for SSRIs and dextromethorphan. One systematic review found insufficient evidence to conclude that lamotrigine is effective for NP (no benefit in six of seven trials).[37]

Table 15. Summary of results of recent systematic reviews of tricyclic antidepressants, carbamazepine, lamotrigine, topiramate, oxcarbazepine, valproic acid), SSRIs, and dextromethorphan for neuropathic pain

Drug	Total # of unique trials	Review	# of included trials	# of trials not included in any other relevant systematic review	Outcome	Benefit vs placebo NNT (95% CI) (unless other outcome specified)	# of trials for pooled effect
Tricyclic Antidepressants	29	Hempenstall, 2005[34]	7	2	Top two values on a five-point scale for pain relief, effectiveness, or improvement, top three values on a six-point scale, top value on a three-point scale, top two values on a four-point scale, 50% or greater reduction on a visual analogue or 11-point scale (hierarchy of outcomes)	PHN: 2.64 (2.1–3.54)	4
		Finnerup, 2005[33]	22	4	>50% pain relief, or proportion reporting at least good pain relief or reporting improvement (hierarchy of outcomes)	Any NP: 3.1 (2.7–3.7)	22
		Saarto, 2005[2]	22	4	Moderate pain relief or better	Any NP: *Relative risk*=2.37(1.96–2.87)	14
		Wong, 2007[38]	3	0	>50% pain relief (defined as number of patients with 'moderate,' 'good,' or 'notable' improvement in global assessment of	DN: *OR*=22.2 (5.83 to 84.8)	3

Drug	Total # of unique trials	Review	# of included trials	# of trials not included in any other relevant systematic review	Outcome	Benefit vs placebo NNT (95% CI) (unless other outcome specified)	# of trials for pooled effect
					treatment or at least moderate pain relief on a categorical scale)		
Antiepileptic medications (carbamazepine, lamotrigine, topiramate, oxcarbazepine, and valproic acid)	29	Wong, 2007[38]	6	2	See Wong above	DN: *OR=5.3 (1.77 to 16.0)*	3
		Finnerup, 2005[33]	24	9	See Finnerup above	Carbamazepine: 2.0 (1.6 to 2.5) Valproate: 2.8 (2.1 to 4.2) Topiramate: 7.4 (4.3 to 28)	5 carb-amezepine 5 valproate 2 topiramate
		Wiffen, 2005[36]	11 (carbamazepine only)	5	>50% pain relief, global impression of clinical change, pain on movement, pain on rest, any other pain related measure (hierarchy of outcomes)	Any NP: *RR*=2.1 (0.7 to 5.9)	4
		Wiffen, 2005[37]	7 (lamotrigine only)	0	Dichotomous outcomes for pain relief (not well defined)	Data not pooled; lamotrigine not effective in 6 of 7 trials	NA
SSRIs	3	Finnerup, 2005[33]	3	0	See Finnerup above	Any NP: 6.8 (3.4–441)	3

Drug	Total # of unique trials	Review	# of included trials	# of trials not included in any other relevant systematic review	Outcome	Benefit vs placebo NNT (95% CI) (unless other outcome specified)	# of trials for pooled effect
		Saarto, 2005[2]	3	0	Moderate pain relief or better	Data insufficient to calculate NNT	NA
		Wong, 2007[38]	1	0	See Wong above	DN: *OR*=3.5 (0.3 to 38.2)	1
Dextromethorphan	3	Finnerup, 2005[33]	3	1	See Finnerup above	Any NP: 4.4 (2.7–12) PHN: No significant difference	2
		Hempenstall, 2005[34]	2	0	See Hempenstall above	Data not pooled; no benefit in 2 studies.	NA
		Wong, 2007[38]	1	1	See Wong above	DN: *OR*=31.2 (1.5 to 633)	1

The usefulness of the systematic reviews for assessing comparative benefits of gabapentin, pregabalin, SNRIs, or topical lidocaine (patch or gel) versus tricyclic antidepressants, other antiepileptic medications, SSRIs, or dextromethorphan for neuropathic pain is quite limited because formal indirect analyses were not attempted. Based on informal indirect comparisons, one systematic review concluded that tricyclic antidepressants are more effective than gabapentin or pregabalin for various NP conditions, based on a NNT for >50% pain relief of 3.1 (95% CI, 2.7 to 3.7) for tricyclics versus placebo, compared to a NNT of 4.7 (95% CI, 4.0 to 5.6) for gabapentin or pregabalin versus placebo.[33] A second systematic review concluded that tricyclic antidepressants and the antiepileptic drugs carbamazepine, lamotrigine, and sodium valproate are more effective than gabapentin, pregabalin, or oxcarbazepine for diabetic neuropathy, based on odds ratios for >50% pain relief of 22.24 (95% CI 5.83 to 84.8), 5.33 (95% CI 1.8 to 16.0), and 3.2 (95% CI 2.3 to 4.7), respectively.[38] However, estimates of treatment benefit from placebo-controlled trials in this systematic review are imprecise because they primarily rely on analyses of trials with relatively small sample sizes, particularly for the tricyclic antidepressants (total of 61 patients in three trials). In these situations, performing formal adjusted indirect analyses could render apparent differences when qualitatively evaluating estimates from placebo-controlled trials across drugs non-significant. In addition, inferences about comparative benefits from informal indirect comparisons should be interpreted cautiously because it is difficult to qualitatively evaluate potential sources of diversity among trials. For example, in the systematic review of medications for neuropathic pain, all trials of tricyclic antidepressants were conducted in 1984 to 1991, compared to 1998 to 2005 for trials of gabapentin, pregabalin, or oxcarbazepine.[38] In patients randomized to placebo, the proportion reporting significant pain relief was 3% (2/61) in trials of tricyclic antidepressants compared to 21% (66/319) in trials of gabapentin, pregabalin, or oxcarbazepine, suggesting that assumptions about similarity of treatment effects could be violated.

Randomized trials: Direct evidence

Four small (N=25 to 70), fair quality, head-to-head trials directly compared gabapentin versus a tricyclic antidepressant for neuropathic pain (Table 16).[39-42] Two trials[40, 41] of gabapentin versus amitriptyline in patients with diabetic neuropathy were included in previously published systematic reviews.[2, 12] We also identified one trial comparing nortriptyline to gabapentin for postherpetic neuralgia,[39] and one trial comparing imipramine to venlafaxine for various types of neuropathic pain (this trial also included a placebo arm).[42] Duration of treatment ranged from four to eight weeks. Three of the four head-to-head trials did not describe funding source. The fourth[39] was funded by Pfizer India.

Table 16. Head-to-head trials of gabapentin or venlafaxine versus tricyclic antidepressants for neuropathic pain: benefits

Study, year (Quality)	Comparison	Population	Pain Results	Conclusions
Dallocchio, 2000[40] Italy (Fair)	amitriptyline mean 53 mg (maximum 90 mg) gabapentin mean 1785 mg (maximum 2400 mg) 8 weeks, parallel group, open-label	Painful diabetic neuropathy N=25	Amitriptyline vs gabapentin (p-value comparing changes from baseline) Pain (0-4): 1.3 vs 1.9 (p=0.026) Paresthesia (0-4): 0.9 vs 1.8 (p=0.04) At least 50% improvement in pain score: 9/12 (75%) vs. 11/13 (85%)	Greater reduction in pain score with gabapentin.
Morello, 1999[41] US (Fair)	amitriptyline mean 59 mg (maximum 75mg) gabapentin mean 1565 mg (maximum 1800 mg) 6 weeks, crossover, placebo-controlled, double-blind	Painful diabetic neuropathy N=25	Amitriptyline vs gabapentin Gracely Pain Scale: mean difference 0.91 favoring amitriptyline (95% CI -0.074 to 0.256; p=0.26) At least moderate pain relief (data on 21 of 25 patients): 14/21 (67%) vs. 11/21 (52%) (p>0.10)	No difference in pain scores.
Chandra, 2006[39] India (Fair)	nortriptyline up to 75 mg gabapentin up to 2700 mg 8 weeks, parallel, double-blind	Postherpetic neuralgia N=70	Nortriptyline vs gabapentin % reduction in pain score (11-point Likert scale): 47.6% vs 42.8% (NS) % of patients reporting good or excellent clinical effectiveness: 17/36 (47%) vs 16/34 (47%) (NS)	No differences in pain scores
Sindrup, 2003[42] Denmark (Fair)	imipramine 150 mg venlafaxine 225 mg 4 weeks, crossover, placebo-controlled, double-blind	Mixed (47% painful diabetic neuropathy) N=32	Mean pain scores (0-10) at 4 weeks, venlafaxine vs imipramine: Pain paroxysms: 2.6 vs 2.5 (p=0.47) Constant pain: 5.3 vs 5.0 (p=0.43) Touch-evoked pain: 2.7 vs 2.5 (p=0.41) Pressure-evoked pain: 4.1 vs 4.0 (p=0.85) Paracetamol consumption (total weekly): 9 vs 8 (p=0.51) Pain summation (% of	No differences in pain scores.

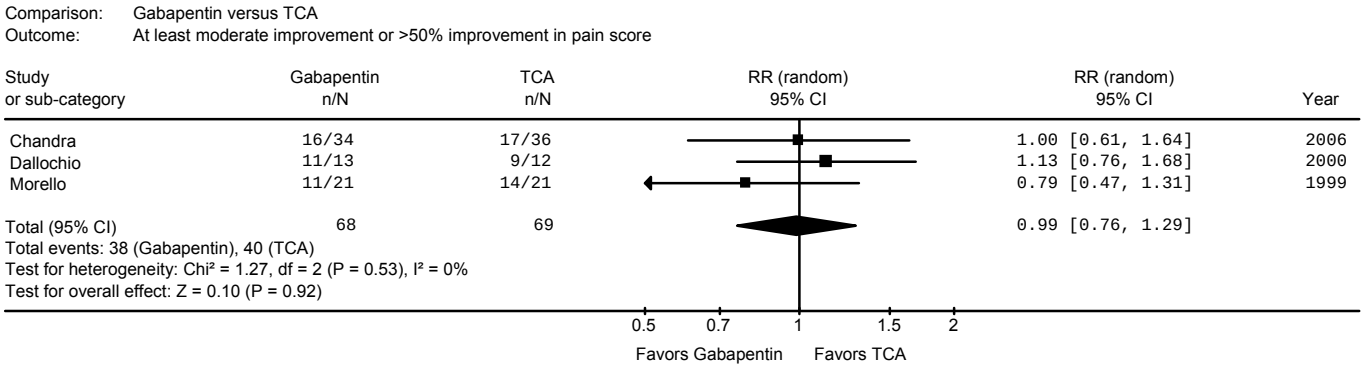
Study, year (Quality)	Comparison	Population	Pain Results	Conclusions
			baseline score): 80% vs 77% (p=0.48) At least moderate pain relief: 8/30 (27%) vs 14/29 (48%), p=0.16	

Qualitatively, results from three small head-to-head trials (N=25 to 76) of gabapentin versus tricyclic antidepressants are inconclusive regarding relative effectiveness.[39-41] Two trials (N=25 in both trials) compared gabapentin to amitriptyline for diabetic neuropathy.[40, 41] Although one 6-week crossover trial[41] found no difference between the medications on the Gracely Pain Scale and patient global assessment of pain, an 8-week parallel-group trial[40] found that patients randomized to gabapentin experienced greater improvements in measures of pain and paresthesia than those randomized to amitriptyline (difference of about 0.5 points on a 0 to 4 pain scale). The two trials differed in several ways that may help explain discrepant results. For example, the dose of gabapentin was slightly lower in the study that found no differences (mean 1565 vs. 1785 mg/day), while the amitriptyline mean dose was similar (53 vs. 59 mg/day). In addition, the trial that found gabapentin more effective than amitriptyline was open-label,[40] but the trial that found no differences used a double-blind design.[41] Outcome measures, treatment duration, and methods of analysis were also different in the two trials. In the crossover trial, patients were allowed to cross over early if they experienced adverse events.[41] The third trial, an 8-week, double-blind, parallel-group trial (N=70) of nortriptyline versus gabapentin in a different population (patients with postherpetic neuralgia) found no differences between groups in mean improvement in pain scores (primary outcome), likelihood of experiencing a good or excellent response, or other secondary outcomes (sleep ratings, disability, or proportion of patients responding to treatment).[39] Gabapentin was titrated to a higher dose (2700 mg/day) compared to the two trials of gabapentin versus amitriptyline.

Quantitatively, there was no difference between gabapentin and tricyclic antidepressants for experiencing >50% pain relief or at least moderate pain relief when the three head-to-head trials of this comparison were pooled (Figure 8) (RR=0.99, 95% CI 0.76 to 1.29, I^2=0%).[39-41] In a subgroup analysis of two trials, there was also no significant difference between gabapentin versus amitriptyline specifically for diabetic neuropathy (RR=0.91, 95% CI 0.66 to 1.28).[40, 41] Results were also similar after excluding data from the single cross-over trial[41] (RR=1.07, 95% CI 0.79 to 1.47).

In one small trial comparing venlafaxine versus imipramine (N=32), about half of enrolled patients had diabetic neuropathy and half had neuropathic pain due to another etiology. Venlafaxine and imipramine were similar in efficacy on a number of pain scales, with no statistically significant difference in the likelihood of achieving pain relief (RR=0.55, 95% CI 0.27 to 1.12).[42]

Figure 8. Relative risk for at least moderate improvement or >50% improvement in pain score from head-to-head trials of gabapentin vs tricyclic antidepressants



Randomized trials: Indirect evidence

We identified 21 placebo-controlled trials of tricyclic antidepressants,[42, 78-97] 3 trials of SSRIs,[93, 98, 99] 21 trials of older antiepileptics (7 carbamazepine,[84, 100-105] 5 valproic acid,[106-110] 7 lamotrigine[111-117] 2 oxcarbazepine[118, 119]), 4 trials of topiramate,[120-123] and 4 trials of dextromethorphan (reported in three articles[124-126]) (Evidence Tables 8-10). Most trials were short term (range 1 week to 18 weeks, median 6 weeks). Forty trials were rated fair quality and 13 poor quality.

Qualitatively, we found some inconsistency among trials of tricyclic antidepressants, with the two largest trials (N=136 and N=145),[81, 91] both in patients with HIV-related neuropathy, finding no differences versus placebo. Fifteen of the sixteen smaller trials (N=12 to 84), none of which evaluated patients with HIV-related neuropathy, found tricyclic antidepressants superior to placebo for pain relief. The exception was one trial (N=39) of amitriptyline versus benztropine (active placebo) for phantom limb pain.[90] Only five trials reported a functional or quality of life-related outcome, with inconsistent findings.[78, 79, 81, 90, 91]

Carbamazepine and valproic acid were also consistently more effective than placebo for pain relief, but trials were small (N=9 to 70). Evidence on lamotrigine was mixed, with poorly reported outcomes or no clear differences versus placebo in six[112-117] of seven trials. The exception was a trial of lamotrigine versus placebo for diabetic neuropathy that found a difference of about one point on a 10 point pain scale.[111] Data were sparse and inconclusive for SSRIs, dextromethorphan, and other antiepileptics (topiramate, oxcarbazepine) included in this review.

Quantitatively, we could only calculate pooled estimates for efficacy of tricyclic antidepressants for experiencing pain relief (achieving at least moderate improvement or >50% improvement in pain scores) because of insufficient poolable data for other outcomes (such as mean improvement in pain scores or effects on functional status or quality of life). Tricyclic antidepressants were superior to placebo for achieving pain relief (RR=3.83, 95% CI 2.18 to 6.75, 12 trials) (Table 17, Figure 9).[42, 81-87, 91, 92, 96, 97] However, statistical heterogeneity was substantial (I^2=81%). In addition, funnel plot asymmetry was present (p<0.001 by Egger test, Figure 10). The two trials with the smallest standard errors (N=145 and N=136), both of which

evaluated patients with HIV-related neuropathic pain, found no differences between amitriptyline and placebo (RR=1.06, 95% CI 0.71 to 1.59[81] and RR=1.10, 95% CI 0.78 to 1.56[91]). In the other trials, estimates of relative risk ranged from 2.75[96] to 19.[85] After using the trim-and fill method to adjust for potential publication bias, however, tricyclics remained superior to placebo for pain relief, with little change in estimates (RR=3.74 95% CI 2.35 to 5.96, I^2=30%).

