Drug Class Review

Neuropathic Pain

Final Update 1 Report

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

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

STRUCTURED ABSTRACT

Purpose

We compared the effectiveness and harms of anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), and the lidocaine patch in adults with neuropathic pain.

Data Sources

To identify published studies, we searched MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and reference lists of included studies. We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for additional unpublished data and dossiers of information submitted by 5 pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project review methods.

Results and Conclusions

Overall, the strength of evidence evaluating the comparative benefits or harms of these drugs to treat neuropathic pain was low to moderate. Based on a small number of short-term trials directly comparing the drugs in patients with painful diabetic neuropathy and postherpetic neuralgia, the evidence did not support a statistically significant difference in response (50% reduction in pain) or withdrawal due to adverse events with gabapentin, pregabalin, and lamotrigine compared with tricyclic antidepressants. Oral pregabalin was similar to lidocaine 5% medicated patch in rate of response, but resulted in more patients withdrawing due to an adverse event. Adjusted indirect comparisons of placebo-controlled trials suggested that duloxetine, pregabalin, and gabapentin were superior to lacosamide and lamotrigine, but no difference in withdrawal from study due to adverse events was found. In these analyses, differences were not found between pregabalin, duloxetine, and gabapentin or comparisons of 5% lidocaine patch and amitriptyline or gabapentin. Tricyclic antidepressants caused more dry mouth than pregabalin or gabapentin while gabapentin and pregabalin resulted in higher rates of ataxia.

In patients with cancer-related neuropathic pain who were taking opioids, there was no difference in pain relief with low-dose gabapentin compared with low-dose imipramine. Monotherapy with either drug was insufficient for pain relief. In patients with spinal cord injury, gabapentin was more effective for pain relief than amitriptyline. The difference was significant only in the subgroup of patients with the highest levels of depression. In patients with central poststroke pain, there was no difference between amitriptyline and carbamazepine. There was no direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve

injury pain. Evidence for comparative effectiveness in patients with types of neuropathic pain other than diabetic or postherpetic was insufficient to assess comparative safety.

Post hoc analyses have not found older age to have an impact on response or treatment-emergent adverse events with duloxetine. Combination therapy with duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine may have had a potential benefit compared with monotherapy, but there was an increased risk of adverse events.

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INTRODUCTION

Neuropathic pain 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] Neuropathic pain can occur because of dysfunction or disease of the nervous system at the peripheral and/or central level.[2] Neuropathic pain can be very severe and disabling, with significant functional, psychological, and social consequences. Regardless of the underlying cause of neuropathic pain, common treatment goals are to decrease pain and/or improve function.

Neuropathic pain 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 neuropathic pain.[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 neuropathic pain is incomplete, and multiple mechanisms may be involved.[4]

Neuropathic pain 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). Neuropathic pain 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 neuropathic pain at some time.[5] The prevalence of different types of neuropathic pain varies widely.[6] Neuropathic pain is most commonly associated with painful diabetic neuropathy, postherpetic neuralgia, 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] Postherpetic neuralgia 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 neuropathic pain include cancer-related pain, spinal cord injury, poststroke pain, HIV-associated neuropathy, and phantom limb pain. Uncommon but potentially debilitating neuropathic pain conditions include trigeminal neuralgia (incidence 4/100,000 population).[12] In the United States, health care and disability-related costs associated with neuropathic pain are estimated at almost $40 billion annually.[13]

A number of medications (oral or topical) are available for treating neuropathic pain (Table 1). 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 neuropathic pain, 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 neuropathic pain is challenging because of the large number of medications available to treat this condition and potential differences between medications in effectiveness or harms. The objective of this report is to compare the effectiveness and safety of the

drugs shown in Table 1. Simple analgesics such as acetaminophen, nonsteroidal 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, 16] reviews available at http://www.ohsu.edu/drugeffectiveness/reports/final.cfm. Black box warnings for the interventions are listed in Appendix A.

Table 1. Included drugs

Drug	Trade name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain
Anticonvulsants			
Gabapentin	Neurontin®	Postherpetic neuralgia	Start at 300 mg, titrate to 900 mg, increase up to 1800 mg (divided tid)
Pregabalin	Lyrica®	Diabetic neuropathy, Postherpetic neuralgia	Start at 150 mg, increase up to 300 mg (divided tid) Start at 150 mg, increase up to 75 to 150 mg bid Adjust dose for renal dysfunction
Carbamazepine	Equetro®	None	NA
	Carbatrol®[a]	Trigeminal neuralgia	Start with 200 mg daily, 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
	Tegretol® Tegretol® XR Tegretol® CR[b]	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
	Epitol®	Trigeminal neuralgia	NA
Topiramate	Topamax®	None	NA
	Topamax Sprinkle®	None	NA
Oxcarbazepine	Trileptal®	None	NA
Lacosamide	Vimpat®	None	NA
Lamotrigine	Lamictal® Lamictal CD® Lamictal® ODT™ Lamictal® XR™	None	NA
Phenytoin	Dilantin®	None	NA
Levetiracetam	Keppra® Keppra XR™	None	NA
Valproic acid/divalproex	Depakote®[a] Depakote ER®[a]	None	NA
	Depakene®	None	NA
	Epival ECT®[b]	None	NA
	Depacon®[a]	None	NA
	Stavzor®[a]	None	NA
SNRIs			
Duloxetine	Cymbalta®	Diabetic neuropathy	60 mg daily; lower starting dose and gradual increase in patients with renal impairment
Venlafaxine	Effexor®[a]	None	NA

Drug	Trade name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain
	Effexor XR®		
Desvenlafaxine	Pristiq®	None	NA
Milnacipran	Savella®	None	NA
Topical analgesic			
Lidocaine	Lidoderm®[a]	Postherpetic neuralgia	Up to 3 patches for up to 12 hours within a 24-hour period
Tricyclic antidepressants			
Amitriptyline	Elavil®[b]	None	NA
Desipramine	Norpramin®	None	NA
Nortriptyline	Aventyl®	None	NA
	Pamelor®[a]	None	NA
Protriptyline	Vivactil®	None	NA
Imipramine	Tofranil®	None	NA
Doxepin	Sinequan®[b]	None	NA
	Silenor™[a]	None	NA

Abbreviations: bid, 2 times daily; CD, chewable dispersible; CR, controlled release; ECT, enteric coated tablet, NA, not applicable; ODT, orally disintegrating tablets; qid, 3 times daily, SNRI, serotonin-norepinephrine reuptake inhibitor; tid, 3 times daily; XR, extended release.
[a] Not available in Canada, available in the United States.
[b] Available in Canada, not available in the United States.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix B and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of absolute risk or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the number needed to treat (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of efficacy studies can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical effectiveness in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one’s practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that not proven does not mean proven not; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

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 Drug Effectiveness Review Project. The participating organizations of Drug Effectiveness Review Project 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 anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), and the lidocaine patch for neuropathic pain?

2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?

3. Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

METHODS

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/poststroke neuropathic pain
- Neuropathy associated with low back pain
- Peripheral nerve injury pain
- Phantom limb pain
- Guillain-Barre syndrome
- Polyneuropathy
- Spinal cord injury related pain
- Complex Regional Pain Syndrome (also known as Reflex Sympathetic Dystrophy)

Drugs

- Gabapentin (Neurontin®)
- Pregabalin (Lyrica®)
- Carbamazepine (Equetro®, Carbatrol®[a], Tegretol®, Tegretol® XR, Tegretol® CR[b], Epitol® [generic])
- Topiramate (Topamax®, Topamax Sprinkle®)
- Oxcarbazepine (Trileptal®)
- Lacosamide (Vimpat®)
- Lamotrigine (Lamictal®, Lamictal CD®, Lamictal® ODT™, Lamictal ®XR™)
- Levetiracetam (Keppra®, Keppra XR™)
- Valproic acid/divalproex (Depakote ®[a], Depakote ER®[a], Depakene®, Epival ECT®[b], Depacon®[a], Stavzor®[a])
- Duloxetine (Cymbalta®)
- Venlafaxine (Effexor®[a], Effexor XR®)
- Desvenlafaxine (Pristiq®)
- Lidocaine (Lidoderm®[a])
- Amitriptyline (Elavil®[b] [generic])

- Desipramine (Norpramin®)
- Nortriptyline (Aventyl®, Pamelor ®[a])
- Imipramine (Tofranil® [generic])
- Doxepin (Sinequan®[b], Silenor™[a])
- Milnacipran (Savella®)
- Protriptyline (Vivactil®)
- Phenytoin (Dilantin®)

[a] Not available in Canada, available in the United States.
[b] Available in Canada, not available in the United States.

Effectiveness Outcomes

- Response (including patient reported pain relief, patient reported global impression of clinical change, any other pain related measure)
- Use of rescue analgesics
- Speed and duration of response
- Relapse
- Functional capacity (quality of life, work productivity)

Harms Outcomes

- Overall adverse effects
- Withdrawals
- Withdrawals due to adverse effects
- 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

For effectiveness:

- Controlled clinical trials
- Recent, good quality systematic reviews
- Comparative observational studies of at least 1 year's duration, reporting functional outcomes

For harms:

- Controlled clinical trials
- Comparative observational studies (cohort or case-control) with a well-defined neuropathic pain population
- Noncomparative observational studies only if the duration is 1 year or longer, and if serious harms are reported; a serious harm is one that results in long-term health effects or mortality

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® (1966 to November Week 3 2010), the Cochrane Database of Systematic Reviews® (4th Quarter 2010), the Cochrane Central Register of Controlled Trials® (4th Quarter 2010), and the Database of Abstracts of Reviews of Effects (4th Quarter 2010), using terms for included drugs, indications, and study designs (see Appendix C 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 US Food and Drug Administration Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technology in Health, and 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.X2).

Study Selection

All citations were reviewed for inclusion using the prespecified criteria detailed above. 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 2 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.[17] We also did not include the IMMPACT recommendations[18-25] as these articles, although important in the field of chronic pain by providing guidance for future research, represent consensus statements rather than a controlled trial.

Data Abstraction

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. The following data were abstracted by 2 independent reviewers from included trials: population characteristics (including gender, age, ethnicity, diagnosis); eligibility; interventions (dose and duration); comparisons; numbers enrolled, lost to follow-up, and analyzed; and results for each outcome and funding. We recorded intent-to-treat results when reported. We considered methods to meet criteria for intent-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 intent-to-treat results if the data to perform these calculations were available. For crossover trials, we abstracted results from both crossover periods.[26] 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 predefined criteria (available at www.ohsu.edu/drugeffectiveness). 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.[27, 28] 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 intent-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 2 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.[29] 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.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[30] Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of drugs for neuropathic pain. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals.

We rated the strength of evidence for outcomes that we judged to represent the most clinically important and reliable: Patient-reported change in pain score, response defined as 50% or 30% reduction in pain, quality of life, and withdrawals due to adverse events.

Table 2. Definitions of the grades of overall strength of evidence[31]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

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).

Meta-analytic Methods

We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one drug for neuropathic pain against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data were the primary focus. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare an included drug for neuropathic pain with any other nonincluded treatment or with placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for which studies were homogeneous enough to provide a meaningful combined estimate. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be preformed, the data were summarized qualitatively.

For continuous outcomes, we used the mean difference between treatment and placebo groups as the effect measure, which we estimated based on mean change scores and standard

errors from baseline to follow up for each group from each study. For dichotomous outcomes, relative risk was used as the effect measure. All combined effects were estimated using random-effects models.[32] The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[33, 34] We conducted sensitivity analyses to check the impact of dosage on the results.

Because head-to-head evidence was sparse, we used the method described by Bucher, et al.[35] to perform indirect comparison meta-analysis to evaluate the difference between drugs based on data from placebo-controlled trials, as the trials were generally comparable in patient population and clinical and methodological characteristics. The magnitude of difference was characterized using relative risk ratio for relative risks and difference of mean difference for mean differences. Negative (−) difference of mean differences were interpreted as suggesting that drug A is associated with a greater reduction in neuropathic pain than drug B. Relative risk ratios greater than 1.0 were interpreted as suggesting that drug A is associated with a higher relative benefit compared to drug B for efficacy outcomes and higher relative risk for adverse events. All analyses were performed using Stata 11.0 (StataCorp, College Station, TX, 2009) or Stats Direct (Version 2.7.8, Stats Direct Ltd, 9 Bonville Chase, Altrincham, Cheshire WA14 4QA, UK).

Peer Review

We requested and received peer review of the report from 3 experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

Public Comment

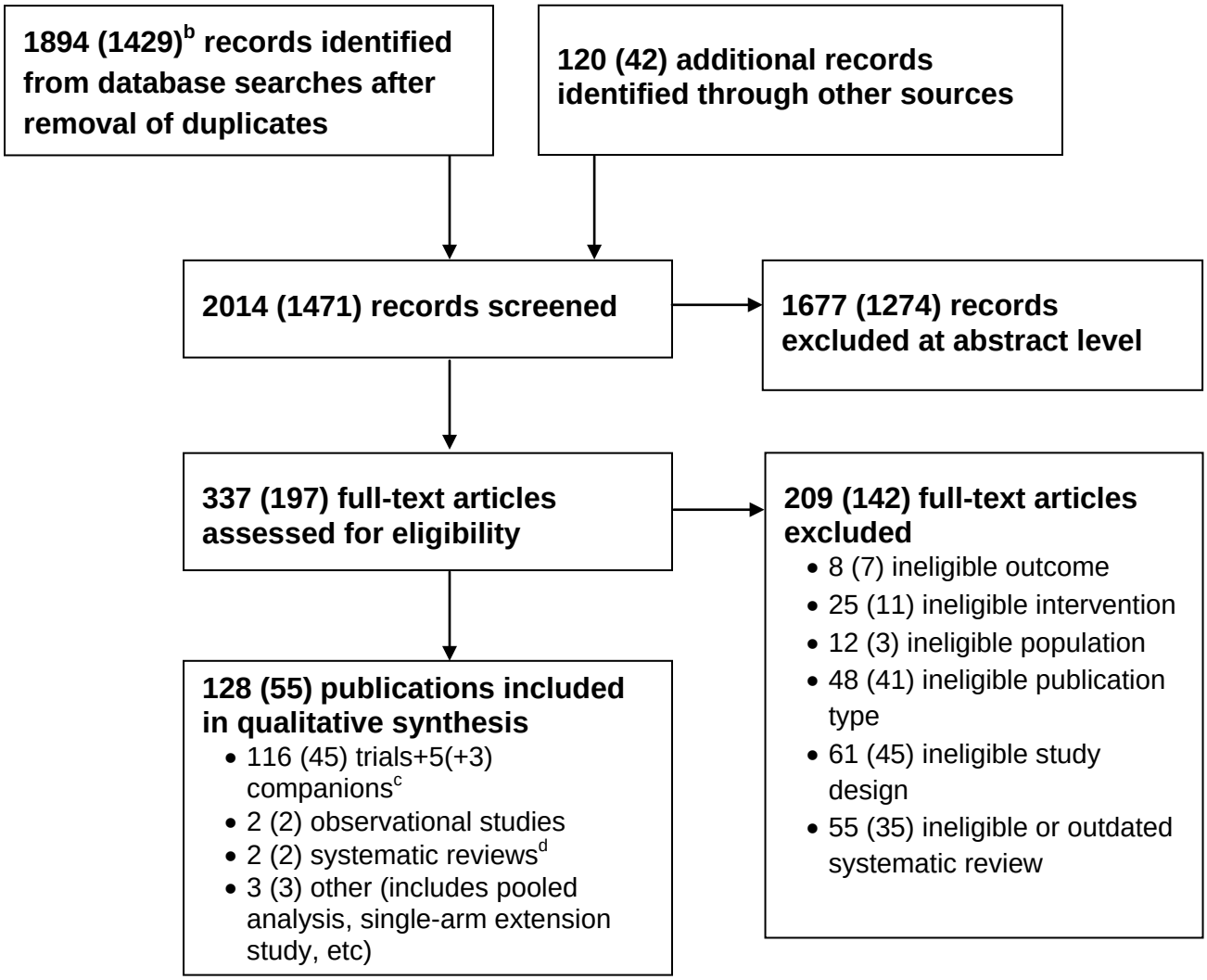
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 2 pharmaceutical companies.

RESULTS

Overview

Overall, 128 studies were included in this report (55 were identified in searches conducted for Update 1). Figure 1 shows the flow of study selection. We received dossiers from 5 pharmaceutical manufacturers: Eli Lilly, Endo, OMJUS, Ortho McNeil, and UCB. Twenty studies that were included in the original report were excluded in Update 1 either because they were outdated (8 systematic reviews) or because the inclusion criteria had changed. See Appendix D for a list of excluded studies and reasons for exclusion at full-text screening. Of the included studies, 14 were direct comparisons of drugs in this review. The remainder was placebo-controlled, observational, or systematic reviews.

Figure 1. Results of literature search[a]



[a] A modified PRISMA diagram was used.[36]
[b] Numbers in parentheses are results of the literature search new to Update 1.
[c] There are 12 trials that were included in original report but excluded now owing to change in eligibility criteria.
[d] There are 8 systematic reviews included in original but excluded in Update 1.

Results of Search: Randomized Trials

We identified 14 head-to-head trials, 7 of which compared amitriptyline to carbamazepine, gabapentin, lamotrigine, or pregabalin.[37-43] Two trials compared gabapentin to nortriptyline[44, 45] and 1 to imipramine.[46] There were 2 trials comparing venlafaxine to imipramine or carbamazepine.[47, 48] There was 1 trial each of pregabalin compared with lidocaine and pregabalin compared with duloxetine.[49, 50] Seven (50%) out of 14 the trials were parallel[40, 42, 45-47, 49, 50] and of patients with diabetic neuropathy.[37, 38, 40, 42, 43, 47, 50] Fourteen percent of trials were mixed, comprising diabetic neuropathy, post herpetic neuralgia, and polyneuropathy.[44, 49] There was 1 trial each of patients with central post stroke pain,[39] spinal cord injury,[41] polyneuropathy,[48] post herpetic neuralgia,[45] and cancer.[46] Sample sizes of the head-to-head trials ranged from 15 to 407 patients. Most trials were short-term with duration of therapy ranging between 1 and 18 weeks. Two trials were rated poor quality[41, 50] while the remainder was rated fair. Included placebo controlled trials are summarized in Table 3 below. We did not find any includable randomized trials of milnacipran, protriptyline, or phenytoin for neuropathic pain.

Table 3. Overview of included placebo-controlled trials[a]

Drug Class	Diabetic neuropathy	Postherpetic neuralgia	Other neuropathic pain	Totals	Quality
Gabapentin	3	2	10	15	13 Fair 2 Poor
Pregabalin	8	5	6	19	18 Fair 1 Good
Duloxetine	5	0	0	5	5 Fair
Venlafaxine	1	0	2	3	3 Fair
Lidocaine patch	0	4	1	5	3 Fair 2 Poor
Tricyclic antidepressants	6	4	13	23	19 Fair 4 Poor
Other anticonvulsants	15	1	23	39	30 Fair 9 Poor
Totals	38	16	55	109	91 Fair 17 Poor 1 Good

[a] Three head-to-head trials with a placebo arm were counted twice.[39, 40]

Effectiveness compared with Efficacy

We considered all of the trials included in this report efficacy studies, as none met all criteria for effectiveness studies.[51] 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.

Key Question 1. What is the comparative effectiveness of anticonvulsants, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors (SNRIs), and the lidocaine patch for neuropathic pain?

Summary of Findings

Diabetic neuropathy and postherpetic neuralgia

- Based on very small studies, moderate-strength direct evidence did not support a statistically significant difference between gabapentin, pregabalin, and lamotrigine compared with tricyclic antidepressants in the rate of response, defined as a 50% or more reduction in baseline pain analyzed individually or when pooled (relative risk, 1.0; 95% CI, 0.84 to 1.18)
- Low-strength evidence indicated that lidocaine 5% medicated patch was not statistically different to oral pregabalin in 50% pain reduction in the short term (relative risk, 1.21; 95% CI, 0.88 to 1.67)
- Using only adjusted indirect comparisons:
    - Duloxetine, pregabalin, and gabapentin were found to be superior to lacosamide and lamotrigine, with low- to moderate-strength evidence
    - Pregabalin was found to be superior to topiramate, with low-strength evidence
    - Differences were not found in other comparisons of pregabalin, duloxetine, gabapentin, and oxcarbazepine or comparisons of 5% lidocaine patch and amitriptyline or gabapentin
- Three drugs (divalproex, oxcarbazepine, and topiramate) had no direct comparative evidence and 1 drug (divalproex) had inadequate data to conduct an indirect analysis; all of these drugs were found superior to placebo in short -term trials.

Other types of neuropathic pain

Direct evidence

- In patients with cancer-related neuropathic pain, no difference in pain relief with low-dose gabapentin (400 mg or 800 mg) plus opioids compared to low-dose imipramine (10 mg) plus opioids; combination with gabapentin plus imipramine plus opioids was more effective than therapy with either gabapentin plus opioids or imipramine plus opioids
- In patients with spinal cord injury, amitriptyline was more effective for pain relief than gabapentin; when data were analyzed in subgroups based on patient's depression scores, the difference was significant only in the subgroup of patients with the highest levels of depression
- In patients with central poststroke pain, there was no difference between amitriptyline and carbamazepine
- There was no direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve injury pain.

Indirect evidence

- Because of differences among studies in populations, study designs, and outcomes, it was not possible to conduct indirect analyses in patients with other types of neuropathic pain.

Evidence from fair-quality placebo-controlled trials

- Chemotherapy-induced pain (prophylaxis)
  - Amitriptyline: no difference
  - Carbamazepine: no difference
  - Oxcarbazepine: among patients with advanced colon cancer who completed treatment (32/40), treatment reduced the occurrence of neuropathic pain (31.2% compared with 75%; $P=0.03$)
- Chemotherapy-induced pain (treatment)
  - Amitriptyline: no difference
  - Nortriptyline: no difference
  - Lamotrigine: no difference
  - Gabapentin: no difference
- HIV-associated neuropathic pain
  - Amitriptyline: no difference (2 trials)
  - Lamotrigine: effective only in the subgroup of patients exposed to neurotoxic antiretrovirals (2 trials)
  - Gabapentin: decrease from baseline in mean pain score (–44.1%; $P<0.05$); analysis by ANCOVA did not show a significant difference between treatment and placebo groups
  - Pregabalin: no difference in pain score or response
- Spinal cord injury
  - Amitriptyline: effective only in patients with depression
  - Lamotrigine: effective only in subgroup with incomplete spinal cord injury
  - Gabapentin: reduction in pain (3 trials)
  - Pregabalin: reduction in pain (2 trials)
  - Levetiracetam: not effective
  - Valproic acid: not effective
- Central poststroke pain
  - Lamotrigine: pain scores decreased, but there was no difference in pain affecting daily activities or use of rescue medication
  - Pregabalin: no difference in pain score or response
- Multiple sclerosis
  - Lamotrigine: no difference in pain or quality of life
  - Levetiracetam: decrease from baseline in pain score
- Central pain (mixed)
  - Pregabalin: decrease in mean pain score and improved quality of life; no difference between subgroups with pain due to brain injury compared with spinal cord injury
- Complex regional pain syndrome
  - Gabapentin: in 1 crossover trial, reduction in pain in the first treatment period; no difference in function or quality of life

- Phantom limb pain
  - Amitriptyline: not effective
  - Gabapentin: decrease in pain; no difference in use of rescue medication or activities of daily living
- Postmastectomy pain syndrome
  - Amitriptyline: not effective
  - Levetiracetam: no difference in pain score, response, or use of rescue medication
  - Venlafaxine: no difference in average pain intensity; pain relief significantly better with treatment; 73% had at least 50% pain relief
- Traumatic nerve injury pain
  - Gabapentin: decrease in pain score
  - Pregabalin: decrease in pain score
- Trigeminal neuralgia
  - Lamotrigine decreased pain score
  - Studies of carbamazepine and topiramate were poor quality
- Chronic lumbar radiculopathy
  - Nortriptyline: not effective for reducing leg or back pain
- Polyneuropathy or mixed populations
  - Levetiracetam: not effective for pain or physical function
  - Valproic acid: not effective for pain relief
  - Amitriptyline: reduced pain in mixed group of patients with diabetic and nondiabetic polyneuropathy
  - Gabapentin: reduced pain and improved some quality of life measures

Detailed Assessment

Diabetic neuropathy and postherpetic neuralgia

In 10 publications and 1 unpublished study[40] we identified 4 trials comparing gabapentin with amitriptyline or nortriptyline, 2 trials comparing pregabalin with amitriptyline, 1 trial comparing venlafaxine with carbamazepine, 1 trial comparing 5% lidocaine patch with oral pregabalin, and 1 trial comparing duloxetine with pregabalin.[37, 38, 40, 42-45, 47, 49, 50, 52] Nine of these studies were rated fair quality with 1 rated poor quality, partly due to high overall attrition and differential lost to follow-up. [50] See Table 4 for a summary of the 10 head-to-head studies. Most of the trials were conducted outside the United States[37, 38, 40, 42, 44, 45, 47, 52] and used adult diabetic patients as subjects,[37, 38, 40, 42, 43, 47, 50] although 2 trials were of postherpetic neuralgia patients[45, 52] and 1 study had a mixed diabetic/postherpetic neuralgia sample.[44] Four studies employed a crossover, rather than a parallel design,[37, 38, 43, 44] and 4 were open label trials.[37, 42, 50, 52]

Table 4. Summary of head-to-head trials with the outcome of ≥50% reduction in pain

Author, Year	N	Study design	Duration of trial	Outcome	Quality rating
Gabapentin vs. amitriptyline or nortriptyline					
Gilron, 2009	47	Crossover	18 weeks	RR 0.86 (0.65 to 1.11)	Fair
Dallocchio, 2000	25	Parallel	12 weeks	RR 1.13 (0.76 to 1.68)	Fair
Morello, 1999	25	Crossover	13 weeks	RR 0.79 (0.45 to 1.38)	Fair
Chandra, 2006	76	Parallel	9 weeks	RR 0.78 (0.32 to 1.87)	Fair
Gabapentin Pooled	173			RR 0.90 (0.74 to 1.10)	
Pregabalin vs. amitriptyline					
Pfizer 1008-040, 2007	175	Parallel	10 weeks	RR 0.89 (0.63 to 1.25)	Fair
Bansal, 2009	75	Crossover	14 weeks	RR 1.35 (0.88 to 2.07)	Fair
Pregabalin Pooled	250			RR 1.07 (0.71 to 1.62)	
Lamotrigine vs. amitriptyline					
Jose, 2007	75	Crossover	14 weeks	RR 1.39 (0.87 to 2.23)	Fair
All Trials Pooled	498			RR 1.00 (0.84 to 1.18)	

Abbreviation: RR, relative risk.