In sensitivity analyses, excluding the two trials of patients with HIV-related neuropathic pain[81, 91] increased estimates of tricyclic antidepressant efficacy versus placebo for achieving at least moderate improvement or >50% improvement in pain scores (RR 4.74, 95% CI 3.15 to 7.14) and substantially decreased heterogeneity (I^2=18%). Excluding two poor-quality trials[82, 92] did not further change estimates or reduce heterogeneity (RR=4.72, 95% CI 2.87 to 7.75, I^2=28%, 8 trials). Nine of the ten trials of tricyclic antidepressants for non-HIV-related neuropathic pain were crossover trials (RR=4.77, 95% CI 3.03 to 7.52, I^2=24%). There was no significant difference between the pooled estimate from the crossover trials and the single parallel-group trial[42] (RR=7.00, 95% CI 1.70 to 28.08, p=0.74 for difference in stratified estimates). After excluding trials of tricyclic antidepressants for HIV-related neuropathic pain, there was also no significant difference between pooled estimates when trials were stratified by those that evaluated a secondary amine tricyclic (RR=7.02, 95% CI 3.76 to 13.12, I^2=0%, 6 trials[82-86, 92]) versus those that evaluated a tertiary amine tricyclic (RR=3.82, 95% CI 2.07 to 7.04, I^2=33%, 4 trials,[42, 87, 96, 97] p=0.23 for difference in stratified estimates).

Table 17. Pooled results, placebo-controlled trials of tricyclic antidepressants, carbamazepine, lamotrigine, topiramate, oxcarbazepine, and valproic acid, SSRIs, and dextromethorphan for neuropathic pain

Outcome type	Scale	Outcome	Drug	Effect	N	Effect size vs Placebo	95% CI	Heterogeneity I^2		
Patient-reported pain	Average pain, 0-10 Likert scale, 10cm VAS, or 0-100 VAS (rescaled)	Mean score*	Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	WMD	6	-0.91	[-1.27; -0.55]	17.4%	6.1	0.301
	SF-McGill Pain Questionnaire, Total score	Mean score*	Valproic acid	WMD	2	-6.03	[-16.68; 4.61]		0.14	0.932
	Pain relief/response	% at least moderate improvement or >50% improvement in pain score	Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	RR	12	1.46	[1.13; 1.88]	58.2%	26.31	0.006
			Tricyclic antidepressants	RR	12	3.83	[2.18; 6.75]	81.2%	58.65	0.000
			SSRIs	RR	2	1.21	[0.77; 1.89]		0.75	0.386
			Dextromethorphan	RR	1	1.67	[0.50; 5.57]	NA		

*Higher score means worse pain

Figure 9. Relative risk for at least moderate improvement or >50% improvement in pain score from placebo-controlled trials of tricyclic antidepressants

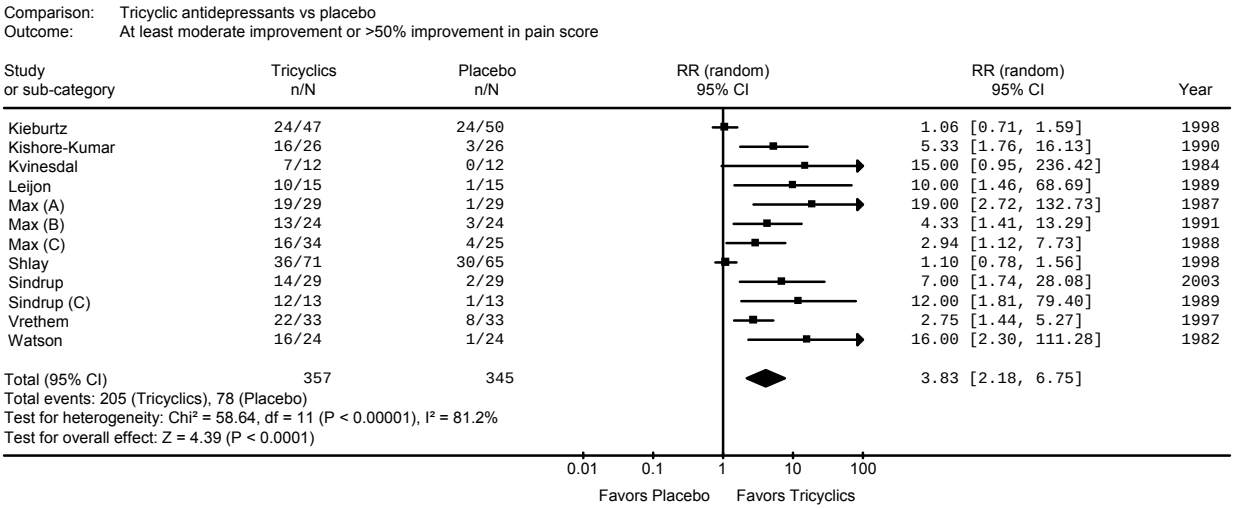
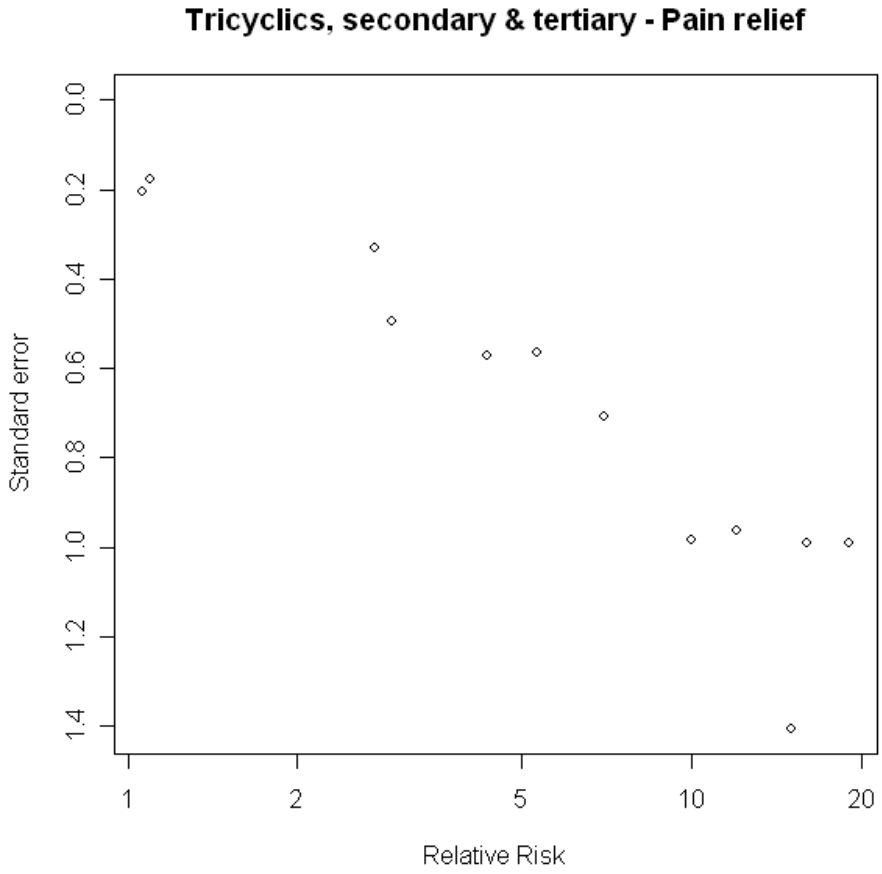


Figure 10. Funnel plot, placebo-controlled trials of tricyclic antidepressants, on relative risk for at least moderate improvement or >50% improvement in pain score



When pooled together, carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic were more effective than placebo for achieving at least moderate pain relief or >50% improvement in pain score (RR=1.50, 95% CI 1.15 to 1.96) in 13 trials (4 trials of lamotrigine,[111, 112, 114, 117] 3 trials of valproic acid,[106, 107, 110] 3 trials of carbamazepine,[84, 104, 105] 2 trials of oxcarbazepine,[118, 119] and one trial of topiramate[122]), though statistical heterogeneity was detected (I^2=60%). Funnel plot asymmetry was not apparent. Excluding the single small (N=15) trial rated poor-quality[84] did not significantly affect estimates or reduce heterogeneity (RR=1.47, 95% CI 1.12 to 1.91, I^2=61%, 12 trials). Excluding one trial evaluating patients with trigeminal neuralgia[117] also had little effect on the estimate (RR=1.53, 95% CI 1.14 to 2.06, I^2=64%). When trials were stratified by individual antiepileptic drugs, point estimates of relative risk were similar (RR ranging from 1.43 to 1.69), though imprecise for carbamazepine and valproic acid (Table 18). Stratification reduced statistical heterogeneity for lamotrigine (4 trials, I^2=0%) but not for valproic acid (3 trials, I^2=81%).

Table 18. Relative risk for at least moderate improvement in pain or >50% pain relief in placebo-controlled trials of carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid

Outcome	Drug	Number of trials	Relative risk vs Placebo	95% CI	Heterogeneity		
					I^2	Q	p(Q)
% mod/excel improvement or 50+% improvement/ decrease in pain score	**Antiepileptics - All**	**12**	**1.46**	**[1.13; 1.88]**	**58.2%**	**26.31**	**0.006**
	Oxcarbazepine	2	1.43	[0.94; 2.17]		1.86	0.173
	Carbamazepine	2	1.61	[0.29; 8.99]		6.27	0.012
	Lamotrigine	4	1.55	[1.21; 1.99]	0.0%	1.96	0.581
	Topiramate	1	1.69	[1.12; 2.53]			Not calculable
	Valproic acid	3	1.52	[0.33; 7.04]	81.0%	10.5	0.005

Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid were also more effective than placebo for mean improvement in pain scores (WMD -0.91 on a 0 to 10 scale, 95% CI -1.27 to -0.55) in six trials (one trial of oxcarbazepine,[119] one trial of lamotrigine,[111] two trials of topiramate,[120, 123] one trial of valproic acid,[109] and one trial of carbamazepine[84]). Differences versus placebo on the SF-McGill Pain Questionnaire (Total Score) were not significant, but data for pooling were only available from two trials of valproic acid.[107, 109]

There were no differences between either SSRI's or dextromethorphan and placebo in the proportion of patients experiencing at least moderate improvement or >50% improvement in pain scores, but only two trials of SSRI's[98, 99] and one trial of dextromethorphan[126] reported analyzable data for this outcome. No trials reported outcomes related to assessment of function suitable for pooling.

Indirect comparisons

In adjusted indirect analyses, gabapentin and duloxetine were both inferior to tricyclic antidepressants (RR=0.54, 95% CI 0.30 to 0.99 for gabapentin and RR=0.45, 95% CI 0.25 to 0.80 for duloxetine). Gabapentin and pregabalin were both superior to other antiepileptics

(RR=1.42, 95% CI 1.04 to 1.96 for gabapentin and RR=1.70, 95% CI 1.23 to 2.35 for pregabalin), and gabapentin and pregabalin were also both superior to SSRI's (RR=1.72, 95% CI 1.05 to 2.80 for gabapentin and RR=2.05, 95% CI 1.25 to 3.35 for pregabalin). However, only two trials of SSRI's[98, 99] contributed data to the indirect analyses. We found no differences between gabapentin or pregabalin and other antiepileptic drugs in mean improvement in pain scores or the SF-McGill Pain Questionnaire (Table 19). There were no differences in comparisons involving venlafaxine, but only two trials of venlafaxine[42, 71] contributed data to the indirect analysis. Only one trial of dextromethorphan reported usable data for indirect analyses, resulting in wide confidence intervals.[126]

Table 19. Indirect analyses of benefits from placebo-controlled trials of gabapentin, pregabalin, or SNRIs versus tricyclic antidepressants, other antiepileptic medications, SSRIs, or dextromethorphan for neuropathic pain

Outcome domain	Scale	Outcome	Treatment comparison	Effect	Effect Size	Lower limit of 95% CI	Upper limit of 95% CI
Patient-reported pain	Average pain, 0-10 Likert scale, 10 cm VAS, or 0-100 VAS (rescaled)	Mean score*	Gabapentin vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	WMD	-1.15	-3.57	1.27
			Pregabalin vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	WMD	-0.65	-1.09	-0.21
			Venlafaxine vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	WMD	-0.09	-1.31	1.13
	SF-McGill Pain Questionnaire, Total score	Mean score*	Gabapentin vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	WMD	2.47	-8.75	13.69
			Pregabalin vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	WMD	0.82	-9.90	11.54
	Pain relief/Response	% at least moderate improvement or >50% improvement in pain score	Gabapentin vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	RR	1.42	1.04	1.96
			Gabapentin vs tricyclics antidepressants	RR	0.54	0.30	0.99

Outcome domain	Scale	Outcome	Treatment comparison	Effect	Effect Size	Lower limit of 95% CI	Upper limit of 95% CI
			Gabapentin vs. SSRIs	RR	1.72	1.05	2.80
			Gabapentin vs. dextromethorphan	RR	1.25	0.37	4.22
			Pregabalin vs carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	RR	1.70	1.23	2.35
			Pregabalin vs tricyclic antidepressants	RR	0.65	0.36	1.18
			Pregabalin vs. SSRIs	RR	2.05	1.25	3.35
			Pregabalin vs. dextromethorphan	RR	1.49	0.44	5.04
			Duloxetine vs. carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	RR	1.17	0.87	1.58
			Duloxetine vs. tricyclic antidepressants	RR	0.45	0.25	0.80
			Duloxetine vs. SSRIs	RR	1.41	0.88	2.28
			Duloxetine vs. dextromethorphan	RR	1.02	0.30	3.45
			Venlafaxine vs. carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	RR	1.23	0.50	3.03
			Venlafaxine vs. tricyclic antidepressants	RR	0.47	0.17	1.32
			Venlafaxine vs. SSRIs	RR	1.48	0.56	3.94
			Venlafaxine vs. dextromethorphan	RR	1.07	0.24	4.74

*Higher score means worse pain
RR=relative risk, WMD=weighted mean difference, VAS=visual analogue scale, CI=confidence interval

The pooled rate for the proportion of patients reporting at least moderate improvement or >50% improvement in pain score in patients randomized to placebo was 16% (95% CI 7% to 24%) in trials of tricyclic antidepressants and 27% (95% CI 18% to 35%) in trials of older antiepileptic medications (compared to 21% for gabapentin and 14% for pregabalin).

Sensitivity and subgroup analyses had little effect on conclusions involving tricyclic antidepressants. For the outcome of at least moderate pain relief or >50% pain relief, excluding one small (N=15), poor-quality trial of carbamazepine[84] had no effect on any of the indirect

estimates. For comparisons involving tricyclic antidepressants, excluding trials of HIV-infected patients,[81, 91] excluding poor-quality trials,[82, 92] limiting the analysis to crossover trials, and adjusting for potential publication bias using the trim-and-fill method only led to small changes in estimates (Table 20). However, for some comparisons estimates that were non-significant based on all trials became significant in sensitivity analyses (venlafaxine or pregabalin versus tricyclics).

Table 20. Sensitivity analyses on indirect estimates for gabapentin, pregabalin, duloxetine, and venlafaxine versus tricyclic antidepressants for pain relief

Outcome	Treatment comparison	Trials included in analysis	Number of trials in indirect analysis	Relative risk	Lower limit of 95% CI	Upper limit of 95% CI
% at least moderate improvement or >50% improvement in pain score	Gabapentin vs tricyclics antidepressants	All trials	20	0.54	0.30	0.99
		Excluding trials of HIV-associated neuropathic pain	18	0.44	0.28	0.69
		Excluding trials of HIV-associated neuropathic pain and poor-quality trials	16	0.44	0.26	0.75
		Excluding trials of HIV-associated neuropathic pain and limiting analysis to crossover trials	11	0.43	0.24	0.76
		Excluding trials of HIV-associated neuropathic pain and adjusted for funnel plot asymmetry using trim-and-fill method	23	0.56	0.34	0.92
	Pregabalin vs tricyclic antidepressants	All trials	19	0.65	0.36	1.18
		Excluding trials of HIV-associated neuropathic pain	17	0.52	0.33	0.83
		Excluding trials of HIV-associated neuropathic pain and poor-quality trials	15	0.53	0.31	0.90
		Excluding trials of HIV-associated neuropathic pain and adjusted for funnel plot asymmetry using trim-and-fill method	22	0.66	0.40	1.10
	Duloxetine vs. tricyclic antidepressants	All trials	15	0.45	0.25	0.80
		Excluding trials of HIV-associated neuropathic pain	13	0.36	0.23	0.56
		Excluding trials of HIV-associated neuropathic pain and poor-quality trials	11	0.36	0.22	0.61

Outcome	Treatment comparison	Trials included in analysis	Number of trials in indirect analysis	Relative risk	Lower limit of 95% CI	Upper limit of 95% CI
		Excluding trials of HIV-associated neuropathic pain and adjusted for funnel plot asymmetry using trim-and-fill method	18	0.46	0.28	0.75
		All trials	14	0.47	0.17	1.32
		Excluding trials of HIV-associated neuropathic pain	12	0.38	0.14	0.99
	Venlafaxine vs. tricyclic antidepressants	Excluding trials of HIV-associated neuropathic pain and poor-quality trials	10	0.38	0.14	1.03
		Excluding trials of HIV-associated neuropathic pain and adjusted for funnel plot asymmetry using trim-and-fill method	17	0.48	0.18	1.28

We also performed a subgroup analysis based on four placebo-controlled trials of lamotrigine.[111, 112, 114, 117] Pregabalin was superior to lamotrigine for achieving pain relief (RR=1.60, 95% CI 1.16 to 2.20), though results were similar to the estimate for pregabalin versus carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid (RR=1.70, 95% CI 1.23 to 2.35). We did not perform subgroup analyses on other individual antiepileptic medications, which were each evaluated in one to three trials and associated with wider confidence intervals than estimates for lamotrigine.