No study of gabapentin, pregabalin, or lamotrigine demonstrated individual superiority over the tricyclic antidepressants amitriptyline and nortriptyline. When the 7 studies were pooled in a meta-analysis, there remained no statistically significant difference in 50% or more improvement in pain between amitriptyline/nortriptyline and pregabalin, gabapentin, and lamotrigine (relative risk, 1.00; 95% CI, 0.84 to 1.18; I^2=13.3%).[37, 38, 40, 42-45] It is possible that nonsignificant difference was influenced by the high attrition in 2 trials,[38, 40] baseline differences in gender distribution and baseline pain scores in 1 trial,[40] and lack of blinding in 2 trials.[37, 42] Other head-to-head comparisons involved single studies only. Venlafaxine was found to be superior to carbamazepine in reducing pain intensity on an 11-point Likert scale in a per protocol analysis in a 2-week study of people with painful diabetic neuropathy (P=0.001). While doses of both drugs were lower than used clinically for other indications, the 25 mg twice daily dose of venlafaxine was relatively closer to the dosage approved by the US Food and Drug Administration than the 100 mg daily dose of carbamazepine (37.5-75 mg venlafaxine 2 to 3 times daily for major depressive disorder compared with 200-400 mg carbamazepine twice daily for trigeminal neuralgia).[47] It is possible that this difference may have influenced the findings.

Lidocaine 5% medicated patch was not better than oral pregabalin in achieving at least a 50% reduction in pain from baseline in an open-label study (relative risk, 1.21; 95% CI, 0.88 to 1.67).[52,49] While the benefits of the lidocaine patch were greater in patients who had postherpetic neuralgia, rather than diabetic neuropathy, neither group reached statistically significant improvement.

Additionally, there was 1 fair-quality systematic review of the 5% lidocaine medicated patch in diabetic peripheral neuropathy in which a network analysis was conducted to compare the lidocaine patch with amitriptyline, gabapentin, and pregabalin.[53] No significant differences were found in pain change from baseline in the lidocaine patch and pregabalin (effect size, 1.43; 95% CI, –2.96 to 5.83), gabapentin (effect size, –0.31; 95% CI, –7.05 to 6.43), and amitriptyline

(effect size, 3.48; 95% CI, –0.77 to 7.74). However, there are concerns about the network analysis' use of a continuous, rather than a dichotomous outcome, where actual counts are known.

Duloxetine and pregabalin were found to have similar impact on pain reduction in a 12-week study of patients who had inadequate pain relief on 900 mg of gabapentin daily using an 11-point Likert Scale. However, we rated this study as poor quality, in part because 43% of the duloxetine patients withdrew from the study compared with 28% of the patients on pregabalin and 22% of the patients taking the combination of duloxetine and gabapentin.[50]

Adjusted indirect analysis of placebo-controlled trials of tricyclic antidepressants compared with gabapentin, pregabalin, and lamotrigine

An indirect comparison meta-analysis found gabapentin, pregabalin, and lamotrigine to be inferior to the tricyclic antidepressants (relative risk, 0.54; 95% CI, 0.30 to 0.80; relative risk, 0.39; 95% CI, 0.18 to 0.88; and relative risk, 0.30; 95% CI, 0.10 to 0.88, respectively). However, an expressed concern within the neuropathic pain literature is the variability of the placebo response.[54-58] Since a drug's effectiveness against placebo is used to calculate its effectiveness against another active drug during adjusted indirect meta-analysis, the differences in placebo response rate becomes quite important. Factors, which have been suggested to influence the magnitude of the placebo response in neuropathic pain trials, include: unadjusted year of publication,[57] duration of the clinical trial,[57] baseline pain scores,[55] and rate of patient recruitment to the study.[55] In our pool of studies, the rate of patient recruitment was rarely reported, but we examined the other factors here to determine if these factors are relevant in our data set. This may indicate that indirect comparisons may not be accurate.

In this review, placebo-controlled trials including the outcome ≥50 % pain reduction from baseline, which were published in the 1980s, had a placebo response rate of 6% compared with those published in the 1990s (23%) or published in the years 2000-2005 (20%) and years 2006 to the present (27%). Duration of the trial also seemed to have affected the placebo response in these studies. Trials of gabapentin, pregabalin, lamotrigine, and tricyclic antidepressants that were 6 weeks or less in duration had a placebo response rate of 15% compared with trials between 7 and 10 weeks duration where the placebo response rate was 21% and trials greater than 10 weeks duration, where the placebo response rate was 27%. Perhaps a better way to examine the effect of trial duration on the placebo response is to compare trials of the same drug using different durations: four 8-week trials of pregabalin with placebo response rates of 19% compared with 5 trials of pregabalin of 12-14 weeks duration with placebo response rates of 25%, which is consistent with Quessy's finding of a weak tendency for the placebo response to increase as the duration of the trial increases.[57] While the placebo response increased with duration, the treatment effect of pregabalin in these trials decreased from 56% in trials ≤6 weeks duration, 43% in trials 7-10 weeks duration, and 38% in trials ≥11 weeks. Both patterns may simply represent a regression to the mean as trial duration lengthens. With regard to the possible relationship between baseline pain levels and the placebo response in neuropathic pain trials, the baseline pain levels in trials of gabapentin, pregabalin, and lamotrigine were between 6 and 7 on an 11-point Likert Scale with the exception of 1 trial with a baseline pain score of 5.7.[59] However, with the exception of the most recent study with a baseline score of 6.3,[40] none of the tricyclic antidepressants trials reported scores on an 11-point Likert Scale. Although the specific year of publication of the study, the duration of the study, and the baseline pain levels appear to predict the placebo response, in studies of gabapentin, pregabalin, lamotrigine, and the tricyclic

antidepressants, factors all correlate highly with each other. An important additional factor, not previously mentioned, is study design. All placebo-controlled trials of tricyclics for painful diabetic neuropathy or postherpetic neuralgia in this review are crossover studies. The majority of studies of the other classes of drugs for neuropathic pain are not crossover, making the tricyclic studies different − not only in their placebo response rate, but also in core ways the studies were conducted.

The differences in placebo response rate that we observed, based on year and duration of study, imply that the indirect meta-analysis may not be valid. Our own assessment of the response rates (both placebo and drug) in the older, tricyclic antidepressant studies compared to any newer study also indicated differences that were concerning. Therefore, although the indirect comparisons of gabapentin, pregabalin, and lamotrigine with tricyclic antidepressants significantly favor the tricyclics for providing ≥50% pain relief, we do not feel that these indirect comparisons are valid.

Indirect analysis of other comparisons

Based on 6 placebo-controlled trials of gabapentin,[59-65] 15 trials of pregabalin,[40, 66-80] 3 trials of duloxetine,[81-83] 1 trial of venlafaxine,[84] 4 trials of lacosamide,[85-88] 2 trials of oxcarbazepine,[89, 90] and 2 studies representing 4 trials of topiramate,[91,92] we conducted adjusted indirect comparisons. The primary outcome for comparison was ≥ 50% reduction in pain from baseline pain scores. See Table 5 below.

Duloxetine, pregabalin, and gabapentin were superior to lamotrigine and lacosamide when measuring ≥50% pain relief.

Table 5. Indirect comparison of pain measured as ≥50% pain reduction

Drug	Total N	Relative risk (95% confidence interval)
Compared with placebo		
Duloxetine	681	1.86 (1.52 to 2.28)
Pregabalin	3636	1.92 (1.53 to 2.40)
Gabapentin	852	2.23 (1.75 to 2.85)
Lamotrigine	875	1.11 (0.84 to 1.47)
Oxcarbazepine	493	1.51 (0.91 to 2.50)
Lacosamide	808	1.22 (0.89 to 1.67)
Indirect comparison		
Duloxetine vs. pregabalin		0.97 (0.72 to 1.31)
Duloxetine vs. gabapentin		0.83 (0.61 to 1.15)
Duloxetine vs. lamotrigine		1.68 (1.19 to 2.36)
Duloxetine vs. lacosamide		1.52 (1.05 to 2.21)
Duloxetine vs. oxcarbazepine		1.23 (0.71 to 2.13)
Pregabalin vs. lamotrigine		1.73 (1.21 to 2.0)
Pregabalin vs. lacosamide		1.57 (1.06 to 2.31)
Pregabalin vs oxcarbazepine		1.27 (0.73 to 2.22)
Gabapentin vs. pregabalin		1.09 (0.78 to 1.55)
Gabapentin vs. lamotrigine		2.01 (1.39 to 2.91)
Gabapentin vs. lacosamide		1.82 (1.22 to 2.72)
Gabapentin vs. oxcarbazepine		1.48 (0.84 to 2.60)
Lamotrigine vs. lacosamide		0.91 (0.60 to 1.38)
Oxcarbazepine vs. lacosamide		1.23 (0.68 to 1.23)

Other indirect comparisons were possible using other, frequently-used neuropathic pain outcomes such as pain rated on an 11-point Likert scale, on a 0-100 visual analogue scale, and on the 0-45 short form of the McGill Pain Questionnaire (SF-MPQ). See table 6 below. (The mean difference indicates that a drug reduces pain scores from baseline more than placebo reduces pain scores. The difference of the difference indicates that a drug reduces pain scores from baseline, better than another drug, after the reductions due to placebo have been taken into account.)

In indirect analysis, duloxetine was again superior to lamotrigine and lacosamide using the 11-point scale. Pregabalin was, again, superior to lamotrigine using the McGill Pain Questionnaire. Pregabalin was also superior to lacosamide on the 11-point scale and the 0-100 visual analogue scale. Gabapentin was, again, superior to lamotrigine on both the 11-point scale and the McGill Pain Questionnaire. In addition, gabapentin was superior to lacosamide on the 11-point Likert scale. No other comparisons were significant using these scales.

Table 6. Significant indirect comparisons of pain reduction on 3 different scales

Drug	Mean difference (95% confidence interval)	Indirect comparison	Difference of difference (95% confidence interval)
11-point Likert Scale			
Duloxetine	–1.11 (–1.42 to –0.82)	Duloxetine vs. lacosamide	–0.62 (–0.97 to –0.27)
Pregabalin	–1.00 (–1.22 to –0.69)	Duloxetine vs. lamotrigine	–0.63 (–1.21 to –0.05)
Gabapentin	–1.31 (–1.80 to –0.81)	Pregabalin vs. lacosamide	–0.50 (–0.83 to –0.18)
Lacosamide	–0.49 (–0.69 to –0.30)	Gabapentin vs. lacosamide	–0.81 (–1.35 to –0.28)
Lamotrigine	–0.48 (–0.98 to 0.02)	Gabapentin vs. lamotrigine	–0.83 (–1.53 to –0.12)
0-100 Visual Analogue Scale			
Pregabalin	–10.82 (–13.90 to –7.73)	Pregabalin vs. lacosamide	–4.65 (–9.25 to –0.04)
Gabapentin	–11.72 (–20.26 to –3.18)	Pregabalin vs topiramate	–7.19 (–12.03 to –2.35)
Lacosamide	–6.17 (–9.58 to –2.75)		
Oxcarbazepine	–10.02 (–16.02 to –4.01)		
Topiramate	–3.63 (–7.35 to 0.10)		
0-45 Short Form of McGill Pain Questionnaire			
Pregabalin	–3.94 (–5.36 to –2.52)	Pregabalin vs. lamotrigine	–3.68 (–5.53 to –1.84)
Gabapentin	–4.73 (–6.64 to –2.83)	Gabapentin vs. lamotrigine	–4.48 (–6.72 to –2.24)
Lamotrigine	–0.26 (–1.43 to 0.92)		

Placebo-controlled trials

For drugs with no head-to-head or indirect comparative evidence regarding efficacy or effectiveness available (divalproex and venlafaxine) and no US Food and Drug Administration approval for treatment of neuropathic pain, placebo-controlled trials were reviewed to determine evidence of basic efficacy. Additionally, there were several diabetic neuropathy and postherpetic trials not incorporated into this review due to poor quality,[93-100] no longer of an included drug,[101] did not report result statistics,[102] substituted drugs based on tolerability,[103] or based drug dosages on sparteine phenotype.[104]

As a group divalproex, lacosamide, lamotrigine, oxcarbazepine, and topiramate were superior to placebo in achieving response, defined as at least a 50% reduction in pain (relative risk, 1.34; 95% CI, 1.11 to 1.62). See Table 7 for a summary of these anticonvulsant trials. The individual anticonvulsant drugs with significant results included divalproex[105] and topiramate.[91]

Table 7. Anticonvulsant trials measuring 50% response rate in pain reduction

Study, year	N	Duration	Relative risk (95% confidence interval)
Divalproex			
Kochar, 2005	40	8 weeks	4.15 (1.37 to 12.59)
Lacosamide			
Shaibani, 2009	468	18 weeks	1.25 (0.81 to 1.92)
Ziegler, 2010	357	18 weeks	1.19 (0.77 to 1.91)
Lacosamide pooled	825		1.22 (0.89 to 1.67)
Lamotrigine			
GSK NPP 30004[a]	360	19 weeks	0.91 (0.61 to 1.38)
GSK NPP 30005[a]	360	19 weeks	1.06 (0.67 to 1.66)
Eisenberg, 2001	59	6 weeks	2.48 (1.00 to 6.17)
Silver, 2007	223	14 weeks	1.13 (0.74 to 1.72)
Lamotrigine pooled	**1002**		**1.11 (0.84 to 1.47)**
Oxcarbazepine			
Dogra, 2005	146	16 weeks	2.07 (1.18 to 3.64)
Beydoun, 2006	347	16 weeks	1.22 (0.90 to 1.65)
Oxcarbazepine pooled	**493**		1.51 (0.91 to 2.50)
Topiramate			
Raskin, 2004	323	12 weeks	1.64 (1.24 to 2.18)
Anticonvulsants pooled	**2683**		**1.34 (1.11 to 1.62)**

[a] Published in Vinik, 2007[106]

Although there was only 1 trial of divalproex which included 50% pain reduction as an outcome, there were a total of 3 trials of divalproex.[105, 107, 108] All 3 trials of divalproex were small (N≤60).[105, 107, 108] Two studies focused on painful diabetic neuropathy,[107, 108] while the third trial was of postherpetic neuralgia patients.[105] All 3 demonstrated significant pain reduction on 1200 mg daily ($P<0.05$)[107] and 1000 mg daily ($P<0.001$)[108] in diabetic patients and 1000 mg daily ($P<0.001$) in postherpetic neuralgia patients.[105]

Of 3 trials of oxcarbazepine, 1 was rated poor quality, in part due to 41% attrition in the oxcarbazepine group compared with 24% in the placebo group and lack of clarity regarding which subjects were analyzed.[94] The remaining 2 were fair-quality, 16-week, parallel group trials.[89, 90] In 1 of the studies, patients experienced a larger decrease in pain as recorded on a visual analogue scale with oxcarbazepine compared to placebo ($P=0.0108$) with a mean of 1445 mg daily.[90] In the second study, there was no difference using the visual analogue scale between oxcarbazepine at doses of 600 mg daily, 1200 mg daily, and 1800 mg daily compared with placebo, although there was a trend toward significance with the latter 2 doses ($P=0.101$, $P=0.096$, respectively).[89] One noted difference between the eligibility criteria of the 2 studies was that the first study required an average pain score of 50 on the visual analogue scale over 4 of the last 7 days prior to randomization and the second study required an average visual analogue scale pain rating of 40 during the prerandomization phase. This difference of baseline pain scores may have contributed to the different findings in the 2 fair-quality trials.

The results from 2 publications representing 4 trials of topiramate were mixed.[91, 92] In a 12-week trial demonstrating significant pain reduction,[91] the mean baseline pain score on a 0-100 visual analogue scale was 68.4, whereas the mean baseline pain score on the same scale was 57.9 in the 18-22 week trials demonstrating no statistically significant effect.[92] Additionally, the differences in trial duration may have contributed to the mixed results.

A single, fair-quality trial of venlafaxine was a parallel study of 6 weeks duration where 150-225 mg daily of extended release venlafaxine showed benefit on a 0-100 visual analogue scale compared to placebo ($P<0.001$), but 75 mg daily did not.[52, 84]

Results of pooled analysis of placebo-controlled trials are mentioned here. Studies of tricyclic antidepressants demonstrated superiority in a pooled analysis of trials reporting ≥ 50% pain relief from baseline (relative risk, 4.85; 95% CI, 1.86 to 12.67).[40, 109-113] Likewise, pooled placebo-controlled trials of pregabalin (relative risk, 1.87; 95% CI, 1.50 to 2.32), [40, 66-71, 73-80] gabapentin (relative risk, 2.19; 95% CI, 1.79 to 2.68), and duloxetine (relative risk, 1.72; 95% CI, 1.42 to 2.07)[81-83] reporting ≥ 50% pain relief from baseline showed effectiveness over placebo.

The lidocaine patch also demonstrated superiority over placebo as a therapy for postherpetic neuralgia. On a 0-100 visual analogue scale, the lidocaine patch averaged a 10.2 mm reduction in pain, which was superior to both observation only ($P<0.001$ to 0.038, depending on time point) and the placebo patch at 2 hours ($P=0.016$) and 6 hours ($P=0.41$). The lidocaine patch was not significantly superior to the placebo patch at other time periods measured.[114] Two studies with a primary outcome of "time to exit the study" found that subjects left the study sooner if they had received the placebo patch rather than the lidocaine patch—by 10.2 days in 1 study[115] and by 4.5 days in the other.[116]

Chemotherapy-induced or cancer-related neuropathic pain

Direct evidence

We identified 1 fair-quality head-to-head trial in 52 patients with cancer-related neuropathic pain.[46] Patients with pain not controlled by opioids and NSAIDs were randomized to low-dose gabapentin (400 or 800 mg), low-dose imipramine (10 mg), or a combination of the 2. All patients continued their opioids. Gabapentin-imipramine combination treatment significantly reduced total pain score, daily paroxysmal pain episodes, and opioid rescue dose. Monotherapy with low-dose gabapentin or low-dose imipramine did not control pain sufficiently.

Indirect evidence

Eight fair-quality randomized controlled trials compared a drug for neuropathic pain to placebo for prevention or treatment of chemotherapy-induced or cancer-related neuropathic pain.[117-124] Three trials, 1 each of amitriptyline, carbamazepine, and oxcarbazepine, were designed to assess the effectiveness of treatment to prevent pain in patients undergoing chemotherapy (Table 8).[117, 119, 124] Only 1 of the 3 trials found a significant reduction in neuropathic pain with treatment. Two trials found no difference in the development of neuropathic pain with either amitriptyline or carbamazepine. An open-label trial of oxcarbazepine compared with usual care in patients with advanced colorectal cancer found a reduction in the development of neuropathic pain in patients given oxcarbazepine (31.2% compared with 75%; $P=0.03$).[117] These percentages are for patients who completed treatment (32 of 40, 80%); intent-to-treat results also showed efficacy of oxcarbazepine ($P=0.05$; data not reported). Severity of pain was also reduced in the oxcarbazepine group (per-protocol results).

Table 8. Placebo-controlled trials of drugs to prevent chemotherapy-induced neuropathic pain

Author, year (Quality)	Drug/comparator Design	N/ Population	Main results
Kautio 2009[119] (Fair)	Amitriptyline 100 mg vs. placebo Parallel	114/ Patients beginning first chemotherapy	No difference between groups in development of neuropathic pain.
Von Delius 2007[124] (Fair)	Carbamazepine vs. usual care Parallel	36/ Patients with advanced colorectal cancer	No difference between groups in peripheral neuropathic pain scores, worst neurotoxicity or occurrence of grade 3 and 4 neurotoxicity.
Argyriou 2006[117] (Fair)	Oxcarbazepine vs. usual care Parallel; open-label	40/ Patients with advanced colon cancer, chemotherapy naïve	Patients who completed treatment (N=32): 5/16 (31.2%) oxcarbazepine vs. 12/16 (75%) usual care group developed neuropathic pain (*P*=0.03). Intent-to-treat results *P*=0.05

Four fair-quality placebo-controlled trials were conducted in patients with chemotherapy-induced neuropathic pain.[118, 120, 122, 123] They included 1 trial each of gabapentin, lamotrigine, amitriptyline, and nortriptyline. None of these found a difference between treatment and placebo in mean pain score, response, or quality-of-life measures.

A fifth trial found gabapentin plus an opioid reduced burning or shooting pain more than an opioid alone.[121] The results of this trial may not be valid, however. It was rated poor quality due to lack of blinding of outcome assessment, baseline differences between groups, and no intent-to-treat analysis combined with a 16% withdrawal rate (Table 9).

Table 9. Randomized controlled trials of drugs for treatment of chemotherapy-induced and cancer-related neuropathic pain

Author, year (Quality)	Drug, dose/comparator Design	Population	N, treatment duration	Main results
Rao 2007[123] (Fair)	Gabapentin vs. placebo Crossover	Chemotherapy-induced neuropathic pain	115 6 weeks	No difference between groups in pain score
Rao 2008[122] (Fair)	Lamotrigine vs. placebo Parallel	Chemotherapy-induced neuropathic pain	125 10 weeks	No difference between groups in pain score
Kautio 2008[120] (Fair)	Amitriptyline 50 mg vs. placebo Parallel	Chemotherapy-induced neuropathic pain	44 (33 analyzed) 8 weeks	No difference between groups in pain score, response, or quality of life
Hammack 2002[118] (Fair)	Nortriptyline 75-100 mg vs. placebo Crossover	Chemotherapy-induced neuropathic pain	51 4 weeks	No difference between groups in pain score, response, or quality of life
Keskinbora 2007[121] (Poor)	Gabapentin plus opioid vs. opioid alone Parallel; open-label	10/75 had pain related to cancer therapy	75 (63 analyzed) 2 weeks	Decrease in burning/shooting pain with gabapentin vs. opioid alone

HIV-associated neuropathic pain

Direct evidence

We identified no head-to-head trials in patients with HIV-associated neuropathic pain.

Indirect evidence

We identified 6 fair-quality placebo-controlled trials of drugs to treat HIV-associated neuropathic pain (Table 10).[125-130] Two trials included amitriptyline, 2 included lamotrigine, 1 included gabapentin, and 1 included pregabalin.

In both amitriptyline trials, there was no difference between treatment and placebo in pain score or response.[126, 127] In the 2 lamotrigine trials, treatment was more effective than placebo only in the subgroup of patients who were on neurotoxic antiretroviral treatment.[128, 129] No other trials reported data by exposure to neurotoxic antiretrovirals. In the trial of gabapentin, both groups significantly improved from baseline but the difference between groups was not significant.[125] Pregabalin was no more effective than placebo in 1 trial.[130]

Table 10. Placebo-controlled trials of drugs for HIV-associated neuropathic pain

Author, year (Quality)	Drug, dose	N Duration Design	Main results
Kieburtz 1998[126] (Fair)	Amitriptyline	96 10 weeks Parallel	No difference from placebo in pain score Moderate or better relief: 23/46 amitriptyline (50%) 24/50 placebo (48%) *P*=0.84
Shlay 1998[127] (Fair)	Amitriptyline	126 14 weeks Parallel	No difference from placebo in pain score Moderate or better relief: 27/61 amitriptyline (44%) 27/60 placebo (45%) *P*=0.81
Simpson 2000[129] (Fair)	Lamotrigine	42 14 weeks Parallel	Intent-to-treat analysis: No difference between treatment groups in pain score (*P*=0.65) Per protocol analysis (29 of 42 patients): Decrease in average pain score with lamotrigine Significant difference only in the subgroup exposed to neurotoxic antiretrovirals
Simpson 2003[128] (Fair)	Lamotrigine	227 11 weeks Parallel	Among patients receiving neurotoxic antiretroviral treatment: At least moderate improvement: 53/62 lamotrigine (85%) 30/30 placebo (100%) Marked improvement: 29/62 lamotrigine (46.8%) 4/30 placebo (13.3%) *P*<0.05 No difference between treatment groups in subgroup not receiving neurotoxic antiretrovirals
Hahn 2004[125] (Fair)	Gabapentin	26 5 weeks Parallel	Both groups improved from baseline; decrease in pain was significant in gabapentin group but not placebo (–44.1%; *P*<0.05 vs. –29.8%; *P*=0.646) Comparison of change from baseline in pain score (ANCOVA) did not show a significant difference between groups Response not reported
Simpson 2010[130] (Fair)	Pregabalin	302 14 weeks Parallel	No difference between groups in pain score (difference –0.25, *P*=0.39) No difference between groups in 30% and 50% responder rates

Spinal cord injury-related neuropathic pain

Direct evidence

A fair quality, head-to-head crossover trial compared gabapentin (maximum dose 3600 mg) to amitriptyline (maximum dose 150 mg) in 38 patients with spinal cord injury.[41] Diphenhydramine (maximum dose 75 mg) was also included as an active placebo so that subjects would think they were getting gabapentin or amitriptyline due to the side effects of diphenhydramine. Twenty-two patients (58%) completed all 3 phases of the trial. Analysis of the 22 completers found average visual analogue scale pain intensity score at week 8 was significantly lower with amitriptyline than with gabapentin (P=0.03) or diphenhydramine (P=0.01). There was no significant difference between gabapentin and diphenhydramine. An analysis by patients' level of depression found that among those with the lowest levels of depression, there was no difference in pain scores between the 3 groups, however. Among those with the highest levels of depression according to The Center for Epidemiologic Studies Depression Scale-Short Form (CESD-SF), amitriptyline reduced pain scores more than gabapentin or diphenhydramine. Among patients in the low CESD-SF group (score <10), response rates (defined as 30% or more decrease in pain score) were 50% with amitriptyline, 42.9% with gabapentin, and 35.7% with diphenhydramine. Among those in the high CESD-SF group (score ≥10), response rates were 62.5%, 12.5%, and 25%, respectively.