Comparison between direct and indirect estimates

For the outcome pain relief (at least 50% improvement in pain score or at least moderate pain relief), the discrepancy between direct (RR=0.99, 95% CI 0.76 to 1.29) and indirect estimates (RR=0.54, 95% CI 0.54 to 0.99) for gabapentin versus tricyclic antidepressants approached but did not reach statistical significance (p=0.07). However, when two trials of tricyclic antidepressants for HIV-associated neuropathic pain[81, 91] were excluded from the indirect analysis (RR=0.44, 95% CI 0.28 to 0.69), the discrepancy was highly statistically significant (p=0.003).

Key Question 3. What are the comparative harms of pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel) for neuropathic pain?

Summary of findings

We found no head-to-head trials directly comparing harms associated with pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel) for neuropathic pain. In adjusted indirect analyses, gabapentin was associated with a lower likelihood of withdrawal due to adverse events compared to pregabalin at comparable doses. We found no differences between gabapentin and

pregabalin in rates of overall withdrawals, somnolence/sedation, or dizziness. Gabapentin and pregabalin are associated with more somnolence/sedation compared to venlafaxine. Pregabalin is also associated with more dry mouth than venlafaxine. There are no clear differences between duloxetine and either gabapentin, pregabalin, or venlafaxine for any adverse event assessed, though analyses were limited by small numbers of trials of duloxetine. Excluding trials that did not enroll previous non-responders to gabapentin and stratifying trials by use of parallel-group versus crossover design had little effect on estimates. There was insufficient data to perform indirect analyses on harms associated with topical lidocaine patch or gel. Few trials reported rates of serious adverse events.

Results of indirect analyses should be interpreted cautiously. It was difficult to judge reliability of harms data due to poor reporting of methods used to define and ascertain adverse events and because estimates for commonly reported adverse events ranged widely across trials. In addition, some adverse events were reported in only a minority of trials.

Detailed assessment

Systematic reviews

Four systematic reviews evaluated adverse events associated with newer drugs for neuropathic pain versus placebo (Table 21).[12, 33, 34, 38] All four reported estimates for withdrawal due to adverse events, which may be a surrogate for more serious adverse events. However, data from systematic reviews are of limited usefulness for assessing comparative risks because none attempted formal indirect analyses. Furthermore, two systematic reviews pooled data on harms together for more than one newer medication for NP.[33, 38] One systematic review reported a number needed to cause one withdrawal due to adverse events) of 17.8 (95% CI, 12 to 30) for gabapentin or pregabalin (13 trials).[33] A second systematic review, which pooled results from trials of gabapentin, pregabalin, and oxcarbazepine, reported an odds ratio for withdrawal due to adverse events of 2.98 (95% CI, 1.75 to 5.07), or a number needed to harm of about 11.[38] However, nearly 70% of the withdrawals due to adverse events occurred in two trials of oxcarbazepine, which reported odds ratios of 4.50 (95% CI 1.68 to 12.06) and 4.13 (95% CI 1.57 to 10.87). From data reported in the systematic review, we re-calculated a pooled odds ratio of 1.78 (95% CI 0.78 to 4.04) for the three trials of gabapentin and pregabalin, or a NNH of about 29. Systematic reviews that reported results separately for gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) were limited by sparse data (1 to 5 trials) or heterogeneity (for pregabalin in one systematic review[34]). Neither venlafaxine nor topical lidocaine were associated with increased withdrawal due to adverse events compared to placebo in two systematic reviews.[33, 34]

Only two systematic reviews estimated risk of minor harms (defined as adverse events not leading to withdrawal).[12, 34] For gabapentin, estimates from the two systematic reviews were similar, with numbers needed to cause one minor adverse event of 3.7 (95% CI, 2.4 to 5.4)[12] and 4.1 (95% CI, 3.2 to 5.7).[34] Estimates of minor harms compared to placebo were similar for gabapentin (NNH 4.1, 95% CI 3.2 to 5.7) and pregabalin (NNH=4.3, 95% CI 2.78 to 9.18) in one systematic review.[34]

Table 21. Summary of results systematic reviews of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine for neuropathic pain: harms

Drug	Review	Type of neuropathic pain	Withdrawals due to AEs Newer medication for neuropathic pain vs. placebo NNH (95% CI)	Minor harms: Newer medication for neuropathic pain vs. placebo NNH (95% CI)
Gabapentin or pregabalin studies (results pooled for both medications)	Finnerup, 2005[33]	Any NP	17.8 (12 to 30); 7 trials of gabapentin and 6 trials of pregabalin	NR
Gabapentin, pregabalin, or oxcarbazepine	Wong, 2007[38]	DN	OR=2.98 (1.75 to 5.07); 1 trial of gabapentin, 2 trials of pregabalin, and 2 trials of oxcarbazepine	NR
Gabapentin	Wiffen, 2005[12]	Any NP	NS; 5 trials	3.7 (2.4 to 5.4); 2 trials
	Hempenstall, 2005[34]	PHN	12.25 (7.69–30.2); 2 trials	4.07 (3.15 to 5.74); 3 trials
Pregabalin	Hempenstall, 2005[34]	PHN	Not calculated (failed heterogeneity analysis); 2 trials	4.27 (2.78-9.18); 1 trial
Duloxetine	Wong, 2007[38]	DN	60 mg: OR=2.55 (1.73-3.77); 2 trials 120 mg: OR=2.10 (1.03-4.27); 2 trials	NR
Venlafaxine	Finnerup, 2005[33]	Any NP	NS; 3 trials	NR
Topical lidocaine	Finnerup, 2005[33]	Any NP	NS; 3 trials	NR
	Hempenstall, 2005[34]	PHN	NS; 1 trial	NR

Direct Evidence: Randomized Trials

We identified no randomized trials directly comparing adverse events for gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) versus one another.

Indirect evidence: Randomized Trials

Placebo-controlled trials of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or gel) for neuropathic pain included in this review are described in more detail in Key Question 1. Details of adverse events reported in these trials are shown in Evidence Table 12. Overall withdrawals and withdrawals due to adverse events, dizziness or vertigo, and somnolence were the most frequently reported adverse events. Among 12 gabapentin trials, for example, total withdrawals were reported in 11 trials, withdrawals due to adverse events in 8,

dizziness or vertigo in 9, and somnolence, sedation, fatigue, or lethargy in 9. Dry mouth was reported in 7 of 8 trials of pregabalin but infrequently reported for the other drugs. Ataxia or gait disturbance was reported in 3 trials of pregabalin and 2 trials of gabapentin.

"Serious" adverse events were reported by 6 trials of pregabalin (range 0% to 3.6%),[60, 62, 64-67] 5 of gabapentin (range 0% to 2.6%),[51, 52, 54-56] 3 of duloxetine (2.6% to 5.1%), [68-70] 1 of venlafaxine (9% to 12%),[71] and 2 of lidocaine patch (0% in both trials).[44, 45] However, only three trials[67, 68, 70] defined the term "serious." One of these trials only reported an overall (duloxetine or placebo) rate of serious adverse events.[68] Seven others trials reporting serious adverse events reported no cases.[44, 45, 51, 52, 55, 60, 64] From pooled estimates involving the remaining trials, we found no differences between gabapentin, pregabalin, duloxetine, or venlafaxine versus placebo for risk of serious adverse events, though most estimates were fairly imprecise and could be affected by selecting outcomes reporting bias (Table 22).

Pooled estimates for other adverse events are also presented in Table 22. Trials that reported no events with either active treatment or placebo could not be pooled. In general, estimates of adverse events for different drugs were similar or associated with overlapping confidence intervals, with no obvious differences between medications. However, gabapentin was the only newer medication for NP not associated with a statistically significant increased rate of withdrawals due to adverse events compared to placebo (RR=1.29, 95% CI, 0.90 to 1.85, I^2=0%). There was little change in estimates when poor-quality trials or trials that excluded previous non-responders to gabapentin were excluded from the analysis, or when trials were stratified by use of parallel-group versus crossover design. In a stratified analysis, pregabalin 150 mg/day was associated with a lower risk of withdrawal due to adverse events compared to placebo than trials evaluating pregabalin 300 to 600 mg/day (RR=1.07, 95% CI 0.59 to 1.97, I^2=0%, 4 trials[62, 63, 65, 67] versus RR=2.49, 95% CI 1.77 to 3.52, I^2=3%, 8 trials;[60-67] p=0.040 for difference in pooled estimates). All trials of gabapentin reporting poolable data for withdrawal due to adverse events titrated patients to doses of at least 2400 mg/day.

Table 22. Pooled results for harms from placebo-controlled trials of gabapentin, pregabalin, duloxetine, and venlafaxine for neuropathic pain

Outcome type	Outcome	Drug	Effect	N	Effect size vs Placebo	95% CI	Heterogeneity I^2	Heterogeneity Q	Heterogeneity p(Q)
Withdrawals		Gabapentin >=2400 mg/day	RR	9	0.95	[0.75; 1.20]	0.0%	7.0	0.533
		Pregabalin 150 to 600 mg/day	RR	8	0.95	[0.70; 1.28]	65.5%	20.3	0.005
	Total withdrawals	Pregabalin 300 to 600 mg/day	RR	8	1.01	[0.76; 2.32]	59.5%	17.3	0.016
		Pregabalin 150 mg/day	RR	4	0.71	[0.42; 1.20]	53.5%	6.45	0.092
		Duloxetine	RR	3	1.14	[0.89; 1.45]	0.0%	0.8	0.684
		Venlafaxine	RR	4	1.51	[0.90; 2.53]	0.0%	1.5	0.687
	Adverse event withdrawals	Gabapentin >=2400 mg/day	RR	6	1.29	[0.90; 1.85]	11.5%	5.7	0.342
		Pregabalin 150 to 600 mg/day	RR	8	2.23	[1.52; 3.28]	23.1%	9.1	0.246
		Pregabalin 300	RR	8	2.49	[1.77; 3.52]	3%	7.24	0.40

		to 600 mg/day							
		Pregabalin 150 mg/day	RR	4	1.07	[0.59; 1.97]	0%	1.09	0.78
		Duloxetine	RR	3	2.26	[1.39; 3.67]	0.0%	0.4	0.823
		Venlafaxine	RR	4	2.39	[1.12; 5.07]	0.0%	0.2	0.984
Adverse events	Dizziness or vertigo	Gabapentin >=2400 mg/day	RR	9	3.00	[2.20; 4.10]	0.0%	7.3	0.508
		Pregabalin 150 to 600 mg/day	RR	8	2.82	[1.98; 4.02]	38.9%	11.5	0.120
		Pregabalin 150 mg/day	RR	4	1.45	[0.82; 2.55]	25.7%	4.0	0.257
		Duloxetine	RR	2	2.06	[1.19; 3.57]		0.2	0.655
		Venlafaxine	RR	1	2.00	[0.19; 21.00]			
	Movement disorder: ataxia, gait abnormal, "drunken", or incoordination	Gabapentin >=2400 mg/day	RR	2	3.72	[0.43; 31.90]		3.0	0.084
		Pregabalin 150 to 600 mg/day	RR	3	4.76	[1.59; 14.26]	0.0%	1.1	0.574
	Somnolence, sedation, fatigue, or lethargy	Gabapentin >=2400 mg/day	RR	9	3.61	[2.51; 5.19]	0.0%	2.1	0.976
		Pregabalin 150 to 600 mg/day	RR	8	3.89	[2.71; 5.59]	0.0%	2.9	0.891
		Pregabalin 150 mg/day	RR	4	1.70	[0.94; 3.09]	0.0%	0.9	0.818
		Duloxetine	RR	2	4.14	[0.90; 18.94]		2.6	0.106
		Venlafaxine	RR	4	1.38	[0.80; 2.41]	96.8%	92.6	0.000
	Dry mouth	Gabapentin >=2400 mg/day	RR	1	5.97	[0.79; 45.35]			Not calculable
		Pregabalin 150 to 600 mg/day	RR	7	2.77	[1.49; 5.13]	14.3%	7.0	0.321
		Pregabalin 150 mg/day	RR	4	2.80	[0.74; 10.68]	25.2%	4.0	0.260
		Duloxetine	RR	1	1.49	[0.67; 3.29]			Not calculable
		Venlafaxine	RR	3	1.10	[0.76; 1.61]	0.0%	0.5	0.763
	Serious adverse events	Gabapentin >=2400 mg/day	RR	2	1.21	[0.38; 3.85]		0.3	0.597
		Pregabalin 150 to 600 mg/day	RR	4	1.09	[0.49; 2.42]	0.0%	1.84	0.61
		Duloxetine	RR	2	0.70	[0.30; 1.62]		0.02	0.90
		Venlafaxine	RR	1	1.23	[0.51; 2.97]			Not calculable

Indirect comparisons

Indirect analyses of placebo-controlled trials found no differences between gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) for neuropathic pain in rates of overall withdrawals (Table 23). In all trials included in the indirect analyses, the goal dose of gabapentin was at least 2400 mg/day, and ranged from 150 to 600 mg/day for pregabalin. Gabapentin was associated with a lower likelihood of withdrawal due to adverse events compared to pregabalin 150 to 600 mg/day (RR=0.58, 96% CI 0.34 to 0.98). Results were similar when gabapentin was compared to pregabalin 300 to 600 mg/day. Gabapentin and pregabalin 150 to 600 mg/day were each associated with greater risk of somnolence compared to venlafaxine (RR=2.62, 95% CI 1.35 to 5.06 and RR=2.82, 95% CI 1.46 to 5.45, respectively). Pregabalin was also associated with a greater risk of dry mouth compared to venlafaxine (RR=2.52, 95% CI 1.22 to 5.19). Gabapentin was associated with a higher risk of dizziness or somnolence compared to pregabalin 150 mg/day (RR=2.12, 95% CI 1.06 to 4.26), but there was no difference when compared to pregabalin 150 to 600 mg/day (RR=0.93, 95% CI 0.56 to 1.55). Excluding trials that did not enroll previous non-responders to gabapentin and stratifying trials by use of parallel-group versus crossover design had little effect on estimates. No trials included in the indirect analyses were rated poor-quality. We did not perform indirect analyses on serious adverse events because few trials reported this outcome, and confidence intervals for pooled estimates from placebo-controlled trials overlapped for different drugs.