Indirect evidence

A recent, good-quality systematic review summarized the evidence for effectiveness of pharmacologic treatments for pain after spinal cord injury, including anticonvulsants and antidepressants.[131] Searches were conducted from 1980 to June 2009; 9 trials were included.[41, 132-139] We did not identify any more recent studies that were not included in this review. Methodological quality of studies was rated based on internal validity of studies, with trials assigned a rating of excellent, good, fair, or poor. A level of evidence hierarchy was used to determine the strength of evidence for each intervention. No quantitative meta-analysis was conducted.

Table 11. Treatment effectiveness summary for drugs to treat neuropathic pain following spinal cord injury (from Teasell 2010)

Drug (references)	Effectiveness
Gabapentin[41, 135, 137]	Effective
Pregabalin[136, 138]	Effective
Lamotrigine[134]	Effective only in subgroup of persons with incomplete spinal cord injury
Valproic acid[133]	Not effective
Amitriptyline[41, 132]	Effective only in depressed persons
Levetiracetam[139]	Not effective

The review concluded that there is Level 1 evidence (based on good-quality randomized controlled trials) of effectiveness of gabapentin and pregabalin in pain after spinal cord injury. Level 1 evidence also showed effectiveness of lamotrigine, but only in persons with incomplete

spinal cord injury. There was Level 1 evidence from 1 small trial that valproic acid was not effective, but there was a trend toward improvement in the treatment group. Amitriptyline was effective only in persons with comorbid depression. Levetiracetam was not effective compared with placebo.

Central pain due to stroke or multiple sclerosis

Direct evidence

We identified 1 fair-quality, head-to-head crossover trial of amitriptyline compared with carbamazepine in 15 patients with central poststroke pain.[39] After 4 weeks, mean pain intensity scores did not differ between treatment groups (4.2 for both). On the global assessment of change in pain, more patients reported improvement with amitriptyline than carbamazepine (67% vs. 36%), but the difference was not statistically significant.

Indirect evidence

Five fair-quality placebo controlled trials were conducted in patients with central pain due to stroke or multiple sclerosis (Table 12).[138, 140-144] One of these is unpublished; its results were provided by the study sponsor.[142] One trial of nortriptyline in patients with various types of central pain was rated poor quality.

Table 12. Placebo-controlled trials in patients with central neuropathic pain

Author, year	Drug Dose Design	Population	N Duration	Main results
Vestergaard 2001[144] (Fair)	Lamotrigine 200 mg Crossover	Central poststroke pain	30 8 weeks	Decrease in pain score from baseline with treatment (*P*=0.01) Global pain assessment 3 (moderate) with lamotrigine vs. strong (4) with placebo (*P*=0.02) Pain affecting daily activities: 3 (some) with lamotrigine vs. 4 (a lot) placebo (*P*=0.11) No difference between groups in use of rescue medication
Breuer 2007[140] (Fair)	Lamotrigine 400 mg Crossover	Multiple sclerosis	12 3 weeks	No differences between groups on any pain or quality of life measures
Pfizer Study # A0081063 2009[142] (Fair)	Pregabalin 150-600 mg Parallel	Central poststroke pain	219 13 weeks	Pain scores in both groups decreased from baseline, no difference between groups (*P*=0.578) Response (30% or more reduction in pain): Pregabalin: 44.4% Placebo: 32.4% *P*=0.87 Response (50% or more reduction in pain): Pregabalin: 24.1% Placebo: 20.4% *P*=0.62
Vranken 2008[138] (Fair)	Pregabalin 600 mg Parallel	Various	40 4 weeks	Decrease in mean pain score with pregabalin (VAS difference from placebo: 2.19; 95% CI, 0.57 to 3.8; *P*=0.01) Improvement with treatment on some measures of quality of life No difference in pain relief in subgroups with pain due to brain injury vs spinal cord injury
Rossi 2009[143] (Fair)	Levetiracetam 500 mg Parallel	Multiple sclerosis	20 12 weeks	Significant decrease in pain score on VAS in treatment group, no difference in placebo group
Panerai 1990[141] (Poor)	Nortriptyline Crossover	Various	39	Results reported graphically only; decrease in pain with treatment vs. placebo on VAS (*P*<0.0001)

Abbreviations: VAS, visual analogue scale.

Two trials of lamotrigine had mixed results, with 1 finding improvement in pain score in patients with central poststroke pain[144] and the other showing no difference from placebo in patients with multiple sclerosis.[140] Pregabalin showed no effect on pain score or response in patients with central poststroke pain in 1 trial.[142] In a second trial of pregabalin in patients with

various kinds of central neuropathic pain, pregabalin was significantly better than placebo for the overall group. There was no difference between the subgroups of patients with pain due to brain injury compared with those with pain due to spinal cord injury.[138] Levetiracetam significantly reduced pain score in patients with multiple sclerosis in 1 trial[141]

Complex regional pain syndrome

We identified 1 placebo controlled crossover trial of gabapentin in 58 patients with Complex Regional Pain Syndrome type I.[145] Patients were treated for 3 weeks with a 2-week washout period in between treatments. All had chronic pain for several years that was refractory to various treatments. The target dose of gabapentin was 1800 mg per day. There was significantly greater pain relief in the first treatment period for gabapentin users. Therapy effect was reduced in the second period and there was no significant effect when the results of both periods were combined. There was no difference between gabapentin and placebo in measures of function or quality of life.

Postmastectomy pain syndrome or phantom limb pain

Five placebo-controlled trials evaluated efficacy of amitriptyline, venlafaxine, levetiracetam, or gabapentin in patients with postmastectomy pain syndrome or phantom limb pain (Table 13).[146-150] Three studies found no significant effect of levetiracetam, venlafaxine, or amitriptyline on pain scores.[148-150] In the 2 trials finding differences, the effect on pain was mild. A crossover study of amitriptyline reported 53% of patients overall had a decrease in pain intensity, but an analysis between groups is not given.[147] The trial of gabapentin found a decrease in pain intensity after 6 weeks of treatment.[146] There was no effect on pain at other time points and no difference between groups in the use of rescue medication, sleep interference, or activities of daily living.

Table 13. Trials in patients with postmastectomy pain syndrome or phantom limb pain

Author, year	Drug Dose Design	Population	N Duration	Main results
Kalso 1996[147] (Fair)	Amitriptyline 100 mg vs. placebo Crossover	Pain after breast cancer treatment	20 (15 analyzed) 4 weeks	8 of 15 patients (53%) had at least a 50% decrease in intensity of arm or scar pain (analysis between groups not reported)
Robinson 2004[148] (Fair)	Amitriptyline vs. placebo Parallel	Amputation-related pain	39 6 weeks	No difference between groups in pain score
Tasmuth 2002[149] (Fair)	Venlafaxine vs. placebo Crossover	Pain after breast cancer treatment	13 4 weeks	No difference between groups in average pain intensity. Pain relief significantly better with venlafaxine (*P*<0.05) 11/15 (73%) had at least 50% pain relief
Vilholm 2008[150] (Fair)	Levetiracetam 3000 mg vs. placebo Crossover	Postmastectomy pain syndrome	27 4 weeks	No difference between groups in pain relief (*P*=0.83) Response (50% pain reduction): 8 patients in each group (*P*=1.00) Use of rescue medication similar between groups
Bone 2002[146] (Fair)	Gabapentin 2400 mg vs. placebo Crossover	Phantom limb pain	19 6 weeks	Pain intensity score decreased with gabapentin at end of therapy No difference between groups in use of rescue medication, sleep interference or activities of daily living

Traumatic nerve injury pain

Two placebo controlled trials evaluated efficacy of gabapentin or pregabalin in patients with neuropathic pain due to traumatic peripheral nerve injury.[151, 152] Both found treatment more effective than placebo in reducing pain scores.

Trigeminal neuralgia

Six placebo-controlled trials evaluated neuropathic pain medications for trigeminal neuralgia.[95, 153-157] Although all 6 trials found carbamazepine (4 trials[95, 153, 154, 156]), lamotrigine (1 trial[157]), or topiramate (1 trial[155]) more effective than placebo, results may not be reliable because 5[95, 153-156]

of the 6 trials were rated poor quality, with 4 of the trials (all of carbamazepine[95, 153, 154, 156]) published in 1966 or 1968.

Patients with polyneuropathy or mixed populations

Seven studies included patients with polyneuropathy, neuropathy of various etiologies, or did not specify the etiology of pain in the population.[48, 97, 98, 158-161] Two of these (1 lamotrigine, 1 lidocaine patch) were rated poor quality[97, 98] and the rest were fair.

In 1 small trial comparing venlafaxine with 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 (relative risk, 0.55; 95% CI, 0.27 to 1.12).[48]

In a 6-week crossover trial of 35 patients, levetiracetam was no more effective than placebo on measures of pain relief (*P*=0.979), total pain intensity (*P*=0.293), or any other outcome measure, including measures of physical function and health-related quality of life.[161] In a trial of 37 patients with polyneuropathy, treatment with valproic acid was no more effective than placebo for reducing total pain score (*P*=0.24).[158] More patients experienced pain relief with valproic acid (42% compared with 17%) but the difference was not statistically significant (*P*=0.13). In a trial including a mixed group of patients with diabetic or nondiabetic polyneuropathy, amitriptyline relieved pain scores more than placebo and was similarly effective in diabetic and nondiabetic patients.[160] Gabapentin was more effective than placebo for reducing average pain score and improving some quality of life measures in 1 trial of patients with different neuropathic pain syndromes.[159]

Chronic lumbar radiculopathy

We identified only 1 placebo-controlled trial in patients with neuropathy associated with lumbar radicular pain.[162] Nortriptyline was not effective in reducing average daily leg pain (the primary outcome) or any other leg or back pain scores.

Key Question 2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?

Summary of Findings

Diabetic neuropathy and postherpetic neuralgia

- Moderate evidence supported a lack of difference in withdrawals due to adverse events between gabapentin, pregabalin, and lamotrigine compared with amitriptyline and nortriptyline (relative risk, 0.61; 95% CI, 0.33 to 1.12)
- Moderate evidence supported the finding of greater withdrawals due to adverse events of oral pregabalin compared with the 5% lidocaine patch (relative risk, 4.39; 95% CI, 2.25 to 8.69)
- Moderate evidence indicated that gabapentin or pregabalin (as a group) were less likely to cause dry mouth than tricyclic antidepressants (relative risk, 0.27; 95% CI, 0.14 to 0.56)

- Low-strength evidence indicated that gabapentin or pregabalin (as a group) were more likely to cause ataxia than tricyclic antidepressants (relative risk, 3.70; 95% CI, 1.18 to 11.65)
- Using only adjusted indirect comparisons:
    - Low-strength evidence supported a lack of difference in withdrawals due to adverse events between duloxetine, pregabalin, lacosamide, and lamotrigine (with a range of relative risks from 0.82 [95% CI, 0.42 to 1.61] for gabapentin compared with lacosamide to 1.78 [95% CI, 0.91 to 3.48] for duloxetine compared with gabapentin)
    - Low-strength evidence indicated that gabapentin and lamotrigine caused fewer withdrawals due to adverse events than topiramate or oxcarbazepine (with a range of relative risks from 0.44 [95% CI, 0.21 to 0.90] for gabapentin compared with oxcarbazepine to 0.60 [95% CI, 0.37, 0.97] for lamotrigine compared with topiramate)

Other types of neuropathic pain

Direct evidence

- Evidence was insufficient to evaluate comparative harms in other types of neuropathic pain
- Among 3 head-to-head trials, 1 reported no withdrawals due to adverse events with either amitriptyline or carbamazepine and the others reported similar proportions of patients withdrawing due to adverse events for amitriptyline or imipramine compared with gabapentin

Detailed Assessment

Painful diabetic neuropathy and postherpetic neuralgia

Withdrawal from study due to an adverse event: direct comparisons

Overall, withdrawal from study due to an adverse event showed wide variability across the studies. Statistically significant differences were found in only 2 comparisons. In a study of 5% lidocaine patch compared with pregabalin, the relative risk of withdrawing due to an adverse event was 4.39 (95% CI, 2.25 to 8.69) times greater in the pregabalin group than the lidocaine group.[52] In a smaller study (N=106), lamotrigine had a lower discontinuation rate than amitriptyline (relative risk, 0.42; 95% CI, 0.20 to 0.85).[38] See Table 14 for a summary of withdrawals due to adverse events in head-to-head trials.