As with all indirect comparisons, results should be interpreted cautiously because of clinical diversity across the different sets of trials in populations, interventions (average doses or methods of dose titration), and duration of exposure. In addition, assessment of harms was a secondary outcome in all of the trials. Very few trials reported pre-defined criteria for different harms, few trials used active methods to assess harms, and assessment and reporting of harms in general was poorly standardized. Trials could vary how they defined adverse events, in measures used to minimize or prevent adverse events or adverse event-related withdrawals, and in whether unmasking of interventions occurred before adverse events were assessed. All of these factors could lead to variation in estimates (and reliability of estimates) for adverse events across trials. For example, rates of withdrawal due to adverse events ranged from none[51, 53] to 19%[54, 55] in patients randomized to gabapentin, and rates of somnolence ranged from 14%[56] to 80%.[52]

Table 23. Indirect analyses on harms from placebo-controlled trials of gabapentin, pregabalin, duloxetine, and venlafaxine for neuropathic pain

Type of outcome	Outcome	Medication comparison	Relative risk	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
Withdrawals	Total withdrawals	Gabapentin >=2400 mg/day vs Pregabalin 150 to 600 mg/day	1.00	0.68	1.47
		Gabapentin >=2400 mg/day vs. Pregabalin 150 mg/day	1.34	0.75	2.38
		Gabapentin >=2400 mg/day vs. Pregabalin 300 to 600 mg/day	0.94	0.65	1.36
		Gabapentin >=2400 mg/day vs Duloxetine	0.83	0.59	1.17
		Gabapentin >=2400 mg/day vs Venlafaxine	0.63	0.36	1.11
		Pregabalin 150 to 600 mg/day vs Duloxetine	0.83	0.57	1.23
		Pregabalin 150 mg/day vs Duloxetine	0.62	0.35	1.11
		Pregabalin 300 to 600 mg/day vs. Duloxetine	0.89	0.61	1.29
		Pregabalin 150 to 600 mg/day vs Venlafaxine	0.63	0.35	1.14
		Pregabalin 150 mg/day vs Venlafaxine	0.47	0.23	0.98
		Pregabalin 300 to 600 mg/day vs Venlafaxine	0.67	0.37	1.21
		Duloxetine vs Venlafaxine	0.75	0.43	1.34
	Adverse events withdrawals	Gabapentin >=2400 mg/day vs Pregabalin 150 to 600 mg/day	0.58	0.34	0.98
		Gabapentin >=2400 mg/day vs. Pregabalin 150 mg/day	1.21	0.60	2.43
		Gabapentin >=2400 mg/day vs. Pregabalin 300 to 600 mg/day	0.52	0.31	0.85
		Gabapentin >=2400 mg/day vs Duloxetine	0.57	0.31	1.04
		Gabapentin >=2400 mg/day vs Venlafaxine	0.54	0.23	1.25
		Pregabalin 150 to 600 mg/day vs Duloxetine	0.99	0.53	1.83
		Pregabalin 150 mg/day vs Duloxetine	0.47	0.22	1.03
		Pregabalin 300 to 600 mg/day vs. Duloxetine	1.10	0.61	2.00
		Pregabalin 150 to 600 mg/day vs Venlafaxine	0.93	0.40	2.18
		Pregabalin 150 mg/day vs Venlafaxine	0.45	0.17	1.18
		Pregabalin 300 to 600 mg/day vs Venlafaxine	1.04	0.45	2.39
		Duloxetine vs Venlafaxine	0.95	0.39	2.32
Adverse events	Dizziness or vertigo	Gabapentin >=2400 mg/day vs Pregabalin 150 to 600 mg/day	1.06	0.66	1.70
		Gabapentin >=2400 mg/day vs Pregabalin 150 mg/day	2.07	1.08	3.95
		Gabapentin >=2400 mg/day vs	1.46	0.77	2.74

Type of outcome	Outcome	Medication comparison	Relative risk	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
		Duloxetine			
		Gabapentin >=2400 mg/day vs Venlafaxine	1.50	0.14	16.10
		Pregabalin vs Duloxetine	1.37	0.71	2.63
		Pregabalin vs Venlafaxine	1.41	0.13	15.22
		Pregabalin 150 mg/day vs Duloxetine	0.70	0.32	1.55
		Pregabalin 150 mg/day vs Venlafaxine	0.73	0.06	8.15
		Duloxetine vs Venlafaxine	1.03	0.09	11.54
	Movement disorder: ataxia, gait abnormal, 'drunken', or incoordination	Gabapentin vs Pregabalin	0.78	0.07	8.76
	Somnolence, sedation, fatigue, or lethargy	Gabapentin >=2400 mg/day vs Pregabalin 150 to 600 mg/day	0.93	0.56	1.55
		Gabapentin >=2400 mg/day vs Pregabalin 150 mg/day	2.12	1.06	4.26
		Gabapentin >=2400 mg/day vs Duloxetine	0.87	0.18	4.17
		Gabapentin >=2400 mg/day vs Venlafaxine	2.62	1.35	5.06
		Pregabalin 150 to 600 mg/day vs Duloxetine	0.94	0.20	4.50
		Pregabalin 150 to 600 mg/day vs Venlafaxine	2.82	1.46	5.45
		Pregabalin 150 mg/day vs Duloxetine	0.41	0.08	2.11
		Pregabalin 150 mg/day vs Venlafaxine	1.23	0.55	2.77
		Duloxetine vs Venlafaxine	3.00	0.59	15.16
	Dry mouth	Gabapentin >=2400 mg/day vs Pregabalin 150 to 600 mg/day	2.16	0.26	17.91
		Gabapentin >=2400 mg/day vs Pregabalin 150 mg/day	2.13	0.19	24.11
		Gabapentin >=2400 mg/day vs Duloxetine	4.01	0.45	35.30
		Gabapentin >=2400 mg/day vs Venlafaxine	5.43	0.69	42.56
		Pregabalin vs Duloxetine	1.86	0.68	5.09
		Pregabalin vs Venlafaxine	2.52	1.22	5.19
		Pregabalin 150 mg/day vs Duloxetine	1.88	0.40	8.89
		Pregabalin 150 mg/day vs Venlafaxine	2.55	0.64	10.18
		Duloxetine vs Venlafaxine	1.35	0.56	3.26
	Serious adverse events	Gabapentin >=2400 mg/day vs Duloxetine	1.61	0.30	8.78

Key Question 4. What are the comparative harms of pregabalin, gabapentin, SNRIs, or topical lidocaine (patch or gel) versus other drugs (other antiepileptics, tricyclic antidepressants (including tertiary versus secondary amines), SSRIs, or dextromethorphan) for neuropathic pain?

Summary of findings

There are insufficient data from four small head-to-head trials to reliably judge comparative harms of gabapentin or venlafaxine versus tricyclic antidepressants. For the outcome withdrawal due to adverse events, adjusted indirect analyses of placebo-controlled trials found gabapentin associated with lower risk compared to the antiepileptic drugs carbamazepine, oxcarbazepine, topiramate, and valproic acid. Pregabalin is associated with higher risk for withdrawal due to adverse events compared to lamotrigine. Both gabapentin and pregabalin are associated with higher risk of somnolence/sedation compared to other antiepileptic drugs or tricyclic antidepressants and higher risk of dizziness/vertigo compared to tricyclic antidepressants. There are no differences in risk for any harm between duloxetine or venlafaxine versus tricyclic antidepressants or the antiepileptic medications carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid, but analyses are limited by small numbers of trials. There are insufficient data from trials of topical lidocaine (patch or gel), SSRIs or dextromethorphan to perform indirect analyses. Few trials reported rates of serious adverse events.

Results of indirect analyses should be interpreted cautiously because it was difficult to judge reliability of harms data due to poor reporting of methods used to define and ascertain adverse events, and because estimates for commonly reported adverse events widely across trials of the same drug or drug class.

Detailed assessment

Systematic Reviews

Five systematic reviews reported pooled estimates for risk of withdrawal due to adverse events for newer medications for neuropathic pain versus placebo (Table 24).[2, 33, 34, 36, 38] The systematic reviews are of limited usefulness for assessing comparative harms of gabapentin, pregabalin, SNRIs, or topical lidocaine (patch or gel) versus other antiepileptics, tricyclic antidepressants, SSRIs, or dextromethorphan for neuropathic pain because none attempted to perform formal indirect analyses. Versus placebo, estimates for tricyclic antidepressants were relatively consistent across three systematic reviews, with numbers needed to cause one withdrawal due to adverse events ranging from 15 to 17, despite differences in the number of trials included.[2, 33, 34] The systematic review reporting estimates from the most trials of tricyclic antidepressants (21 trials of any neuropathic pain condition) estimated a number needed to cause one withdrawal due to adverse event of 15 (95% CI 10 to 25).[33] Among the antiepileptic drugs, topiramate appeared associated with a greater likelihood of withdrawal due to adverse events compared to carbamazepine, though estimates for topiramate were based on two trials.[33] Estimates of withdrawal due to adverse events for SSRIs and dextromethorphan were imprecise due to sparse data.[2, 33, 34, 38] Estimates of numbers needed to cause a minor harm (an adverse event not resulting in discontinuation of the medication) were similar for tricyclic

antidepressants, carbamazepine, and SSRI's in three systematic reviews (each versus placebo).[2, 33, 34]

Table 24. Summary of results of systematic reviews of tricyclic antidepressants, SSRIs, dextromethorphan and the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid for neuropathic pain

Drug	Review	Type of neuropathic pain	Withdrawals due to AEs: Newer medication for neuropathic pain vs. placebo NNH (95% CI)	Minor harms: Newer medication for neuropathic pain vs. placebo NNH (95% CI)
Tricyclic Antidepressants	Hempenstall, 2005[34]	PHN	16.9 (8.85 to 178); 4 trials	5.67 (3.34-18.58); 3 trials
	Finnerup, 2005[33]	Any NP	14.7 (10 to 25); 21 trials	NR
	Saarto, 2005[2]	Any NP	16 (10 to 45); number of trials not reported	4.6 (3.5 to 6.7); number of trials not reported
	Wong, 2007[38]	DN	OR=2.32 (0.59 to 9.69); 3 trials	NR
Older antiepileptics (carbamazepine, lamotrigine, valproic acid, carbamazepine, topiramate)	Wong, 2007[38]	DN	OR=1.51 (0.33 to 6.96); 1 carbamazepine, 1 lamotrigine, 2 sodium valproate	NR
	Wiffen, 2005[36]	Any NP	NS; number of trials not reported	3.7 (2.4 to 7.8); number of trials not reported
	Finnerup, 2005[33]	Any NP	Carbamazepine: 22 (13 to 79); 4 trials Topiramate: 6.3 (5 to 8); 2 trials	NR
SSRIs	Finnerup, 2005[33]	Any NP	NS; 2 trials	NR
	Saarto, 2005[2]	Any NP	16 (10 to 45); number of trials not reported	4.6 (3.5 to 6.7)
	Wong, 2007[38]	DN	OR=5.6 (0.3 to 125); 1 trial	NR
Dextromethorphan	Finnerup, 2005[33]	Any NP	8.8 (6 to 21); 3 trials	NR
	Hempenstall, 2005[34]	PHN	3.8 (2.09 to 21.3); 1 trial	NR

Randomized Trials: Direct Evidence

There was insufficient evidence from four small (N=25 to 70), fair quality, head-to-head trials directly comparing a newer versus an older medication for neuropathic pain to determine whether one medication or another is associated with fewer harms.[39-42] Study characteristics of these trials are described in more detail in Key Question 2.

In two small (N=25 in both) trials comparing gabapentin versus amitriptyline for diabetic neuropathy, data on adverse events were somewhat inconsistent (Table 25). Amitriptyline was associated with a higher likelihood of experiencing any adverse event compared to gabapentin in one open-label trial,[40] but there were no differences in overall frequency of adverse events in a second (double-blinded) trial.[41] In a trial of nortriptyline versus gabapentin for post-herptetic neuralgia (N=70), some adverse events occurred more frequently in patients randomized to nortriptyline (dry mouth, constipation, postural hypotension), but the proportion of patients randomized to gabapentin that experienced adverse events was not reported.[39] There was no clear difference between gabapentin and tricyclics in withdrawal due to adverse events, but only three cases were reported in two trials,[39, 41] with the third trial[40] reporting none.

Table 25. Head-to-head trials of gabapentin or venlafaxine versus tricyclic antidepressants: adverse events

Study, year (Quality)	Comparison	Population	Withdrawals due to adverse events	Specific adverse Events	Conclusions
Dallocchio, 2000[40] Italy (Fair)	amitriptyline mean 53 mg (maximum 90 mg) gabapentin mean 1785 mg (maximum 2400 mg) 8 weeks, parallel group	Painful diabetic neuropathy N=25	0/13 vs. 0/12	11 amitriptyline (somnolence, dizziness, dry mouth most common) vs 4 gabapentin (2 dizziness, 1 somnolence, 1 ataxia) 92% vs 31%; p=0.003	Adverse events significantly more frequent with amitriptyline.
Morello, 1999[41] US (Fair)	amitriptyline mean 59 mg (maximum 75mg) gabapentin mean 1565 mg (maximum 1800 mg) 6 weeks, crossover, placebo-controlled	Painful diabetic neuropathy N=25	0/23 gabapentin vs. 2/24 amitriptyline 1 in each group crossed over early due to adverse events	Sedation: 12/23 gabapentin vs. 8/24 amitriptyline Dry mouth: 4/23 vs. 8/24 Dizziness: 7/23 vs. 2/24 No difference between treatments in frequency of adverse events except weight gain (6 amitriptyline vs 0 gabapentin)	Similar frequency of adverse events.

Study, year (Quality)	Comparison	Population	Withdrawals due to adverse events	Specific adverse Events	Conclusions
Chandra, 2006[39] India (Fair)	nortriptyline up to 75 mg gabapentin up to 2700 mg 8 weeks, parallel	Postherpetic neuralgia N=70	0/34 gabapentin vs. 1/36 nortriptyline	Sedation: 4/34 gabapentin vs. 6/36 nortriptyline Dry mouth: 0/34 vs. 18/36 Dry mouth, constipation, and postural hypotension significantly more frequent in nortriptyline group.	Some adverse events significantly more frequent with nortriptyline.
Sindrup, 2003[42] Denmark (Fair)	imipramine 150 mg venlafaxine 225 mg 4 weeks, crossover, placebo-controlled	Mixed (47% painful diabetic neuropathy) N=40 (32 analyzed)	0/40 imipramine vs 4/40 venlafaxine	20 patients in each treatment group had AEs; similar frequency except more dry mouth with imipramine (N=12 vs 4) and more tiredness with venlafaxine (N=9 vs 3).	Similar frequency of adverse events

Quantitatively, there was no difference between gabapentin versus tricyclic antidepressants in rates of withdrawal due to adverse events, but estimates are imprecise (RR 0.27, 95% CI 0.03 to 2.34).[39, 41] Other adverse events were only reported by one or two of the trials. There was no significant difference between gabapentin and tricyclics in overall adverse events (RR 0.64, 95% CI 0.18 to 2.26, 2 trials[40, 41]), sedation (RR 1.22, 95% CI 0.59 to 2.52, 2 trials[39, 41]), dry mouth (RR 0.16, 95% CI 0.01 to 2.66, 2 trials[39, 41]), or dizziness (RR 3.65, 95% CI 0.85 to 15.78, 1 trial[41]).

In one trial comparing imipramine versus venlafaxine (N=32) for mixed pain conditions, the frequency of experiencing any adverse event was similar in both treatment groups, though dry mouth was more common with amitriptyline and tiredness more common with venlafaxine.[42]

Randomized Trials: Indirect evidence

Placebo-controlled trials of tricyclic antidepressants, SSRIs, dextromethorphan, and the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid for neuropathic pain included are described in more detail in Key Question 2. Adverse events reported in these trials are shown in Evidence Table 13.

Serious adverse events were reported in one trial of lamotrigine,[114] two trials of oxcarbazepine[118, 119], and two trials of topiramate.[122, 123] Only two[114, 122] of the five trials, however, defined the term "serious." The trial of lamotrigine reported no serious adverse events.[114] No trials of tricyclic antidepressants reported serious adverse events.

Overall withdrawals and withdrawals due to adverse events, dizziness or vertigo, somnolence were the most frequently reported adverse events. Most (20 of 24) trials of carbamazepine, oxcarbazepine, topiramate, lamotrigine, and valproic acid reported overall withdrawals and withdrawals due to adverse events. Among 21 trials of tricyclic antidepressants, 13[79, 81-84, 86, 88-90, 92, 94, 95, 97] reported overall withdrawals and 14[79, 81-84, 86, 88-90, 92, 94-97]reported withdrawals due to adverse events. Somnolence, sedation, fatigue, or lethargy was reported in 12 trials[100, 103, 104, 109, 111, 117-123] of carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid and 12 trials[79-82, 85-87, 89, 90, 93, 96, 97] of tricyclic antidepressants and dizziness in 10[100, 103, 104, 106, 111, 117-120, 122]and 9 trials,[80-82, 85, 87, 89, 90, 93, 96] respectively. No trials of carbamazepine, oxcarbazepine, topiramate, lamotrigine, or valproic acid reported rates of dry mouth, though 13 trials[80-83, 85-87, 89, 90, 92, 93, 96, 97]of tricyclic antidepressants reported this outcome. Poolable data on harms were only reported by two trials of SSRIs[98, 99] and two trials of dextromethorphan.[124, 126]

Pooled estimates for adverse events are presented in Table 26. In a stratified analysis, secondary and tertiary amines tricyclic antidepressants were associated with similar rates of total withdrawals, adverse event related withdrawals, somnolence, or dry mouth. In general, estimates of adverse events for tricyclic antidepressants, SSRIs, dextromethorphan, and the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, and valproic acid were associated with overlapping confidence intervals, even when point estimates suggested potential differences in risk. For example, the antiepileptic drugs but not tricyclic antidepressants (either secondary or tertiary amines) were associated with increased risk of withdrawal, withdrawal due to adverse events, and dizziness compared to placebo, but confidence intervals for each of these outcomes overlapped for the two drug classes.

Table 26. Pooled results for harms from placebo-controlled trials of tricyclic antidepressants, SSRIs, dextromethorphan, carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid for neuropathic pain

Outcome type	Outcome	Drug	N	Relative risk vs Placebo	95% CI	Heterogeneity I^2		
Withdrawals	Total withdrawals	Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid	9	1.30	[0.99; 1.71]	51.2%	26.7	0.014
		Tricyclic antidepressants, secondary amines	4	1.00	[0.52; 1.93]	0.0%	1.4	0.713
		Tricyclic antidepressants, tertiary amines	5	1.18	[0.65; 2.15]	0.0%	2.9	0.568
		Tricyclic antidepressants, secondary or tertiary	9	1.10	[0.71; 1.70]	0.0%	4.9	0.767
		SSRIs	1	1.00	[0.16; 6.35]	NA		
	Adverse event withdrawals	Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid	12	2.43	[1.69; 3.50]	27.6%	15.2	0.174
		Tricyclic antidepressants, secondary amines	4	1.22	[0.51; 2.90]	0.0%	1.9	0.604
		Tricyclic antidepressants, tertiary amines	6	1.09	[0.42; 2.81]	0.0%	4.8	0.441
		Tricyclic antidepressants, secondary or tertiary amines	10	1.16	[0.61; 2.19]	0.0%	6.7	0.674
		SSRIs	2	5.93	[0.73; 47.82]		0.0	0.862
Adverse events	Dizziness or vertigo	Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid	6	3.09	[1.16; 8.27]	59.9%	12.5	0.029
		Tricyclic antidepressants, secondary amines	1	1.40	[0.54; 3.64]	NA		
		Tricyclic antidepressants, tertiary amines	6	1.53	[0.74; 3.18]	31.3%	7.3	0.201
		Tricyclic antidepressants, secondary or tertiary	7	1.39	[0.81; 2.38]	17.4%	7.3	0.297
		Dextromethorphan	2	18.04	[2.54; 128.0]		0.0	0.888

		Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid	7	1.88	[1.09; 3.24]	38.2%	9.7	0.137
	Somnolence, sedation, fatigue, or lethargy	Tricyclic antidepressants, secondary amines	3	1.23	[0.63; 2.40]	41.9%	3.5	0.178
		Tricyclic antidepressants, tertiary amines	7	1.48	[1.10; 1.99]	35.2%	9.3	0.159
		Tricyclic antidepressants, secondary or tertiary	10	1.41	[1.09; 1.83]	31.8%	13.2	0.154
		SSRIs	1	0.78	[0.31; 1.94]	NA		
		Dextromethorphan	2	5.68	[0.35; 93.2]		8.0	0.005
	Dry mouth	Tricyclic antidepressants, secondary amines	3	1.50	[0.97; 2.32]	41.7%	3.4	0.180
		Tricyclic antidepressants, tertiary amines	8	1.66	[1.22; 2.25]	61.7%	18.3	0.011
		Tricyclic antidepressants, secondary or tertiary amines	11	1.58	[1.25; 2.00]	51.4%	20.6	0.024
		SSRIs	1	0.32	[0.14; 0.73]	NA		
	Serious adverse events	Oxcarbazepine	2	4.05	[1.15; 14.27]	NA	1.41	0.24
		Topiramate	2	1.47	[0.88; 2.47]	NA	0	0.99

Excluding poor-quality trials[73, 82, 88, 92, 113] and stratifying trials that used a parallel-group versus crossover design had little effect on estimates. In stratified analyses, lamotrigine was associated with no increased risk of adverse event withdrawal or total withdrawal compared to placebo (Table 27). Carbamazepine/oxcarbazepine, topiramate, and valproic acid were all associated with a similar increased risk for adverse event withdrawal versus placebo. Topiramate and carbamazepine/oxcarbazepine were associated with an increased risk of total withdrawals compared to placebo, but valproic acid was not.

Table 27. Relative risk for total withdrawals or withdrawals due to adverse events in placebo-controlled trials of carbamazepine/oxcarbazepine, lamotrigine, topiramate, and valproic acid

Outcome	Drug	Number of trials	Relative risk vs Placebo	95% CI	Heterogeneity		
					I^2	Q	p(Q)
Total withdrawals	**Antiepileptics - All**	**12**	**1.46**	**[1.13; 1.88]**	**58.2%**	**26.31**	**0.006**
	Carbamazepine or oxcarbazepine	2	1.94	[1.36; 2.75]		0.03	0.85
	Lamotrigine	4	0.86	[0.60; 1.24]	0%	1.92	0.75
	Topiramate	3	1.65	[1.05; 2.58]	73.9%	7.68	0.022
	Valproic acid	4	0.38	[0.12; 1.23]	0%	2.88	0.41
Adverse event withdrawals	**Antiepileptic drugs – all**	12	2.43	[1.69; 3.50]	27.6%	15.2	0.174
	Carbamazepine or oxcarbazepine	2	3.64	[2.03; 6.54]		0.01	0.92
	Lamotrigine	3	0.81	[0.41; 1.61]	0%	1.46	0.48
	Topiramate	3	3.01	[2.21; 4.09]	0%	1.46	0.48
	Valproic acid	4	2.51	[0.60; 10.61]	0%	0.06	1.0

An analysis of trials of tricyclic antidepressants stratified by use of active placebo (benztropine) or inert placebo found no clear differences in estimates of adverse events (Table 28).

Table 28. Estimates of adverse events in placebo-controlled trials of tricyclic antidepressants, stratified by use of an active (benztropine) or inert placebo

	Outcome	Drug	N	RR vs Placebo	95% CI	Heterogeneity I^2	Heterogeneity Q	Heterogeneity p(Q)
Withdrawals	Total withdrawals	Tricyclics, secondary+tertiary	9	1.10	[0.71; 1.70]	0.0%	4.9	0.767
		Tricyclics, secondary+tertiary, active placebo	4	1.28	[0.73; 2.25]	0.0%	1.1	0.782
		Tricyclics, secondary+tertiary, inert placebo	5	0.86	[0.42; 1.74]	0.0%	3.1	0.540
	AE withdrawals	Tricyclics, secondary+tertiary	10	1.16	[0.61; 2.19]	0.0%	6.7	0.674
		Tricyclics, secondary+tertiary, active placebo	4	1.44	[0.61; 3.40]	0.0%	1.4	0.706
		Tricyclics, secondary+tertiary, inert placebo	6	0.89	[0.34; 2.31]	0.0%	4.8	0.447
Adverse events	Dizziness or vertigo	Tricyclics, secondary+tertiary	7	1.39	[0.81; 2.38]	17.4%	7.3	0.297
		Tricyclics, secondary+tertiary, active placebo	4	1.53	[0.77; 3.03]	0.0%	1.7	0.646
		Tricyclics, secondary+tertiary, inert placebo	3	1.80	[0.57; 5.62]	43.5%	5.3	0.070
	Somnolence, sedation, fatigue, or lethargy	Tricyclics, secondary+tertiary	10	1.41	[1.09; 1.83]	31.8%	13.2	0.154
		Tricyclics, secondary+tertiary, active placebo	5	1.50	[0.83; 2.71]	60.2%	10.1	0.040
		Tricyclics, secondary+tertiary, inert placebo	5	1.42	[1.09; 1.84]	3.0%	4.1	0.390
	Dry mouth	Tricyclics, secondary+tertiary	11	1.58	[1.25; 2.00]	51.4%	20.6	0.024
		Tricyclics, secondary+tertiary, active placebo	5	1.26	[0.95; 1.69]	40.7%	6.8	0.150
		Tricyclics, secondary+tertiary, inert placebo	6	1.89	[1.47; 2.42]	6.8%	5.4	0.372

Indirect comparisons

For adjusted indirect analyses, we pooled data for all tricyclics because we found few differences between tertiary and secondary amine drugs in stratified analyses (Table 29). Antiepileptic medications were stratified based on differences observed between drugs in risk of withdrawal due to adverse events or total withdrawals (Table 29). We did not perform indirect analyses on adverse events for SSRIs or dextromethorphan because of insufficient data (one or two small trials) for meaningful results, and no trials of topical lidocaine patch or gel reported poolable data on adverse events.

For total withdrawals, gabapentin and pregabalin were both superior to carbamazepine, oxcarbazepine, and topiramate (RR=0.55, 95% CI 0.38 to 0.81 and RR=0.55, 95% CI 0.36 to 0.85, respectively) (Table 29). Gabapentin was also superior to carbamazepine, oxcarbazepine, topiramate, and valproic acid for withdrawals due to adverse events (RR=0.31, 95% CI 0.26 to 0.65). Pregabalin was inferior to lamotrigine for withdrawal due to adverse events (RR=2.75, 95% CI 1.26 to 6.03). We found no other statistically significant differences between gabapentin, pregabalin, or SNRIs versus other antiepileptic medications or tricyclic antidepressants in risk of total withdrawals or withdrawal due to adverse events.

For specific adverse events, there were no differences for any comparison between gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine (patch or gel) versus tricyclic antidepressants or other antiepileptic medications except for somnolence/sedation and dizziness. Both gabapentin and pregabalin were associated with increased risk of somnolence compared to other antiepileptic medications (RR=1.92, 95% CI 1.00 to 3.70 for gabapentin and RR=2.07, 95% CI 1.08 to 3.98 for pregabalin) or tricyclic antidepressants (RR=2.52, 95% CI 1.60 to 3.99 for gabapentin and RR=2.72, 95% CI 1.72 to 4.30 for pregabalin). Gabapentin and pregabalin were also associated with increased risk of dizziness compared to tricyclic antidepressants (RR 2.21, 95% CI 1.14 to 4.28 for gabapentin and RR=2.07, 95% CI 1.05 to 4.11 for pregabalin). Estimates were similar and conclusions unchanged after excluding poor-quality trials,[73, 82, 88, 92, 113] stratifying trials by use of a crossover versus parallel-group design, or excluding trials evaluating lower doses of pregabalin (<=150 mg/day).

Table 29. Indirect analyses on harms for gabapentin, pregabalin, duloxetine, or venlafaxine versus tricyclic antidepressants, SSRIs, dextromethorphan, carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid for neuropathic pain

Type of outcome	Outcome	Medication comparison	Relative risk	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
Withdrawals	Total withdrawals	Gabapentin vs Carbamazepine, oxcarbazepine, and topiramate	0.55	0.38	0.81
		Gabapentin vs Lamotrigine	1.10	0.72	1.70
		Gabapentin vs Valproic acid	2.50	0.76	8.19
		Gabapentin vs. Tricyclic antidepressants	0.84	0.51	1.40
		Pregabalin vs Carbamazepine, oxcarbazepine, and topiramate	0.55	0.36	0.85
		Pregabalin vs Lamotrigine	1.10	0.69	1.77
		Pregabalin vs Valproic acid	2.50	0.75	8.32
		Pregabalin vs Tricyclic antidepressants	0.84	0.49	1.44
		Duloxetine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.81	0.56	1.18
		Duloxetine vs Tricyclic antidepressants	1.01	0.60	1.68
		Venlafaxine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	1.04	0.57	1.92
		Venlafaxine vs Tricyclic antidepressants (secondary or tertiary)	1.29	0.64	2.62
	Adverse event withdrawals	Gabapentin vs Carbamazepine, oxcarbazepine, topiramate, and valproic acid	0.41	0.26	0.65
		Gabapentin vs lamotrigine	1.59	0.74	3.45
		Gabapentin vs Tricyclic antidepressants	1.02	0.48	2.17
		Pregabalin vs Carbamazepine, oxcarbazepine, topiramate, and valproic acid	0.72	0.45	1.15
		Pregabalin vs lamotrigine	2.75	1.26	6.03
		Pregabalin vs Tricyclic antidepressants	1.77	0.83	3.79
		Duloxetine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.88	0.45	1.71
		Duloxetine vs Tricyclic antidepressants	1.79	0.79	4.06
		Venlafaxine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.97	0.37	2.55
		Venlafaxine vs Tricyclic antidepressants	1.98	0.68	5.81

Type of outcome	Outcome	Medication comparison	Relative risk	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval
Adverse events	Dizziness or vertigo	Gabapentin vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.97	0.35	2.72
		Gabapentin vs Tricyclic antidepressants	2.21	1.14	4.28
		Pregabalin vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.91	0.32	2.59
		Pregabalin vs Tricyclic antidepressants	2.07	1.05	4.11
		Duloxetine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.67	0.22	2.05
		Duloxetine vs Tricyclic antidepressants	1.51	0.68	3.38
		Venlafaxine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.65	0.05	8.28
		Venlafaxine vs Tricyclic antidepressants	1.47	0.13	16.61
	Somnolence, sedation, fatigue, or lethargy	Gabapentin vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	1.92	1.00	3.70
		Gabapentin vs Tricyclic antidepressants	2.52	1.60	3.99
		Pregabalin vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	2.07	1.08	3.98
		Pregabalin vs Tricyclic antidepressants	2.72	1.72	4.30
		Duloxetine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	2.20	0.44	11.10
		Duloxetine vs Tricyclic antidepressants	2.90	0.62	13.62
		Venlafaxine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	0.73	0.34	1.59
		Venlafaxine vs Tricyclic antidepressants	0.97	0.52	1.79
	Dry mouth	Gabapentin vs Tricyclic antidepressants	3.93	0.51	30.13
		Pregabalin vs Tricyclic antidepressants	1.82	0.94	3.52
		Duloxetine vs Tricyclic antidepressants	0.98	0.43	2.24
		Venlafaxine vs Tricyclic antidepressants	0.72	0.47	1.12

As with other indirect analyses in this report, results should be interpreted cautiously because of clinical diversity across the different sets of trials. For example, several trials of tricyclic antidepressants used benztropine as an 'active' placebo,[78, 81, 82, 85, 86, 90] which could result in differential estimates of adverse events versus inert placebo. However, we found no clear differences in estimates when trials were stratified by type of placebo (Table 28). We also found no clear differences in estimates involving tricyclic antidepressants when trials were stratified by tertiary versus secondary amines. In all trials, assessment of harms was a secondary outcome. Few trials reported pre-defined criteria for different harms, used active methods to assess harms, or described standardized methods for assessment and reporting of harms. Estimates for commonly reported adverse events varied widely. For example, in patients randomized to tricyclic antidepressants, rates of somnolence, sedation, or fatigue ranged from 21%[81] to 80%.[80]

Key Question 5. What are the comparative effectiveness and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine (patch or gel) plus a tricyclic antidepressant or another antiepileptic versus monotherapy with a tricyclic antidepressant or another antiepileptic?

Summary of findings

We found no randomized trials or controlled observational studies evaluating benefits and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine (patch or gel) plus a tricyclic antidepressant or another antiepileptic medication versus monotherapy with a tricyclic antidepressant or another antiepileptic medication.

Detailed assessment

We identified no studies addressing this question. The only evidence related to combination treatment was a very small (N=11) trial that found venlafaxine plus gabapentin combination therapy superior to gabapentin monotherapy in patients who did not previously respond to gabapentin monotherapy.[57] This trial did not meet inclusion criteria because it evaluated efficacy of combination therapy with two newer medications for NP (rather than one newer medication plus one older medication versus an older medication).

Key Question 6. Are there differences in effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions?

Summary of findings

Direct evidence on effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions is very limited. For diabetic neuropathy, two head-to-head trials of gabapentin versus amitriptyline found no clear differences

between drugs. For post-herpetic neuralgia, one head-to-head trial of gabapentin versus nortriptyline also found no clear differences.

Adjusted indirect estimates of comparative efficacy of different neuropathic pain medications for diabetic neuropathy found pregabalin superior to duloxetine, venlafaxine, or SSRIs for achieving significant pain relief. Pregabalin, gabapentin, duloxetine, and venlafaxine were all inferior to tricyclic antidepressants. However, indirect analyses involving tricyclic antidepressants should be interpreted with caution because the discrepancy between direct and indirect estimates of gabapentin versus tricyclic antidepressants for pain relief was highly statistically significant.

Analyses of comparative efficacy for postherpetic neuralgia are limited by small numbers of trials and small sample sizes (resulting in imprecise estimates). There is insufficient evidence to judge comparative effectiveness or harms for other neuropathic pain conditions, including central neuropathic pain, HIV-related neuropathic pain, or trigeminal neuralgia.