Table 14. Adverse event withdrawals in head-to-head trials for painful diabetic neuropathy/postherpetic neuralgia

Study	Drug	Adverse event withdrawals	Drug	Adverse event withdrawals	Relative risk (95% confidence interval)
Gilron, 2009	Gabapentin	7/54	Nortriptyline	2/52	3.37 (0.84 to 13.89)
Dallocchio, 2000	Gabapentin	NR	Amitriptyline	NR	
Morello, 1999	Gabapentin	1/25	Amitriptyline	2/25	0.50 (0.07 to 3.61)
Chandra, 2006	Gabapentin	NR	Nortriptyline	NR	
Pooled					**1.61 (0.26 to 9.95)**
Pfizer 1008-040, 2007	Pregabalin	11/87	Amitriptyline	16/88	0.70 (0.35 to 1.39)
Bansal, 2009	Pregabalin	6/51	Amitriptyline	17/51	0.35 (0.15 to 0.79)
Pooled					**0.52 (0.27 to 1.00)**
Jose, 2007	Lamotrigine	8/53	Amitriptyline	19/53	0.42 (0.20 to 0.85)
Tricyclics pooled					**0.61 (0.33 to 1.12)**
Jia, 2006	Venlafaxine	4/66	Carbamazepine	2/66	2.00 (0.44 to 9.14)
Baron, 2009	Pregabalin	39/153	Lidocaine	9/155	4.39 (2.25 to 8.69)

Adjusted indirect comparison

Withdrawals due to adverse events were higher in the treatment arm, regardless of the drug, than in the placebo arm. See Table 15 for a summary of indirect comparisons of withdrawals due to adverse events. There were no significant differences in the withdrawal rate due to adverse events among duloxetine, pregabalin, gabapentin, and lacosamide trials. There were fewer withdrawals due to adverse events among patients receiving gabapentin or lamotrigine when compared to topiramate or oxcarbazepine.

Table 15. Indirect comparisons of withdrawals due to adverse events

Drug	Placebo rate	Relative risk (95% confidence interval)
Compared with placebo		
Duloxetine	0.04	3.03 (1.82 to 5.03)
Pregabalin	0.06	2.42 (1.89 to 3.08)
Gabapentin	0.08	1.70 (1.10 to 2.62)
Lacosamide	0.08	2.07 (1.24 to 3.47)
Lamotrigine	0.11	1.75 (1.21 to 2.53)
Oxcarbazepine	0.08	3.90 (2.18 to 6.97)
Topiramate	0.08	2.91 (2.13 to 3.97)
Indirect comparison		
Duloxetine vs. pregabalin		1.25 (0.71 to 2.20)
Duloxetine vs. gabapentin		1.78 (0.91 to 3.48)
Duloxetine vs. lacosamide		1.46 (0.71 to 3.02)
Duloxetine vs. lamotrigine		1.73 (0.92 to 3.24)
Pregabalin vs. gabapentin		1.42 (0.87 to 2.34)
Pregabalin vs. lacosamide		1.17 (0.66 to 2.07)
Pregabalin vs. lamotrigine		1.38 (0.89 to 2.14)
Gabapentin vs. lacosamide		0.82 (0.42 to 1.61)
Gabapentin vs. lamotrigine		0.97 (0.55 to 1.71)
Lacosamide vs. lamotrigine		1.18 (0.63 to 2.23)
Duloxetine vs. topiramate		1.04 (0.57 to 1.89)
Pregabalin vs. topiramate		0.83 (0.56 to 1.23)
Gabapentin vs. topiramate		0.58 (0.34 to 0.99)
Lacosamide vs. topiramate		0.71 (0.39 to 1.30)
Lamotrigine vs. topiramate		0.60 (0.37 to 0.97)
Duloxetine vs. oxcarbazepine		0.77 (0.36 to 1.68)
Pregabalin vs. oxcarbazepine		0.62 (0.33 to 1.16)
Gabapentin vs. oxcarbazepine		0.44 (0.21 to 0.90)
Lacosamide vs. oxcarbazepine		0.53 (0.24 to 1.16)
Lamotrigine vs. oxcarbazepine		0.45 (0.23 to 0.89)
Topiramate vs. oxcarbazepine		0.75 (0.39 to 1.44)

Most common adverse events

Gabapentin and pregabalin combined were significantly less likely to cause dry mouth than amitriptyline/nortriptyline (relative risk, 0.27; 95% CI, 0.14 to 0.56).[37, 40, 43-45] However, gabapentin and pregabalin combined were significantly more likely to cause ataxia than the tricyclic antidepressants (relative risk, 3.70; 95% CI, 1.18 to 11.65).[40, 43, 44]

There were no deaths or suicide attempts reported in any of the 7 head-to-head studies which included a tricyclic antidepressant arm. Blurred vision was reported in 2 studies of gabapentin (relative risk, 1.56; 95% CI, 0.12 to 20.97).[43, 44] There was also 1 instance of

pneumonia and 1 instance of cholecystitis in the pregabalin arm of 1 study[40] and 4 instances of an elevated creatinine by 25% in the lamotrigine arm of 1 study.[38]

In the comparison of venlafaxine and carbamazepine, there were a total of 46 adverse events during the trial, 29 adverse events in the venlafaxine group (43.9%) and 17 (25.8%) in the carbamazepine group.[47] This difference in total numbers in each group was not significant (P=0.06). In the venlafaxine group the most frequent adverse events were gastrointestinal discomfort (18%), dizziness (14%), and somnolence (12%). In the carbamazepine group, the most frequent adverse events were dizziness (11%) and somnolence (14%). There was also 1 patient in the venlafaxine group who withdrew due to palpitations and 1 patient in the carbamazepine group whose alanine aminotransferase increased from 15 to 121 IU.

Five percent lidocaine medicated patch resulted in significantly fewer adverse events in the lidocaine group (48/155 patients) compared with oral pregabalin (194/153 patients; P<0.0001).[52] The most common adverse events occurred in the pregabalin arm: dizziness (12%), fatigue (9%), and vertigo (8%). Five percent of the pregabalin group developed headache compared to 1% in the lidocaine group. One percent of the lidocaine group developed application site reaction.

Adverse events in placebo-controlled trials

The most common adverse events in duloxetine trials were nausea, dizziness, somnolence, constipation, and increased sweating.[81, 83] The relative risk for the most common adverse event, nausea, was 1.45 (95% CI, 0.87 to 2.42) at the dose of 20 mg daily;[81] 2.70 (95% CI, 1.10 to 6.64) at 60 mg daily;[81, 83] 3.62 (95% CI, 2.12 to 6.16) at 120 mg daily;[81, 83] and 2.97 (95% CI, 1.31 to 6.77) regardless of dose.[81, 83] Vomiting was reported by 3.4% of duloxetine patients treated with 60 mg twice daily.[82] Long-term trials indicated that duloxetine may slightly increase fasting glucose[163] or hemoglobin A1C,[164] although 1 long-term trial[165] showed no effect.

The most common adverse events in the trials of lacosamide, lamotrigine, oxcarbazepine, topiramate, and divalproex were dizziness, nausea, headache, and somnolence.[85-92, 108, 166-169] The most common adverse event was dizziness and was reported by 402/3624 (11.1%) study participants (relative risk, 2.46; 95% CI, 1.52 to 3.98).[85-91, 100, 166-169]

Additionally, 3 drugs were studied in long-term, open label trials or extension studies—duloxetine, lacosamide, and the lidocaine patch. The long-term effects of 60 mg duloxetine twice daily compared to usual care were explored in 3 publications of 2 trials.[163-165] There was no difference in withdrawals due to adverse events between groups in either study (relative risk, 1.49, 95% CI 0.82, 2.71). Two studies examined the long-term effects of lacosamide titrated to a maximum dose of 400 mg daily[170] or with a modal dose of 400 mg daily.[171] All patients were treated with lacosamide without a placebo or usual care group. In the larger study 18.3% of patients withdrew due to treatment emergent adverse events,[171] whereas 23.2% withdrew due to total adverse events in the smaller study.[170] The most common adverse events were nausea (13.2%), dizziness (20.2%),[171] and headache (16%).[170] A 12-month study of the lidocaine patch in postherpetic neuralgia patients found that 12.4% experienced a drug-related adverse event, the most common of which was pruritus at the administration site (2.8%).[172] None of the long-term studies noted significant safety concerns with extended use.

Other types of neuropathic pain

There was very little direct evidence available to evaluate comparative harms in patients with other types of neuropathic pain. Among 3 head-to-head trials, 1 reported no withdrawals due to

adverse events with either amitriptyline or carbamazepine[39] and the others reported similar proportions of patients withdrawing due to adverse events for amitriptyline or imipramine compared to gabapentin.[41, 46] Dizziness was more frequent with gabapentin, whereas dry mouth and constipation were more frequently reported with amitriptyline (Table 16).

Table 16. Withdrawals due to adverse events in head-to-head trials of drugs for other types of neuropathic pain

Comparison (reference)	Population	Withdrawals due to adverse events	Specific adverse events
Amitriptyline vs. carbamazepine[39]	Poststroke	None	Most frequent Amitriptyline: tiredness and dry mouth Carbamazepine: vertigo, tiredness, gait disturbances
Amitriptyline vs. gabapentin[41]	Spinal cord injury	4/38 amitriptyline (11%) 5/38 gabapentin (13%) *P*=0.72	More frequent with amitriptyline: dry mouth, constipation, difficulty emptying bowels, nausea, difficulty emptying the bladder
Imipramine vs. gabapentin[46]	Cancer-related pain	0/12 imipramine 20 mg 3/12 gabapentin 800 mg *P*=0.10	More dizziness with gabapentin 800 mg than imipramine 20 mg: 4 mild, 3 severe with gabapentin 800 mg vs. 1 mild with imipramine (*P*=0.014)

Key Question 3. Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

Summary of Evidence

- There was no evidence assessing differences in effectiveness or harms based on demographics, socioeconomic status, comorbidities, or cointerventions
- Post hoc analyses have not found older age to have an impact on response or treatment emergent adverse events with duloxetine, but older patients withdrew from studies more often than younger patients due to adverse events, regardless of assigned treatment (duloxetine or placebo)
- Only insufficient to low-strength evidence suggests that combinations of duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine had a potential benefit compared to monotherapy, but that there was a risk of increased adverse events – although if lower doses of the combined drugs are used, benefits may be seen in both efficacy and harms.

Detailed Assessment

The strength of evidence to answer Key Question 3 was insufficient. We identified no studies addressing differences in effectiveness or harms based on demographics, socioeconomic status, or comorbidities.

Age

In a post hoc analysis of three 12-week placebo-controlled trials of duloxetine (N=701 < 65 years and N=323 ≥ 65 years), the incidence of treatment emergent adverse events, serious adverse events, and specific adverse events did not differ between patients < 65 years and those ≥ 65 years, regardless of assigned treatment group (placebo or duloxetine 60 mg or 120 mg).[173] In all 3 treatment groups, more patients ≥ 65 years withdrew from the studies due to adverse events compared with the younger groups (P<0.001). The rate of withdrawal was highest in the 120 mg daily group (24%). Rates of response, based on 24-hour pain assessments, were similar between age groups.

Cointerventions

We could not address the impact of cointerventions with other drugs on effectiveness or harms of the drugs included in this review because no study analyzed results based on *specific* cointerventions taken by participants during the study period.

Combination therapy

While 5 studies[44, 46, 49, 50, 65] examined combination therapy of drugs included in this review compared with monotherapy, we found the evidence to be insufficient to low strength to answer the question because of the dearth of evidence for a given combination, the small sizes, and only fair- or poor-quality studies. The drug combinations studied were duloxetine and pregabalin; lidocaine patch and pregabalin; and gabapentin with imipramine, nortriptyline, or venlafaxine.

A fair-quality randomized, double-dummy crossover trial (N = 56) found that combination therapy with gabapentin and nortriptyline was superior to monotherapy with either drug in pain control.[44] The daily pain intensity was 2.3 (out of 10) on combination therapy compared with 3.2 on gabapentin (P=0.01) and 4.1 with nortriptyline (P=0.02). The mean percentage pain reduction was also greater (52.8% compared with 38.8% and 31.1%, respectively). The total drug exposure period for each assigned treatment was 35 days, but only 5 days were at the maximum tolerated doses. A greater percentage withdrew during a gabapentin monotherapy phase (14%) than either of the other drug assignments (nortriptyline 3.6%, combination 1.8%). Dry mouth was the most common adverse event, significantly more common in the combination and nortriptyline monotherapy groups compared to the gabapentin group (P<0/0001).

In an attempt to determine if lower doses of gabapentin taken with imipramine would result in better pain control and fewer adverse events, a fair-quality pilot study randomized 52 patients with neuropathic pain due to cancer and who were having inadequate response to opioids to low-dose gabapentin (800 mg daily) plus imipramine (20 mg daily), gabapentin 800 mg daily, gabapentin 400 mg daily, or imipramine 20 mg daily for 7 days.[46]

Although only 7 days long, the results indicated that the combination was superior to the other treatments. In total pain score, the combination therapy resulted in a lower final score (2)

than the other groups (4.5 to 5); the difference was statistically significant for the comparison with 400 mg gabapentin and imipramine ($P<0.05$ for both), but not compared to 800 mg daily of gabapentin. Nausea and drowsiness were seen in all groups, with drowsiness being the most common adverse event across all groups. The 800 mg daily gabapentin group had statistically significantly higher rates of mild and severe dizziness compared with the other groups ($P=0.014$ and 0.015, respectively).

Following completion of a fair-quality randomized trial of gabapentin or placebo, 11 patients on gabapentin who had not achieved adequate response after 8 weeks were then randomized to treatment with gabapentin (at their maximum tolerated dose) plus venlafaxine (titrated to 150 mg per day) or continuing gabapentin with placebo added.[65] In addition to being very small, the study selection criteria were biased against gabapentin monotherapy, which they have already shown not to respond to. After 5 weeks of the maximum tolerated doses, patients who had failed gabapentin monotherapy had more improvement in pain scores with combination therapy (–2 out of 11 points) than those continuing monotherapy (–0.5). Similarly, 75% of patients in the combination group reported much or moderately improved symptoms compared with only 33.3% in the monotherapy group. One of 6 patients in the combination group stopped the study due to adverse events while none in the monotherapy group did.

In a small nonrandomized study (N = 250), patients who had reached the end of a 4-week randomized trial of pregabalin and lidocaine 5% patch continued their originally assigned drug (pregabalin or lidocaine 5%) if they were having clinical response (numerical rating scale over past 3 days of ≤ 4 on a 0 to 10 scale) for 8 more weeks. If their pain was > 4 on the rating scale they were given a combination of the currently assigned drug and the other drug.[49] The number of patients who withdrew from the study due to drug-related adverse events was greater in the combination group (5.5%) than in either monotherapy group (lidocaine 1.3%, pregabalin 1.6%). Similarly, the number of patients reporting drug-related adverse events was also greater in the combination drug group (18% compared with 5.1% and 7.9%, respectively).

A poor-quality, 12-week, open-label trial of pregabalin compared with duloxetine, reported only in a poster from a conference presentation to date, found duloxetine noninferior to the combination.[50] The study was rated poor quality in part because the limited study report does not provide details on randomization and allocation concealment or on the number of patients included in each of the multiple analyses reported. The unusually high percentage of patients who withdrew from this short-term study (31%) and the open-label nature of this study (given the subjective, patient-assessed outcomes) increase the risk for bias.

Demographics, socio-economic status, or comorbidities

No evidence was found.

SUMMARY

Strength of Evidence

The results of this review are summarized in Table 17, below, and Appendix E summarizes the strength of the evidence for each key question. The strongest evidence in neuropathic pain trials was in patients with painful diabetic neuropathy. Even within this group, there was no high-strength, comparative evidence available for this review. Evidence of the direct comparison

between gabapentin and pregabalin compared with tricyclic antidepressants in patients with either painful diabetic neuropathy or postherpetic neuralgia was moderate. Evidence of indirect comparisons of duloxetine, pregabalin, and gabapentin compared with both lacosamide and lamotrigine in the same population was also moderate. In comparisons involving drugs limited to a single study (lamotrigine, lidocaine, venlafaxine, carbamazepine, and duloxetine), the strength of evidence was generally low to insufficient. There was no direct evidence concerning the effectiveness of 4 drugs (divalproex, oxcarbazepine, lacosamide, and topiramate) in the diabetic or postherpetic neuralgia population.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups: those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results are limited by the scope of the key questions and inclusion criteria and by the generalizability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had fewer comorbidities, and used fewer concomitant medications than many neuropathic pain patients not participating in trials. Minorities, young adults, and the least healthy were under represented as were patients whose pain was less severe or unrelated to diabetes.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. Few direct head-to-head comparisons of many of the included drugs have been conducted, which limited our conclusions to indirect comparison of placebo-controlled trials for many of the outcomes. This also limited the strength of the evidence due to heterogeneity of trial populations, interventions, and outcomes assessment. One potential limitation to the applicability of this review is it relates to a narrower range of drugs than are available in clinical practice.

Applicability

Based on the scope of this review the evidence presented and synthesized here is applicable to a somewhat limited group of patients. Patients in direct comparison trials included in this review were most often from Europe or Asia, female (53%), 60 years old, and had diabetes or postherpetic neuralgia for 7 years (mean range 4-13 years). Only 1 trial was based in the United States; this trial consisted of 26 United States military veterans who included 25 males and 23 Caucasians. Therefore, it is difficult to know whether the results presented here apply equally well to African Americans, Hispanics, or to Caucasians in the United States. The selection of drugs included in this review was influenced by the specific programmatic interests of the organizations participating in the Drug Effectiveness Review Project and were not meant to be read as a usage guideline. Of the drugs studied, trials differed with respect to dosing regimens limiting any conclusions about optimal dose. While evidence on how the drugs compared directly was the goal, the evidence with direct comparison is limited; much of the evidence consisted of placebo-controlled trials. Given that neuropathic pain is a chronic condition, the applicability of results from short-term trials such as those included in this report may be limited. Outcomes studied were primarily measures of pain, with multiple methods used to assess pain response. Neuropathic pain may impact a patient's life in other ways as well, such as causing

fatigue, depression, lack of ability to have full employment, or reduced quality of life. These outcomes were not well studied, and the evidence does not provide insight here.

Studies Pending Review

The following unpublished studies were identified just after completion of this report (summaries of these studies can be found at http://clinicaltrials.gov and/or http://www.clinicalstudyresults.org) and will be considered for inclusion in the next update: NCT01117766, NCT00570310, NCT00424372, NCT01138124, NCT00552175, NCT00385671, NCT00408993, NCT00654940, NCT00232141, NCT00159705, GSK-PXN110448.

Table 17. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
Key Question 1. What is the comparative effectiveness of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?		
Diabetic neuropathy and postherpetic neuralgia	Gabapentin, pregabalin, lamotrigine vs. tricyclic antidepressants: Moderate	No difference in rate of response defined as ≥50% reduction in baseline pain
	5% lidocaine patch vs. oral pregabalin: Low	No difference in ≥50% reduction in baseline pain
	Duloxetine, pregabalin, gabapentin vs. lacosamide, lamotrigine: Low-moderate	Duloxetine, pregabalin, gabapentin superior to lacosamide, lamotrigine in providing pain relief in adjusted, indirect comparisons
	Pregabalin vs. topiramate: Low	Pregabalin superior to topiramate in pain relief
Other neuropathic pain	Low	Cancer-related neuropathic pain: no difference in pain relief with low-dose gabapentin (400 mg or 800 mg) plus opioids compared with low-dose imipramine (10 mg) plus opioids Combination with gabapentin + imipramine + opioids was more effective than therapy with either gabapentin + opioids or imipramine + opioids
	Low	Spinal cord injury: amitriptyline was more effective for pain relief than gabapentin The difference was significant only in the subgroup of patients with the highest levels of depression
	Low	Central poststroke pain: no difference between amitriptyline and carbamazepine
	Insufficient	No direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve injury pain

Key question	Strength of evidence	Conclusion
Key Question 2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch for neuropathic pain?		
Diabetic neuropathy and postherpetic neuralgia	Gabapentin, pregabalin, lamotrigine vs. tricyclic antidepressants: Moderate	No difference in withdrawals due to adverse events
	Pregabalin vs. 5% lidocaine patch: Moderate	Significantly more withdrawals in the oral pregabalin group than the lidocaine patch group
	Gabapentin/pregabalin vs. tricyclic antidepressants: Moderate	Gabapentin/pregabalin cause less dry mouth than the tricyclic antidepressants
	Gabapentin/pregabalin vs. tricyclic antidepressants: Low	Gabapentin/pregabalin combined cause more ataxia than the tricyclic antidepressants
	Duloxetine vs. pregabalin vs. lacosamide vs. lamotrigine: Low	No difference in withdrawals due to adverse events using adjusted indirect comparisons
	Gabapentin, lamotrigine vs. topiramate, oxcarbazepine: Low	Fewer withdrawals due to adverse events in gabapentin and lamotrigine when compared to either topiramate or oxcarbazepine
Other types of neuropathic pain	Insufficient	Among 3 head-to-head trials, 1 reported no withdrawals due to adverse events with either amitriptyline or carbamazepine, and the others reported similar proportions of patients withdrawing due to adverse events for amitriptyline or imipramine compared to gabapentin
Key Question 3. Are there differences in effectiveness or harms of anticonvulsants, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?		
	Low	*Age:* Post hoc analyses have not found older age to have an impact on response or treatment emergent adverse events with duloxetine *Combination therapy*: Combinations of duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine have a potential benefit compared to monotherapy, but increased adverse events occurred *Demographics, socioeconomic status, comorbidities or cointerventions*: no evidence

CONCLUSIONS

Overall, the strength of evidence evaluating the comparative benefits or harms of these drugs to treat neuropathic pain was low to moderate. Based on a small number of short-term trials directly comparing the drugs in patients with painful diabetic neuropathy and postherpetic neuralgia, the evidence did not support a statistically significant difference in response (50% reduction in pain) or withdrawal due to adverse events with gabapentin, pregabalin, and lamotrigine compared with tricyclic antidepressants. Oral pregabalin was similar to lidocaine 5% medicated patch in rate of response, but resulted in more patients withdrawing due to an adverse event. Adjusted indirect comparisons of placebo-controlled trials suggested that duloxetine, pregabalin, and gabapentin were superior to lacosamide and lamotrigine, but no difference in withdrawal from study due to adverse events was found. In these analyses, differences were not found between pregabalin, duloxetine, and gabapentin or comparisons of 5% lidocaine patch and amitriptyline or gabapentin. Tricyclic antidepressants caused more dry mouth than pregabalin or gabapentin while gabapentin and pregabalin resulted in higher rates of ataxia.

In patients with cancer-related neuropathic pain who were taking opioids, there was no difference in pain relief with low-dose gabapentin compared with low-dose imipramine. Monotherapy with either drug was insufficient for pain relief. In patients with spinal cord injury, gabapentin was more effective for pain relief than amitriptyline. The difference was significant only in the subgroup of patients with the highest levels of depression. In patients with central poststroke pain, there was no difference between amitriptyline and carbamazepine. There was no direct evidence in patients with HIV-associated neuropathic pain, multiple sclerosis, complex regional pain syndrome, postmastectomy pain syndrome, phantom limb pain, or traumatic nerve injury pain. Evidence for comparative effectiveness in patients with types of neuropathic pain other than diabetic or postherpetic was insufficient to assess comparative safety.

Post hoc analyses have not found older age to have an impact on response or treatment-emergent adverse events with duloxetine. Combination therapy with duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine may have had a potential benefit compared with monotherapy, but there was an increased risk of adverse events.

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Appendix A. Boxed warnings of included drugs[1-16]

Drugs	Boxed warnings
Black box warning for Depakote® is listed in the right column. Similar warnings have been used for Depakote ER, Depakene®, Depacon® and Stavzor®.	**Hepatotoxicity** Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Experience has indicated that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation and those with organic brain disease. When Depakote is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of the therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fetal hepatotoxicity decreases considerably in progressively older patient groups. These incidents usually have occurred during the first 6 months of treatment. Serious or fatal hepatotoxicity may be preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia and vomiting. In patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for appearance of these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter, especially during the first 6 months. **Teratogenicity** Valproate can produce teratogenic effects such as neural tube defects (e.g., Spina Bifida). Accordingly, the use of Depakote tablets in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinarily associated with permanent injury or risk of death (e.g. migraine) is contemplated. See Warnings, information for patients. Patient information leaflet describing the teratogenic potential of valproate is available for patients. **Pancreatitis** Cases of life threatening pancreatitis have been reported in both children and adults receiving valproate. Some of the cases have been described as hemorrhagic with rapid progression from initial use as well as after several years of use. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation. If pancreatitis is diagnosed, pancreatitis should ordinarily be discontinued.

Drugs	Boxed warnings
	Alternative treatment for the underlying medical condition should be initiated as clinically indicated. (See Warnings and Precautions.)
	Serious dermatological reactions and HLA-B* 1502 Allele Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (Ten) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/Ten and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit carefully outweighs the risk. (See Warnings and Precautions, Laboratory Tests).
Black box warning for Tegretol® is listed in the right column. Similar black box warnings have been issued for Tegretol XR®, Carbatrol® and Equetro®.	**Aplastic Anemia and agranulocytosis** Aplastic anemia and agranulocytosis have been reported in association with the use of Tegretol. Data from a population-based case control study demonstrate that the risk of developing these reactions is 5-8 times greater than the general population. However, the overall risk of these reactions in the untreated general population is low, approximately 6 patients per 1 million population per year for agranulocytosis and two patients per 1 million population per year for aplastic anemia. Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of Tegretol, data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis. Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on Tegretol are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or

Drugs	Boxed warnings
	decreased white blood cell counts, the patient should be monitored closely. Discontinuation of the drug should be considered I any evidence of significant bone marrow depression develops.
Black box warning for Lamictal® is listed in the right column. Similar black box warnings have been issued for Lamictal ODT®, Lamictal XR®, and Lamictal CD®.	**Warning: Serious Skin Rashes** LAMICTAL® can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in adult patients receiving LAMICTAL as initial monotherapy and 0.13% (1.3 per 1,000) in adult patients receiving LAMICTAL as adjunctive therapy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking adjunctive LAMICTAL, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate. Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have occurred in the absence of these factors. Nearly all cases of life-threatening rashes caused by LAMICTAL have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash. Although benign rashes are also caused by LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, LAMICTAL should ordinarily be discontinued at the first sign of rash,

Drugs	Boxed warnings
	unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring [see Warnings and Precautions (5.1)].
Black box warning for Norpramin is listed in the right column. Similar boxed warnings have been issued for Pamelor®, Cymbalta®, Effexor®, Effexor XR®, Pristiq®, Savella®	Suicidality and Antidepressant Drugs Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of NORPRAMIN or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. NORPRAMIN is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

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Appendix B. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intent to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intent to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intent-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix C. Search strategies