Detailed assessment

We identified no study designed to assess differences in effectiveness or harms of medications for neuropathic pain based on demographics, co-morbidities, or drug-drug interactions. One higher-quality systematic review reported estimates for pain relief for different medications versus placebo, stratified by underlying neuropathic pain condition (Table 30).[33] However, with the exception of peripheral pain or painful polyneuropathy, data for specific neuropathic pain conditions were sparse. For peripheral pain and painful polyneuropathy, gabapentin and pregabalin both appeared less effective compared to tricyclic antidepressants for pain relief. However, formal indirect analyses were not performed by the authors of the systematic review.

Table 30. Efficacy of different medications for different types of neuropathic pain, NNT to achieve >50% pain relief (hierarchy of outcomes), from Finnerup et al[112]

Medication	Central pain	Peripheral pain	Painful polyneuropathy	Post-herpetic neuralgia	Peripheral nerve injury	Trigeminal neuralgia	HIV neuropathy	Mixed neuropathic pain
SNRI	No data	5.5 (3.4-14)	No data	No data	No data	No data	No data	No data
Gabapentin/pregabalin	No data	4.3 (3.7-5.2)	3.9 (3.2-5.1)	4.6 (3.7-6.0)	No data	No data	No data	8.0 (4.8-24)
Topical lidocaine (patch or gel)	No data	No data	No data	No data	No data	No data	No data	4.4 (2.5-17)
Tricyclic antidepressants	4.0 (2.6-8.5)	2.3 (2.1-2.7)	2.1 (1.9-2.6)	2.8 (2.2-3.8)	2.5 (1.4-11)	No data	Not significant	No data
SSRI	No data	6.8 (3.4 to 441)	No data	No data	No data	No data	No data	No data
Carbamazepine	3.4 (1.7 to 105)	2.3 (1.6 to 3.9)	2.3 (1.6-3.9)	No data	No data	1.7 (1.3 to 2.2)	No data	No data
Valproate	Not significant	2.4 (1.8-3.4)	2.5 (1.8-4.1)	2.1 (1.4-4.2)	No data	No data	No data	No data
Gabapentin/pregabalin	No data	4.3 (3.7-5.2)	3.9 (3.2-5.1)	4.6 (3.7-6.0)	No data	No data	No data	8.0 (4.8-24)
Topiramate	No data	7.4 (4.3-28)	7.4 (4.3-28)	No data	No data	No data	No data	No data
Dextromethorphan	No data	3.4 (2.2 - 7.6)	2.5 (1.6-5.4)	Not significant	No data	No data	No data	No data

Three head-to-head trials of gabapentin versus tricyclic antidepressants specifically evaluated patients with diabetic neuropathy or post-herpetic neuralgia. There were no differences between gabapentin and tricyclics in likelihood of achieving at least moderate pain relief or >50% pain

relief for either condition (RR=0.91, 95% CI 0.66 to 1.28 for diabetic neuropathy, 2 trials and RR=1.00, 95% CI 0.61 to 1.64 for postherpetic neuralgia, 1 trial).

We also performed subgroup analyses on placebo-controlled trials of medications for diabetic neuropathy and postherpetic neuralgia (Table 31). For diabetic neuropathy, adjusted indirect analyses found no statistically significant differences in likelihood of achieving pain relief between gabapentin, pregabalin, duloxetine, or venlafaxine, with the exception of pregabalin versus venlafaxine (RR=1.74, 95% CI 1.09 to 2.78) and pregabalin versus duloxetine (RR=1.42, 95% CI 1.00 to 2.01). For comparisons between gabapentin, pregabalin, duloxetine, or venlafaxine versus tricyclic antidepressants, SSRIs, dextromethorphan, or other antiepileptic medications, tricyclic antidepressants were superior to gabapentin, pregabalin, duloxetine, and venlafaxine (Table 31). However, analyses involving tricyclic antidepressants should be interpreted with caution because of pronounced funnel plot asymmetry (see Figure 10). There were no other significant differences between medications for neuropathic pain in the likelihood of achieving significant pain relief, with the exception of pregabalin versus SSRIs (RR=2.00, 95% CI 1.16 to 3.45).

Table 31. Subgroup analyses of placebo-controlled trials of medications for neuropathic pain on likelihood of achieving at least moderate improvement in pain or >50% pain relief

Subgroup	Analysis	Drug	Number of studies	RR	LCL	UCL
Diabetic neuropathy	Versus placebo	Gabapentin	3	1.93	1.46	2.55
		Pregabalin	3	2.42	1.77	3.30
		Duloxetine	3	1.71	1.46	2.01
		Venlafaxine	1	1.39	0.98	1.97
		Carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid	5	1.76	1.22	2.52
		Tricyclic antidepressants	4	7.67	3.36	17.48
		SSRIs	2	1.21	0.77	1.89
	Adjusted indirect analyses	Gabapentin vs Pregabalin	6	0.80	0.53	1.21
		Gabapentin vs Duloxetine	6	1.13	0.82	1.56
		Gabapentin vs Venlafaxine	4	1.39	0.89	2.17
		Gabapentin vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	8	1.10	0.69	1.73
		Gabapentin vs Tricyclic antidepressants	7	0.25	0.11	0.60
		Gabapentin vs SSRIs	5	1.60	0.94	2.71
		Pregabalin vs Duloxetine	6	1.42	1.00	2.01
		Pregabalin vs Venlafaxine	4	1.74	1.09	2.78
		Pregabalin vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	8	1.38	0.85	2.22
		Pregabalin vs Tricyclic antidepressants	7	0.32	0.13	0.76
		Pregabalin vs SSRIs	5	2.00	1.16	3.45

Subgroup	Analysis	Drug	Number of studies	RR	LCL	UCL
		Duloxetine vs Venlafaxine	4	1.23	0.84	1.81
		Duloxetine vs Carbamazepine, oxcarbazepine, lamotrigine, topiramate, or valproic acid	8	0.97	0.65	1.44
		Duloxetine vs Tricyclic antidepressants	7	0.22	0.10	0.52
		Duloxetine vs. SSRIs	5	1.41	0.88	2.28
		Venlafaxine vs Tricyclic antidepressants	5	0.18	0.07	0.44
		Venlafaxine vs SSRIs	3	1.15	0.65	2.03
Post-herpetic neuralgia	Versus placebo	Gabapentin	2	2.83	1.84	4.35
		Pregabalin	3	2.80	1.98	3.96
		Tricyclic antidepressants	3	4.75	2.17	10.39
		Dextromethorphan	1	1.67	0.50	5.57
	Adjusted indirect analyses	Gabapentin vs Pregabalin	5	1.01	0.45	1.50
		Gabapentin vs Tricyclic antidepressants	5	0.60	0.24	1.46
		Pregabalin vs Tricyclic antidepressants	6	0.59	0.25	1.39
		Gabapentin vs Dextromethorphan	3	1.69	0.47	6.09
		Pregabalin vs Dextromethorphan	4	1.68	0.48	5.88

For post-herpetic neuralgia, similar but nonsignificant trends were observed for gabapentin[54, 55] and pregabalin[60, 65, 67] versus tricyclic antidepressants[82, 87, 97] (RR=0.33, 95% CI 0.11 to 0.97 and RR=0.40, 95% CI 0.14 to 1.11). However, both subgroup analyses were limited by small numbers of trials. There were no significant differences between gabapentin or pregabalin and dextromethorphan, but only one trial of dextromethorphan contributed data to the indirect analyses.

As in the analysis comparing gabapentin versus tricyclic antidepressants for pain relief in patients with non-HIV-related neuropathic pain, the discrepancy between direct (RR=0.98, 955 CI 0.69 to 1.38) and indirect (RR=0.25, 95% CI 0.11 to 0.60) estimates for pain relief was highly statistically significant (p=0.004). For post-herpetic neuralgia, the discrepancy was non-significant, but direct and indirect estimates were less precise because of fewer trials (Table 32).

Table 32. Discrepancies between direct and indirect analysis of gabapentin versus tricyclic antidepressants on likelihood of achieving at least moderate pain relief or >50% improvement in pain

Analysis	Direct analysis: Number of trials	Relative risk (95% confidence interval)	Indirect analysis: Number of trials	Relative risk (95% confidence interval	Discrepancy
All trials	3	0.99 (0.76 to 1.29)	20	0.54 (0.54 to 0.99)	p=0.07
Excluding patients with HIV-related neuropathic pain	3	0.99 (0.76 to 1.29)	18	0.44 (0.28 to 0.69)	p=0.003
Diabetic neuropathy	2	0.98 (0.69 to 1.38)	7	0.25 (0.11 to 0.60)	p=0.004
Post-herpetic neuralgia	1	1.00 (0.61 to 1.64)	5	0.60 (0.24 to 1.46)	p=0.32

We did not perform meta-regression or additional stratified analyses because of small numbers of trials reporting individual outcomes. We also did not perform additional analyses for other specific neuropathic pain conditions because of limited numbers of trials. However, evidence on efficacy of neuropathic pain medications for HIV-associated neuropathic pain and trigeminal neuralgia is quite limited. Two trials of amitriptyline for HIV-associated neuropathic pain both found no benefit over placebo in the proportion of patients experiencing at least moderate improvement or >50% improvement in pain score.[81, 91] We identified four other placebo-controlled trials of neuropathic pain medications for HIV-associated neuropathic pain (two lamotrigine,[114, 115] one gabapentin,[52] and one topical lidocaine gel[75]), but none reported pain relief outcomes that could be categorized dichotomously. Qualitatively, one trial found topical lidocaine gel no more effective than placebo,[75] two trials reported mixed results for lamotrigine versus placebo,[114, 115] and results from one trial of gabapentin versus placebo were difficult to interpret because it performed no statistical comparison of outcomes versus placebo.[52]

Six-placebo-controlled trials evaluated neuropathic pain medications for trigeminal neuralgia.[100-103, 117, 120] Although all six trials found carbamazepine (four trials[100-103]), lamotrigine (one trial[117]), or topiramate (one trial[120]) more effective than placebo, results may not be reliable because five [100-103, 120] of the six trials were rated poor-quality, with four of the trials (all of carbamazepine[100-103]) published in 1966 or 1968.

SUMMARY

Results of this evidence review are summarized in Table 33.

Table 33. Summary of the evidence by key question

Key question	Quality of evidence	Conclusion
1. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel) versus each other for neuropathic pain?	Fair for gabapentin and pregabalin Poor to fair for venlafaxine and duloxetine Poor for topical lidocaine patch or gel	We found no head-to-head trials of gabapentin, pregabalin, SNRIs, or topical lidocaine (patch or gel) versus one another for neuropathic pain. Gabapentin was consistently more effective than placebo for pain relief or improvement in function in twelve placebo-controlled trials. Pregabalin (eight trials) and duloxetine (three trials) were also more consistently effective than placebo. Trials of topical lidocaine patch or gel and venlafaxine were inconsistent or showed no clear benefit. Adjusted indirect analyses of placebo-controlled trials found gabapentin, duloxetine, and venlafaxine similarly effective for pain relief and improvement in function compared to one another. Pregabalin was moderately superior to duloxetine for the proportion of patients experiencing significant pain relief, but there were no differences between pregabalin and gabapentin or venlafaxine. Conclusions were not affected by trial quality, use of crossover versus parallel group design, or differences in drug dosing. Trials of neuropathic pain medications are characterized by different methods for assessing and reporting outcomes, which limited the number of trials that could be pooled for some comparisons. There were no suitable data from placebo-controlled trials of topical lidocaine patch or gel to perform indirect analyses.
2. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, or topical lidocaine (patch or gel) versus other drugs (other antiepileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or dextromethorphan) for neuropathic pain?	Fair for comparisons involving tricyclic antidepressants (direct analyses), poor to fair for SSRIs, carbamazepine, oxcarbazepine, lamotrigine, topiramate, and	Direct analyses of three head-to-head trials found no difference between gabapentin and tricyclic antidepressants for pain relief. However, estimates are relatively imprecise and do not rule out a clinically significant difference. One other small trial found no difference between venlafaxine and imipramine. Adjusted indirect analyses of placebo-controlled trials found gabapentin and

Key question	Quality of evidence	Conclusion
	valproic acid Poor for comparisons involving dextromethorphan	pregabalin each moderately superior to other antiepileptic medications (carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid) for achieving pain relief. Gabapentin and duloxetine were both inferior to tricyclic antidepressants, and gabapentin and pregabalin both superior to SSRIs for achieving pain relief. There were no significant differences between either duloxetine or venlafaxine versus other medications for neuropathic pain or in comparisons involving dextromethorphan, but analyses were limited by small numbers of trials. Results of indirect analyses should be interpreted cautiously because funnel plot asymmetry and heterogeneity was present among placebo-controlled trials of tricyclic antidepressants and data for different antiepileptic drugs were pooled. There were statistically significant discrepancies between direct and indirect estimates of gabapentin versus tricyclic antidepressants, and the direct estimates are likely to be more reliable.
3. What are the comparative harms of pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel) for neuropathic pain?	Fair for gabapentin and pregabalin Poor to fair for venlafaxine and duloxetine Poor for topical lidocaine patch or gel	We found no head-to-head trials directly comparing harms associated with pregabalin, gabapentin, SNRIs, and topical lidocaine (patch or gel). In adjusted indirect analyses, gabapentin was associated with a lower likelihood of withdrawal due to adverse events compared to pregabalin at comparable doses. WE found no differences between gabapentin and pregabalin in rates of overall withdrawals, somnolence/sedation, or dizziness. Gabapentin and pregabalin are associated with more somnolence/sedation compared to venlafaxine. There are no clear differences between duloxetine and either gabapentin, pregabalin, or venlafaxine for any adverse event assessed, though analyses were limited by small numbers of trials. There was insufficient data to perform indirect analyses involving topical lidocaine patch or gel. Few trials reported rates of serious adverse events. Results of indirect analyses should be interpreted cautiously. It was difficult to judge the reliability of harms data due to poor reporting of methods used to define and ascertain adverse events and because estimates for commonly reported adverse events ranged widely across trials.

Key question	Quality of evidence	Conclusion
4. What are the comparative harms of pregabalin, gabapentin, SNRIs, or topical lidocaine (patch or gel) versus other drugs (other antiepileptics, tricyclic antidepressants (including tertiary versus secondary amines), SSRIs, or dextromethorphan) for neuropathic pain?	Poor to fair for comparisons versus tricyclic antidepressants and the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid Poor for comparisons versus SSRIs and dextromethorphan	There are insufficient data from four small head-to-head trials to reliably judge comparative harms of gabapentin versus tricyclic antidepressants. For the outcome withdrawal due to adverse events, adjusted indirect analyses of placebo-controlled trials found gabapentin associated with lower risk compared to the antiepileptic drugs carbamazepine, oxcarbazepine, and topiramate, and valproic acid. Pregabalin is associated with higher risk for withdrawal due to adverse events compared to lamotrigine. Both gabapentin and pregabalin are associated with higher risk of somnolence/sedation compared to other antiepileptic drugs or tricyclic antidepressants and higher risk of dizziness/vertigo compared to tricyclic antidepressants. There are no differences between duloxetine or venlafaxine and either tricyclic antidepressants or these antiepileptic medications, but analyses are limited by small numbers of trials. There are insufficient data from trials of SSRIs or dextromethorphan to perform indirect analyses. Few trials reported rates of serious adverse events. Results of indirect analyses should be interpreted cautiously because it was difficult to judge reliability of harms data due to poor reporting of methods used to define and ascertain adverse events and because estimates for commonly reported adverse events ranged widely.
5. What are the comparative effectiveness and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine (patch or gel) plus a tricyclic antidepressant or another antiepileptic versus monotherapy with a tricyclic antidepressant or another antiepileptic?	Poor	No evidence meeting inclusion criteria
6. Are there differences in effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions?	Fair (diabetic neuropathy) to poor (other demographics, co-morbidities, or drug-drug interactions)	Direct evidence on effectiveness or harms of drugs used to treat neuropathic pain based on demographic, co-morbidities, or drug-drug interactions is very limited. For diabetic neuropathy, two head-to-head trials of gabapentin versus amitriptyline found no differences between drugs. For post-herpetic neuralgia, one head-to-head trial of

Key question	Quality of evidence	Conclusion
		gabapentin versus nortriptyline also found no clear differences. Adjusted indirect estimates of comparative efficacy of different neuropathic pain medications for diabetic neuropathy found pregabalin superior to duloxetine, venlafaxine, or SSRIs for achieving significant pain relief. Pregabalin, gabapentin, duloxetine, and venlafaxine were all inferior to tricyclic antidepressants. However, indirect analyses involving tricyclic antidepressants should be interpreted with caution because the discrepancy between direct and indirect estimates of gabapentin versus tricyclic antidepressants for pain relief was highly statistically significant. Analyses of comparative efficacy for postherpetic neuralgia are limited by small numbers of trials and small sample sizes (resulting in imprecise estimates). There is insufficient evidence to judge comparative effectiveness or harms for other neuropathic pain conditions, including central neuropathic pain, HIV-related pain, or trigeminal neuralgia. Evidence on effectiveness of medications for HIV-related neuropathic pain or trigeminal neuralgia is limited due to inconsistent or mixed results (HIV-related neuropathic pain) or evidence from primarily poor-quality trials (trigeminal neuralgia).

Assessing comparative effectiveness and harms of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or gel) for neuropathic pain is challenging because there are large numbers of comparisons and few head-to-head trials. We found no trials comparing one of these medications to another, and only four small (N≤70) trials comparing gabapentin or venlafaxine to a tricyclic antidepressant. Assessments of comparative effectiveness and harms therefore rely heavily on indirect comparisons from placebo-controlled trials.

To our knowledge, this is the first review is to conduct formal, adjusted indirect analyses to compare benefits and harms of different medications for neuropathic pain. Other reviews evaluating multiple drugs for neuropathic pain reached conclusions regarding comparative benefits and harms based on informal indirect comparisons[33, 38] or did not draw conclusions about comparative effectiveness or harms.[34] The two systematic reviews that reached conclusions regarding comparative benefits and harms both found tricyclic antidepressants more effective than medications including gabapentin and pregabalin for pain relief.[33, 38] However, although informal or implicit indirect comparisons based on a qualitative examination of point estimates and confidence intervals for treatment effects from placebo-controlled trials (or trials against another common comparator) can be helpful for generating hypotheses about

comparative effectiveness or harms, they can also be misleading. Apparent differences observed in such informal comparisons may be rendered statistically insignificant when formal adjusted indirect analysis is performed, because the latter method incorporates additional uncertainty (variance) from combining sets of trials.[28, 29] In addition, for all indirect analysis (implicit or formal), the validity of indirect comparisons (whether formal or informal) depends on how well they meet the critical assumption of similar treatment effects across all of the trials.[28, 29] Such assumptions can be violated by methodological shortcomings, differences in populations, interventions (e.g. non-equivalent dosing or different methods for dose titration), or assessment of outcomes, or other factors. For example, when evaluating a recently introduced medication to an older medication for neuropathic pain, there may be a higher likelihood that indirect comparisons are invalid because of differences over time in how patients with neuropathic pain are managed and assessed.[30] This is illustrated by a recent systematic review of medications for diabetic neuropathy, which found rates of pain relief of 4% in patients randomized to placebo in trials of tricyclic antidepressants compared to 21% in patients randomized to placebo in trials of medications classified by the authors as newer antiepileptic drugs.[38] Performing formal indirect analysis promotes a more explicit framework for exploring (through sensitivity and subgroup analyses and other methods) whether the key assumptions for indirect analyses are likely to be violated.

In our analyses, which included a greater number of trials and conditions, placebo response rates were roughly comparable across medications and medication classes. We found few differences in estimates or conclusions when we performed sensitivity and subgroup analyses based on differences in drug dose, methodological quality, use of parallel-group or crossover design, and other factors. Strong funnel plot asymmetry and heterogeneity were present in placebo-controlled trials of tricyclic antidepressants, but adjustment for funnel plot asymmetry and exclusion of trials evaluating patients with HIV-associated neuropathic pain (which appeared to explain much of the heterogeneity) had little effect on estimates and conclusions. Nonetheless, we found statistically significant and clinically important discrepancies between trials directly comparing gabapentin and tricyclic antidepressants (no differences) and indirect comparisons of gabapentin and tricyclic antidepressants (tricyclics superior). We believe that results based on head-to-head trials are likely to be more reliable than results based on indirect analyses. Our results underscore the importance of verifying results of indirect analyses with head-to-head trials as they become available. In this case, discrepancies between direct and indirect analyses of gabapentin versus tricyclic antidepressants may be related to the fact that all trials of gabapentin were published in or after 1998, while 12 of the 21 trials of tricyclic antidepressants were published prior to 1993. It is unlikely that patient characteristics, treatment regimens, assessment of outcomes, and study designs would be similar enough to combine two sets of trials conducted in different eras. Indirect analyses comparing gabapentin, pregabalin, duloxetine, and venlafaxine to each other may be more reliable than indirect analyses comparing these drugs to SSRIs, tricyclics, and other antiepileptic medications because trials evaluating the former set of drugs are roughly contemporary and may be less likely to violate assumptions about similarity of treatment effects. However, head-to-head trials directly comparing these drugs are needed to test this hypothesis.

A potential limitation of our study is that we pooled studies across NP conditions, drug dosages, and follow-up intervals. However, we felt that clinical homogeneity was generally sufficient to

justify our approach. We also used a random effects model to pool data because of known diversity between trials. For most comparisons there was little difference in estimates and conclusions after performing subgroup and stratified analyses, other than less precise estimates of effects. The issue of appropriateness of pooling is probably most relevant for the antiepileptic drugs oxcarbazepine, carbamazepine, valproic acid, lamotrigine, topiramate, which we attempted to analyze together, in order to limit the number of comparisons evaluated in this review. However, most of these drugs are not pharmacologically related and have different mechanisms of actions. Nonetheless, our analysis of individual antiepileptic medications indicates similar estimates for efficacy, suggesting that pooling may be reasonable in this case. For harms, we ended up stratifying these drugs according to observed differences in estimates for individual drugs.

Another issue is that about half of the trials identified for this review used a crossover design. Of the ten placebo-controlled trials of tricyclic antidepressants that evaluated patients with non-HIV-related neuropathic pain, nine used a crossover design. About one-quarter of the trials using a crossover design did not incorporate a washout period between interventions, or did not report whether a washout was used. Results from such trials could be affected by carryover effects.[17] Crossover trials may also be particularly susceptible to attrition bias because patients who withdraw during the first intervention period are usually not exposed to the second intervention and therefore excluded from analyses. We abstracted data from crossover trials for both intervention periods, because results for the first intervention period were infrequently reported. However, optimal methods for analyzing and combining data from parallel-group with crossover trials remain uncertain.[17] Nonetheless, we found similar results when we stratified trials by use of parallel-group versus crossover design.

As in previous reviews, we analyzed as one of our outcomes a composite dichotomous measure for pain relief (proportion of patients with at least moderate improvement or >50% improvement in pain score). A number of previously published systematic reviews also pooled dichotomous pain outcomes using a 'hierarchy' of outcomes. An advantage of pooling using such hierarchies is that more trials can be entered into analyses. A disadvantage is that it is not certain how valid pooling of disparate methods for measuring pain outcomes is, particularly for poorly validated or described categorical scales.[127] Another problem with categorizing dichotomous outcomes retrospectively from different scales is that systematic reviews may differ in how they classify outcomes. For example, for the same trial,[85] one systematic review[38] abstracted results of 19/29 versus 0/29 for the equivalent of 50% of pain relief, while another abstracted results as 15/29 versus 1/29 for the same outcome. This discrepancy appears to be due to differences in how "moderate" relief was classified (considered a success in one systematic review, but not as a success in the other). Some research suggests that 50% pain relief may correlate to higher ratings than moderate or better on categorical scales.[128] However, we were unable to perform sensitivity analyses on different methods for classifying dichotomous pain outcomes because most trials only reported the proportion of patients with 50% pain relief or the proportion experiencing at least moderate relief. In addition, in trials of gabapentin, rates of pain relief were roughly comparable in trials reporting 50% pain relief compared and trials in which we classified significant pain relief according to at least improvement in a categorical pain score. Further research is needed to better understand the reproducibility of methods for converting categorical scales to dichotomous outcomes, how differences in methods for classifying outcomes affect

results, and whether the advantage of including more trials in analyses outweighs the potential for generating misleading conclusions. More standardized assessment and reporting of important patient-centered outcomes (including the proportion of patients experiencing a clinically relevant improvement in pain or function) in clinical trials of neuropathic pain medications would help avoid the need to use composite outcomes in meta-analyses in the first place.

We identified several methodological challenges in interpreting trials of neuropathic pain. No trial met all methodological criteria for a high quality study. However, excluding poor-quality trials from the analyses did not alter any of our main conclusions. In addition, most trials in this review evaluated multiple outcomes measures, such as all 8 subscales of the SF-36, 3 parts of the SF-MPQ, multiple measures from the BPI, and multiple variations on a visual analogue or categorical scale of pain. No trial made statistical corrections for assessment of multiple outcomes measures. In addition, the findings of statistical significance in a small subset from multiple outcomes could represent chance findings, overstating the true significance of the results. This is also a problem with our review, since we evaluated a large number of comparisons and outcomes. When multiple outcomes are reported, statistically significant results should be interpreted cautiously, particularly when results just meet traditional ($p<0.05$) criteria for statistical significance. One method we used to limit the number of comparisons was to pool together older antiepileptic medications. Network analysis may be another potentially useful method for evaluating multiple comparisons.[129]

We found some evidence suggesting the presence of selective outcomes reporting bias[130] and publication bias in trials of neuropathic pain. For example, trials frequently reported only a subset of SF-36 measures—usually those reaching statistical significance. In some cases the authors indicated that they measured all subscales, but for reasons that were not explicit, only reported the significant values. In addition, funnel plot asymmetry was present in trials of tricyclic antidepressants, suggesting the possibility of publication bias. However, funnel plot asymmetry can be difficult to interpret because it can be due to factors other than publication bias, such as clinical diversity, different methods for assessing outcomes, or methodological shortcomings in the trials.[27] In the case of tricyclic antidepressants, the source of funnel plot asymmetry is unclear. Excluding two large trials of HIV-associated neuropathy finding no benefit from tricyclic antidepressants did not reduce funnel plot asymmetry, and funnel plot asymmetry was not explained by study quality, use of crossover design, or evaluation of specific tricyclic antidepressants. Nonetheless, adjustment for funnel plot asymmetry using the trim and fill method resulted in similar estimates of treatment effect.

Finally, the applicability of the trials included in this report to patients encountered in everyday practice may be limited.[131] Nearly all trials applied numerous inclusion and exclusion criteria, were conducted in academic or specialty settings, and were relatively short-term. Longer-term trials in non-academic/specialty settings with broader inclusion criteria would be very useful for evaluating real-world effectiveness of neuropathic pain medications.

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Appendix A. Search Strategies for Neuropathic Pain Drugs

Database: Ovid MEDLINE(R) <1966 to November Week 3 2006>
Search Strategy:
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1 (neuropath$ adj5 (pain$ or ache$ or discomfort$ or agony or agoniz$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp Pain/
3 exp Pain Measurement/
4 exp Hyperalgesia/
5 2 or 3 or 4
6 neuropath$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7 5 and 6
8 1 or 7
9 exp Diabetic Neuropathies/
10 ((herpe$ or postherpe$) adj5 (pain$ or neuralg$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11 Trigeminal Neuralgia/
12 exp Peripheral Nerves/in [Injuries]
13 exp Phantom Limb/
14 Guillan Barre syndrome.mp.
15 exp Polyradiculoneuropathy/
16 exp Polyneuropathies/
17 exp Spinal Cord Injuries/
18 exp Neoplasms/
19 exp HIV Infections/
20 exp Central Nervous System Diseases/
21 exp Cerebrovascular Disorders/
22 exp Back Pain/
23 9 or 10 or 11 or 12 or 13 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 8 and 23
25 Gabapentin.mp.
26 Neurontin.mp.
27 Pregabalin.mp.
28 Lyrica.mp.
29 exp Carbamazepine/
30 (Tegretol or Carbatrol or Epitol).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31 Topirimate.mp.
32 Topamax.mp.
33 Oxcarbazepine.mp.
34 Trileptal.mp.
35 Lamotrigine.mp.
36 Lamictal.mp.
37 exp Valproic Acid/

38 (Depakote or Depacon or divalproex or Epival or Deproic).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 exp Anticonvulsants/
40 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
41 24 and 40
42 24 and 39
43 41 or 42
44 exp Antidepressive Agents, Tricyclic/
45 exp Amitriptyline/
46 (Elavil or Vanatrip).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
47 exp Desipramine/
48 Norpramin.mp.
49 exp Nortriptyline/
50 Pamelor.mp.
51 exp Imipramine/
52 Tofranil.mp.
53 exp Doxepin/
54 (Sinequan or Zonalon).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
55 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56 24 and 55
57 24 and 44
58 56 or 57
59 exp Serotonin Uptake Inhibitors/
60 Duloxetine.mp.
61 Cymbalta.mp.
62 Venlafaxine.mp.
63 Effexor.mp.
64 exp Citalopram/
65 Celexa.mp.
66 Fluoxetine.mp. or exp Fluoxetine/
67 Prozac.mp.
68 Paroxetine.mp. or exp Paroxetine/
69 Paxil.mp.
70 Sertraline.mp. or exp Sertraline/
71 Zoloft.mp.
72 Escitalopram.mp.
73 Lexapro.mp.
74 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75 24 and 59
76 24 and 74
77 75 or 76
78 (Lidocaine adj5 (transderm$ or patch$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
79 Lidoderm.mp.

80 Lidocaine/ and Administration, Cutaneous/
81 78 or 79 or 80
82 24 and 81
83 Dextromethorphan.mp. or exp Dextromethorphan/
84 24 and 83
85 limit 43 to humans
86 limit 85 to english language
87 limit 85 to abstracts
88 86 or 87
89 limit 58 to humans
90 limit 89 to english language
91 limit 89 to abstracts
92 90 or 91
93 limit 77 to humans
94 limit 93 to english language
95 limit 93 to abstracts
96 94 or 95
97 82 or 84
98 limit 97 to humans
99 limit 98 to english language
100 limit 98 to abstracts
101 99 or 100
102 88 or 92 or 96 or 101

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2006>
Search Strategy:
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1 (pain$ or ache$ or discomfort$ or agony or agoniz$ or hyperalges$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 neuropath$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 and 2
4 Gabapentin.mp.
5 Neurontin.mp.
6 Pregabalin.mp.
7 Lyrica.mp.
8 Carbamazepine.mp.
9 (Tegretol or Carbatrol or Epitol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
10 Topirimate.mp.
11 Topamax.mp.
12 Oxcarbazepine.mp.
13 Trileptal.mp.
14 Lamotrigine.mp.
15 Lamictal.mp.
16 Valproic Acid.mp.
17 (Depakote or Depacon or divalproex or Epival or Deproic).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
18 Anticonvulsant$.mp.
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
20 (Antidepressive Agent$ adj2 Tricyclic$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21 Amitriptyline.mp.
22 (Elavil or Vanatrip).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23 Desipramine.mp.
24 Norpramin.mp.
25 Nortriptyline.mp.
26 Pamelor.mp.
27 exp Imipramine/
28 Tofranil.mp.
29 exp Doxepin/
30 (Sinequan or Zonalon).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
33 Duloxetine.mp.
34 Cymbalta.mp.
35 Venlafaxine.mp.
36 Effexor.mp.

37 Citalopram.mp.
38 Celexa.mp.
39 Fluoxetine.mp. or exp Fluoxetine/
40 Prozac.mp.
41 Paroxetine.mp. or exp Paroxetine/
42 Paxil.mp.
43 Sertraline.mp. or exp Sertraline/
44 Zoloft.mp.
45 Escitalopram.mp.
46 Lexapro.mp.
47 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
49 Lidoderm.mp.
50 48 or 49
51 Dextromethorphan.mp. or exp Dextromethorphan/
52 19 or 31 or 47 or 50 or 51
53 3 and 52

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2006>
Search Strategy:
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1 (pain$ or ache$ or discomfort$ or agony or agoniz$ or hyperalges$).mp. [mp=title, abstract, full text, keywords, caption text]
2 neuropath$.mp. [mp=title, abstract, full text, keywords, caption text]
3 1 and 2
4 Gabapentin.mp.
5 Neurontin.mp.
6 Pregabalin.mp.
7 Lyrica.mp.
8 Carbamazepine.mp.
9 (Tegretol or Carbatrol or Epitol).mp. [mp=title, abstract, full text, keywords, caption text]
10 Topirimate.mp.
11 Topamax.mp.
12 Oxcarbazepine.mp.
13 Trileptal.mp.
14 Lamotrigine.mp.
15 Lamictal.mp.
16 Valproic Acid.mp.
17 (Depakote or Depacon or divalproex or Epival or Deproic).mp. [mp=title, abstract, full text, keywords, caption text]
18 Anticonvulsant$.mp.
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
20 (Antidepressive Agent$ adj2 Tricyclic$).mp. [mp=title, abstract, full text, keywords, caption text]
21 Amitriptyline.mp.
22 (Elavil or Vanatrip).mp. [mp=title, abstract, full text, keywords, caption text]
23 Desipramine.mp.
24 Norpramin.mp.
25 Nortriptyline.mp.
26 Pamelor.mp.
27 [exp Imipramine/]
28 Tofranil.mp.
29 [exp Doxepin/]
30 (Sinequan or Zonalon).mp. [mp=title, abstract, full text, keywords, caption text]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. [mp=title, abstract, full text, keywords, caption text]
33 Duloxetine.mp.
34 Cymbalta.mp.
35 Venlafaxine.mp.
36 Effexor.mp.
37 Citalopram.mp.
38 Celexa.mp.
39 Fluoxetine.mp. or exp Fluoxetine/

40 Prozac.mp.
41 Paroxetine.mp. or exp Paroxetine/
42 Paxil.mp.
43 Sertraline.mp. or exp Sertraline/
44 Zoloft.mp.
45 Escitalopram.mp.
46 Lexapro.mp.
47 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. [mp=title, abstract, full text, keywords, caption text]
49 Lidoderm.mp.
50 48 or 49
51 Dextromethorphan.mp. or exp Dextromethorphan/
52 19 or 31 or 47 or 50 or 51
53 3 and 52

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2006>
Search Strategy:
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1 (pain$ or ache$ or discomfort$ or agony or agoniz$ or hyperalges$).mp. [mp=title, full text, keywords]
2 neuropath$.mp. [mp=title, full text, keywords]
3 1 and 2
4 Gabapentin.mp.
5 Neurontin.mp.
6 Pregabalin.mp.
7 Lyrica.mp.
8 Carbamazepine.mp.
9 (Tegretol or Carbatrol or Epitol).mp. [mp=title, full text, keywords]
10 Topirimate.mp.
11 Topamax.mp.
12 Oxcarbazepine.mp.
13 Trileptal.mp.
14 Lamotrigine.mp.
15 Lamictal.mp.
16 Valproic Acid.mp.
17 (Depakote or Depacon or divalproex or Epival or Deproic).mp. [mp=title, full text, keywords]
18 Anticonvulsant$.mp.
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
20 (Antidepressive Agent$ adj2 Tricyclic$).mp. [mp=title, full text, keywords]
21 Amitriptyline.mp.
22 (Elavil or Vanatrip).mp. [mp=title, full text, keywords]
23 Desipramine.mp.
24 Norpramin.mp.
25 Nortriptyline.mp.
26 Pamelor.mp.
27 [exp Imipramine/]
28 Tofranil.mp.
29 [exp Doxepin/]
30 (Sinequan or Zonalon).mp. [mp=title, full text, keywords]
31 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. [mp=title, full text, keywords]
33 Duloxetine.mp.
34 Cymbalta.mp.
35 Venlafaxine.mp.
36 Effexor.mp.
37 Citalopram.mp.
38 Celexa.mp.
39 Fluoxetine.mp. or exp Fluoxetine/
40 Prozac.mp.
41 Paroxetine.mp. or exp Paroxetine/

42 Paxil.mp.
43 Sertraline.mp. or exp Sertraline/
44 Zoloft.mp.
45 Escitalopram.mp.
46 Lexapro.mp.
47 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. [mp=title, full text, keywords]
49 Lidoderm.mp.
50 48 or 49
51 Dextromethorphan.mp. or exp Dextromethorphan/
52 19 or 31 or 47 or 50 or 51
53 3 and 52

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to follow-up or overall high loss to follow-up? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition)

For Non-randomized Studies Reporting Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Appendix C. Criteria for assessing scientific quality of research reviews*

1. Were the search methods reported? *Were the search methods used to find evidence (original research) on the primary questions stated?* **"Yes" if the review states the databases used, date of most recent searches, and some mention of search terms.**	The purpose of this index is to evaluate the scientific quality (i.e. adherence to scientific principles) of research overviews (review articles) published in the medical literature. It is not intended to measure literary quality, importance, relevance, originality, or other attributes of overviews. The index is for assessing overviews of primary ("original") research on pragmatic questions regarding causation, diagnosis, prognosis, therapy, or prevention. A research overview is a survey of research. The same principles that apply to epidemiological surveys apply to overviews: a question must be clearly specified, a target population identified and accessed, appropriate information obtained from that population in an unbiased fashion, and conclusions derived, sometimes with the help of formal statistical analysis, as is done in "meta-analyses". The fundamental difference between overviews and epidemiological studies is the unit of analysis, not the scientific issues that the questions in this index address. Since most published overviews do not include a methods section, it is difficult to answer some of the questions in the index. Base your answers, as much as possible, on information provided in the overview. If the methods that were used are reported incompletely relative to a specific question, score it as "can't tell", unless there is information in the overview to suggest either the criterion was or was not met.
2. Was the search comprehensive? *Was the search for evidence reasonably comprehensive?* **"Yes" if the review searches at least 2 databases and looks at other sources (such as reference lists, hand searches, queries experts).** *Note: EMBASE was launched in 1972, and CDSR was launched in 1994, therefore papers prior to 1994 can be graded "Yes" if only one database is searched.*	
3. Were the inclusion criteria reported? *Were the criteria used for deciding which studies to include in the overview reported?*	
4. Was selection bias avoided? ***Was bias in the selection of studies avoided?*** **"Yes" if the review reports how many studies were identified by searches, numbers excluded, and gives appropriate reasons for excluding them (usually because of pre-defined inclusion/exclusion criteria).**	
5. Were the validity criteria reported? *Were the criteria used for assessing the validity of the included studies reported?*	
6. Was validity assessed appropriately? *Was the validity of all the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)?* **"Yes" if the review reports validity assessment and did some type of analysis with it (e.g. sensitivity analysis of results according to quality ratings, excluded low-quality studies, etc.)**	

Appendix C. Criteria for assessing scientific quality of research reviews*

7. Were the methods used to combine studies reported? *Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?* **"Yes" for studies that did qualitative analysis if there is some mention that quantitative analysis was not possible and reasons that it could not be done, or if 'best evidence' or some other grading of evidence scheme used.**	For Question 8, if not attempt has been made to combine findings, and no statement is made regarding the inappropriateness of combining findings, check "No". if a summary (general) estimate is given anywhere in the abstract, the discussion, or the summary section of the paper, and it is not reported how that estimate was derived, mark "No" even if there is a statement regarding the limitations of combining the findings of the studies reviewed. If in doubt, mark "Can't tell".
8. Were the findings combined appropriately? *Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?* **"Yes" if the review performs a test for heterogeneity before pooling, does appropriate subgroup testing, appropriate sensitivity analysis, or other such analysis.**	For an overview to be scored as "Yes" in Question 9, data (not just citations) must be reported that support the main conclusions regarding the primary question(s) that the overview addresses. The score for Question 10, the overall scientific quality, should be based on your answers to the first nine questions. The following guidelines can be used to assist with deriving a summary score: If the "Can't tell" option is used one or more times on the preceding questions, a review is likely to have minor flaws at best and it is difficult to rule out major flaws (i.e. a score of 4 or lower). If the "No" option is used on Question 2, 4, 6 or 8, the review is likely to have major flaws (i.e. a score of 3 or less, depending on the number and degree of the flaws).
9. Were the conclusions supported by the reported data? *Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?*	
10. What was the overall scientific quality of the overview? *How would you rate the scientific quality of this overview?*	

Each Question is scored as Yes, Partially/Can't tell or No

Extensive Flaws		**Major Flaws**		**Minor Flaws**		**Minimal Flaws**
1	2	3	4	5	6	7

*Table created using information from Oxman & Guyatt, J Clin Epidemiol. 1991;44(11):1271-8 and Furlan, Clarke, et al., Spine. 2001 Apr 1;26(7):E155-62.

Appendix D. Table of Excluded Studies

Study	Reason for Exclusion
Adriaensen H, Plaghki L, Mathieu C, Joffroy A, Vissers K. Critical review of oral drug treatments for diabetic neuropathic pain-clinical outcomes based on efficacy and safety data from placebo-controlled and direct comparative studies. Diabetes/Metabolism Research Reviews. May-Jun 2005;21(3):231-240.	Outdated systematic review (searches prior to 2003)
Aldrete JA, Aldrete VT, Williams SK, Johnson S. Reduction of neuropathic pain in patients with arachnoiditis: Crossover study of gabapentin versus phenytoin. *Pain Digest.* 2000;10(2):64-67.	Population not included
Alper BS, Lewis PR. Treatment of postherpetic neuralgia: a systematic review of the literature.[see comment]. *Journal of Family Practice.* Feb 2002;51(2):121-128.	Outdated systematic review (searches prior to 2003)
Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clinical Therapeutics.* Jan 2003;25(1):81-104.	Outdated systematic review (searches prior to 2003)
Beydoun A, Wan Y, Hopwood M, Liebel J. Results of a randomized, placebo-controlled trial suggest oxcarbazepine has a therapeutic effect in the treatment of painful diabetic neuropathy. *European Journal of Neurology.* 2004;11(Suppl 2):101.	Abstract only (insufficient data)
Bosnjak S, Jelic S, Susnjar S, Luki V. Gabapentin for relief of neuropathic pain related to anticancer treatment: a preliminary study. *Journal of Chemotherapy.* Apr 2002;14(2):214-219.	Study design not included
Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.[see comment]. *Journal of Clinical Oncology.* Jul 15 2004;22(14):2909-2917.	Population not included
Challapalli, Tremont L, Iw, et al. Systemic administration of local anesthetic agents to relieve neuropathic pain [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2006;4:4.	Intervention not included
Collins SL, Moore RA, McQuayHj, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *Journal of Pain & Symptom Management.* Dec 2000;20(6):449-458.	Outdated systematic review (searches prior to 2003)
Criner TM, Perdun CS. Dextromethorphan and diabetic neuropathy. *Annals of Pharmacotherapy.* Nov 1999;33(11):1221-1223.	Outdated systematic review (searches prior to 2003)
Davis JL, Smith RL. Painful peripheral diabetic neuropathy treated with venlafaxine HCl extended release capsules.[see comment]. *Diabetes Care.* Nov 1999;22(11):1909-1910.	Study design not included

Study	Reason for Exclusion
Derbyshire E, Martin D. Neutropenia occurring after starting gabapentin for neuropathic pain. *Clinical Oncology (Royal College of Radiologists).* Dec 2004;16(8):575-576.	Study design not included
Deshpande MA, Holden RR, Gilron I. The impact of therapy on quality of life and mood in neuropathic pain: what is the effect of pain reduction? *Anesthesia & Analgesia.* May 2006;102(5):1473-1479.	Intervention not included
Donofrio PD, Raskin P, Rosenthal NR, et al. Safety and effectiveness of topiramate for the management of painful diabetic peripheral neuropathy in an open-label extension study. *Clin Ther.* Sep 2005;27(9):1420-1431.	Study design not included
Dubinsky RMMM, Kabbani HM, El-Chami ZM, Boutwell CM, Ali HM. Practice Parameter: Treatment of postherpetic neuralgia: An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology *. *Neurology.* 2004;63(6):959-965.	Outdated systematic review (searches prior to 2003)
Edwards KR, Bennington V, Marykay S, Hes M, LaMoreaux E, Harofolo E. Gabapentin for pain associated with diabetic peripheral neuropathy. A double-blind, placebo controlled study (945-2100). *Neurology.* 1998.	Abstract only (insufficient data)
Fishbain D. Evidence-based data on pain relief with antidepressants. *Annals of Medicine.* Jul 2000;32(5):305-316.	Outdated systematic review (searches prior to 2003)
Guay DRP. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? *American Journal Geriatric Pharmacotherapy.* Dec 2005;3(4):274-287.	No original data (e.g., Letter, editorial, non-systematic review)
Hamandi K, Sander JW. Pregabalin: a new antiepileptic drug for refractory epilepsy. *Seizure.* Mar 2006;15(2):73-78.	No original data (e.g., Letter, editorial, non-systematic review)
He, Wu, Zhou. Non-antiepileptic drugs for trigeminal neuralgia [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2006;4:4.	Intervention not included
Joss JD. Tricyclic antidepressant use in diabetic neuropathy. *Annals of Pharmacotherapy.* Sep 1999;33(9):996-1000.	Outdated systematic review (searches prior to 2003)
Jung AC, Staiger T, Sullivan M. The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain.[see comment]. *Journal of General Internal Medicine.* Jun 1997;12(6):384-389.	Outdated systematic review (searches prior to 2003)
Katz NP, Gammaitoni AR, Davis MW, Dworkin RH, Lidoderm Patch Study G. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. *Pain Medicine.* Dec 2002;3(4):324-332.	Study design not included
Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes.[see comment]. *Pain.* Nov 1997;73(2):123-139.	Outdated systematic review (searches prior to 2003)

Study	Reason for Exclusion
Lithner F. Venlafaxine in treatment of severe painful peripheral diabetic neuropathy. *Diabetes Care.* Nov 2000;23(11):1710-1711.	Study design not included
Mack A. Examination of the evidence for off-label use of gabapentin.[see comment]. *Journal of Managed Care Pharmacy.* Nov-Dec 2003;9(6):559-568.	No original data (e.g., Letter, editorial, non-systematic review)
McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review.[see comment]. *BMJ.* Oct 21 1995;311(7012):1047-1052.	Outdated systematic review (searches prior to 2003)
McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain.[see comment]. Pain. Dec 1996;68(2-3):217-227.	Outdated systematic review (searches prior to 2003)
Mellegers MA, Furlan AD, Mailis A. Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature. *Clinical Journal of Pain.* Dec 2001;17(4):284-295.	Outdated systematic review (searches prior to 2003)
Mendel CM, Klein RF, Chappell DA, et al. A trial of amitriptyline and fluphenazine in the treatment of painful diabetic neuropathy. *JAMA.* Feb 7 1986;255(5):637-639.	Intervention not included
Mercadante S, Arcuri E, Tirelli W, Villari P, Casuccio A. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study. *Tumori.* May-Jun 2002;88(3):239-242.	Population not included
Nalamachu S, Crockett RS, Mathur D. Lidocaine patch 5% for carpal tunnel syndrome: how it compares with injections: a pilot study. *Journal of Family Practice.* Mar 2006;55(3):209-214.	Population not included
Nikolajsen L, Finnerup NB, Kramp S, Vimtrup A-S, Keller J, Jensen TS. A randomized study of the effects of gabapentin on postamputation pain. *Anesthesiology.* Nov 2006;105(5):1008-1015.	Population not included
Pandey CK, Bose N, Garg G, et al. Gabapentin for the treatment of pain in guillain-barre syndrome: a double-blinded, placebo-controlled, crossover study. *Anesthesia & Analgesia.* of contents, 2002 Dec 2002;95(6):1719-1723.	Population not included
Pappagallo M. Newer antiepileptic drugs: possible uses in the treatment of neuropathic pain and migraine. *Clinical Therapeutics.* Oct 2003;25(10):2506-2538.	Outdated systematic review (searches prior to 2003)
Perez HE, Sanchez GF. Gabapentin therapy for diabetic neuropathic pain. *Am J Med.* Jun 1 2000;108(8):689.	Abstract only (insufficient data)
Raskin J, Wang F, Pritchett YL, Goldstein DJ. Duloxetine for patients with diabetic peripheral neuropathic pain: a 6-month open-label safety study. *Pain Medicine.* Sep-Oct 2006;7(5):373-385.	Study design not included

Study	Reason for Exclusion
Rosenberg JM, Harrell C, Ristic H, Werner RA, de Rosayro AM. The effect of gabapentin on neuropathic pain. *Clinical Journal of Pain.* Sep 1997;13(3):251-255.	Study design not included
Rowbotham MC, Reisner LA, Davies PS, Fields HL. Treatment response in antidepressant-naive postherpetic neuralgia patients: double-blind, randomized trial. *Journal of Pain.* Nov 2005;6(11):741-746.	Study design not included
Saudek CD, Werns S, Reidenberg MM. Phenytoin in the treatment of diabetic symmetrical polyneuropathy. *Clin Pharmacol Ther.* Aug 1977;22(2):196-199.	Intervention not included
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