Searches were repeated in December 2010 to identify additional citations.
Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to July Week 4 2010>
Search Strategy:
---
1 (neuropath$ adj5 (pain$ or ache$ or discomfort$ or agony or agoniz$)).mp. (8243)
2 neuropath$.mp. (76687)
3 1 or 2 (76687)
4 Gabapentin.mp. (3178)
5 Neurontin.mp. (111)
6 Pregabalin.mp. (766)
7 Lyrica.mp. (36)
8 Carbamazepine.mp. (11878)
9 (Tegretol or Carbatrol or Epitol).mp. (353)
10 Topiramate.mp. (2335)
11 Topamax.mp. (64)
12 Oxcarbazepine.mp. (1051)
13 Trileptal.mp. (34)
14 Lamotrigine.mp. (3043)
15 Lamictal.mp. (54)
16 Valproic acid.mp. (9781)
17 (Depakote or Depacon or Divalproex or Epival or Deproic).mp. (636)
18 Anticonvulsant$.mp. (41721)
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (25561)
20 3 and 19 (1127)
21 3 and 18 (969)
22 20 or 21 (1672)
23 (antidepressive Agent$ adj2 Tricyclic$).mp. (8881)
24 Amitriptyline.mp. (7255)
25 Elavil.mp. (29)
26 Desipramine.mp. (7152)
27 Norpramin.mp. (13)
28 Pamelor.mp. (0)
29 Aventyl.mp. (5)
30 exp Imipramine/ (9036)
31 tofranil.mp. (357)
32 exp Doxepin/ (723)
33 Sinequan.mp. (30)
34 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (21175)
35 3 and 34 (329)
36 3 and 23 (231)
37 35 or 36 (480)
38 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. (13468)
39 Duloxetine.mp. (890)
40 Cymbalta.mp. (23)

41 Venlafaxine.mp. (2206)
42 Effexor.mp. (33)
43 39 or 40 or 41 or 42 (2941)
44 3 and 43 (175)
45 3 and 38 (126)
46 44 or 45 (246)
47 (Lidocaine adj5 (transderm$ or skin or cutaneous$)).mp. (240)
48 Lidoderm.mp. (14)
49 47 or 48 (252)
50 22 or 37 or 46 or 49 (2317)
51 (20061$ or 2007$ or 2008$ or 2009$ or 2010$).ed. (2946608)
52 50 and 51 (891)
53 limit 52 to (english language and humans) (607)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2010>
Search Strategy:
---
1 (pain$ or ache$ or discomfort$ or agony or agoniz$ or hyperalges$).mp. (49132)
2 neuropath$.mp. (2938)
3 1 or 2 (51221)
4 Gabapentin.mp. (450)
5 Neurontin.mp. (40)
6 Pregabalin.mp. (141)
7 Lyrica.mp. (2)
8 Carbamazepine.mp. (1210)
9 (Tegretol or Carbatrol or Epitol).mp. (81)
10 Topiramate.mp. (396)
11 Topamax.mp. (1)
12 Oxcarbazepine.mp. (169)
13 Trileptal.mp. (15)
14 Lamotrigine.mp. (498)
15 Lamictal.mp. (50)
16 Valproic acid.mp. (702)
17 (Depakote or Depacon or divalproex or Epival or Deproic).mp. (261)
18 Anticonvulsant$.mp. (1770)
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (3140)
20 3 and 18 (123)
21 3 and 19 (362)
22 20 or 21 (404)
23 (Antidepressive Agent$ adj2 Tricyclic$).mp. (849)
24 Amitriptyline.mp. (1855)
25 Elavil.mp. (7)
26 Desipramine.mp. (619)
27 Norpramin.mp. (1)
28 Nortriptyline.mp. (552)
29 Pamelor.mp. (0)

30 exp Imipramine/ (986)
31 Tofranil.mp. (48)
32 exp Doxepin/ (139)
33 Sinequan.mp. (11)
34 Silenor.mp. (0)
35 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (3813)
36 3 and 35 (305)
37 3 and 23 (77)
38 36 or 37 (321)
39 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. (1976)
40 Duloxetine.mp. (242)
41 Cymbalta.mp. (1)
42 Venlafaxine.mp. (761)
43 Effexor.mp. (11)
44 40 or 41 or 42 or 43 (989)
45 3 and 44 (99)
46 3 and 39 (105)
47 45 or 46 (178)
48 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. (218)
49 Lidoderm.mp. (2)
50 48 or 49 (218)
51 3 and 50 (173)
52 22 or 38 or 47 or 51 (1018)
53 desvenlafaxine.mp. (24)
54 Pristiq.mp. (0)
55 53 or 54 (24)
56 52 or 55 (1042)
57 limit 56 to yr="2006 -Current" (344)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2010>
Search Strategy:
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1 (pain$ or ache$ or discomfort$ or agony or agoniz$ or hyperalges$).mp. (2733)
2 neuropath$.mp. (421)
3 1 or 2 (2896)
4 Gabapentin.mp. (74)
5 Neurontin.mp. (3)
6 Pregabalin.mp. (30)
7 Lyrica.mp. (2)
8 Carbamazepine.mp. (110)
9 (Tegretol or Carbatrol or Epitol).mp. (5)
10 Topiramate.mp. (44)
11 Topamax.mp. (5)
12 Oxcarbazepine.mp. (30)
13 Trileptal.mp. (7)
14 Lamotrigine.mp. (51)
15 Lamictal.mp. (4)

16 Valproic acid.mp. (38)
17 (Depakote or Depacon or divalproex or Epival or Deproic).mp. (21)
18 Anticonvulsant$.mp. (216)
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (178)
20 3 and 18 (99)
21 3 and 19 (92)
22 20 or 21 (146)
23 (Antidepressive Agent$ adj2 Tricyclic$).mp. (20)
24 Amitriptyline.mp. (98)
25 Elavil.mp. (1)
26 Desipramine.mp. (61)
27 Norpramin.mp. (1)
28 Nortriptyline.mp. (63)
29 Pamelor.mp. (1)
30 [exp Imipramine/] (0)
31 Tofranil.mp. (2)
32 [exp Doxepin/] (0)
33 Sinequan.mp. (3)
34 Silenor.mp. (0)
35 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (125)
36 3 and 35 (61)
37 3 and 23 (10)
38 36 or 37 (63)
39 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. (35)
40 Duloxetine.mp. (42)
41 Cymbalta.mp. (1)
42 Venlafaxine.mp. (58)
43 Effexor.mp. (0)
44 40 or 41 or 42 or 43 (67)
45 3 and 44 (22)
46 3 and 39 (17)
47 45 or 46 (32)
48 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. (6)
49 Lidoderm.mp. (1)
50 48 or 49 (6)
51 3 and 50 (6)
52 22 or 38 or 47 or 51 (185)
53 desvenlafaxine.mp. (2)
54 Pristiq.mp. (0)
55 imipramine.mp. (82)
56 doxepin.mp. (54)
57 53 or 54 or 55 or 56 (94)
58 3 and 57 (36)
59 52 or 58 (191)
60 limit 59 to full systematic reviews (134)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2010>

Search Strategy:

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1 (pain$ or ache$ or discomfort$ or agony or agoniz$ or hyperalges$).mp. (1680)
2 neuropath$.mp. (106)
3 1 or 2 (1731)
4 Gabapentin.mp. (27)
5 Neurontin.mp. (1)
6 Pregabalin.mp. (8)
7 Lyrica.mp. (0)
8 Carbamazepine.mp. (57)
9 (Tegretol or Carbatrol or Epitol).mp. (0)
10 Topiramate.mp. (16)
11 Topamax.mp. (0)
12 Oxcarbazepine.mp. (9)
13 Trileptal.mp. (0)
14 Lamotrigine.mp. (19)
15 Lamictal.mp. (0)
16 Valproic acid.mp. (27)
17 (Depakote or Depacon or divalproex or Epival or Deproic).mp. (9)
18 Anticonvulsant$.mp. (91)
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (105)
20 3 and 18 (9)
21 3 and 19 (28)
22 20 or 21 (30)
23 (Antidepressive Agent$ adj2 Tricyclic$).mp. (57)
24 Amitriptyline.mp. (100)
25 Elavil.mp. (0)
26 Desipramine.mp. (65)
27 Norpramin.mp. (0)
28 Nortriptyline.mp. (50)
29 Pamelor.mp. (0)
30 [exp Imipramine/] (0)
31 Tofranil.mp. (0)
32 [exp Doxepin/] (0)
33 Sinequan.mp. (0)
34 Silenor.mp. (0)
35 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (133)
36 3 and 35 (34)
37 3 and 23 (6)
38 36 or 37 (34)
39 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. (104)
40 Duloxetine.mp. (14)
41 Cymbalta.mp. (0)
42 Venlafaxine.mp. (47)
43 Effexor.mp. (2)
44 40 or 41 or 42 or 43 (53)

45 3 and 44 (8)
46 3 and 39 (6)
47 45 or 46 (13)
48 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. (3)
49 Lidoderm.mp. (0)
50 48 or 49 (3)
51 3 and 50 (3)
52 22 or 38 or 47 or 51 (63)
53 desvenlafaxine.mp. (0)
54 Pristiq.mp. (0)
55 imipramine.mp. (105)
56 doxepin.mp. (26)
57 53 or 54 or 55 or 56 (113)
58 3 and 57 (14)
59 52 or 58 (66)

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to July Week 4 2010>
Search Strategy:
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1 Complex regional pain syndrome.mp. or Complex Regional Pain Syndromes/ (1145)
2 Reflex sympathetic Dystrophy.mp. (3253)
3 1 or 2 (3965)
4 Gabapentin.mp. (3178)
5 Neurontin.mp. (111)
6 Pregabalin.mp. (766)
7 Lyrica.mp. (36)
8 exp carbamazepine/ (8484)
9 (Tegretol or Carbatrol or Epitol).mp. (353)
10 Topiramate.mp. (2335)
11 Topamax.mp. (64)
12 Oxcarbazepine.mp. (1051)
13 Lamotrigine.mp. (3043)
14 Lamictal.mp. (54)
15 exp valproic acid/ (8507)
16 (Depakote or Depacon or Divalproex or Epival or Deproic).mp. (636)
17 Trileptal.mp. (34)
18 exp Anticonvulsants/ (107441)
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 (22524)
20 3 and 19 (59)
21 3 and 18 (63)
22 20 or 21 (104)
23 exp Antidepressive Agents, Tricyclic/ (27370)
24 exp Amitriptyline/ (5627)
25 (Elavil or Vanatrip).mp. (29)
26 exp Desipramine/ (5260)
27 Norpramin.mp. (13)

28 exp Nortriptyline/ (1879)
29 (Pamelor or Aventyl).mp. (5)
30 exp Imipramine/ (9036)
31 tofranil.mp. (357)
32 exp Doxepin/ (723)
33 (Sinequan or Zonalon).mp. (30)
34 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (19292)
35 3 and 34 (11)
36 3 and 23 (23)
37 35 or 36 (23)
38 exp Serotonin Uptake Inhibitors/ (26286)
39 Duloxetine.mp. (890)
40 Cymbalta.mp. (23)
41 Venlafaxine.mp. (2206)
42 Effexor.mp. (33)
43 39 or 40 or 41 or 42 (2941)
44 3 and 43 (0)
45 3 and 38 (6)
46 44 or 45 (6)
47 (Lidocaine adj5 (transderm$ or patch$)).mp. (208)
48 Lidoderm.mp. (14)
49 Lidocaine/ and Administration, Cutaneous/ (292)
50 47 or 48 or 49 (412)
51 3 and 50 (5)
52 limit 22 to humans (100)
53 limit 52 to english language (63)
54 limit 52 to abstracts (70)
55 53 or 54 (83)
56 limit 37 to humans (22)
57 limit 56 to english language (19)
58 limit 56 to abstracts (18)
59 57 or 58 (22)
60 limit 46 to humans (6)
61 limit 60 to english language (5)
62 limit 60 to abstracts (5)
63 61 or 62 (6)
64 limit 51 to humans (5)
65 limit 64 to english language (5)
66 limit 64 to abstracts (5)
67 65 or 66 (5)
68 55 or 59 or 63 or 67 (104)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2010>
Search Strategy:
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1 Complex regional pain syndrome.mp. or Complex Regional Pain Syndromes/ (96)
2 Reflex sympathetic Dystrophy.mp. (137)

3 1 or 2 (184)
4 Gabapentin.mp. (450)
5 Neurontin.mp. (40)
6 Pregabalin.mp. (141)
7 Lyrica.mp. (2)
8 Carbamazepine.mp. (1210)
9 Topiramate.mp. (396)
10 Topamax.mp. (1)
11 Oxcarbazepine.mp. (169)
12 Trileptal.mp. (15)
13 Lamotrigine.mp. (498)
14 Lamictal.mp. (50)
15 Valproic acid.mp. (702)
16 (Depakote or Depacon or Depakene or Divalproex or Epival or Deproic).mp. (267)
17 (Tegretol or Carbatrol or Epitol).mp. (81)
18 Anticonvulsant$.mp. (1770)
19 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (3140)
20 3 and 19 (4)
21 3 and 18 (3)
22 20 or 21 (5)
23 (Antidepressive Agent$ adj2 Tricyclic$).mp. (849)
24 Amitriptyline.mp. (1855)
25 Elavil.mp. (7)
26 Desipramine.mp. (619)
27 Norpramin.mp. (1)
28 Nortriptyline.mp. (552)
29 Pamelor.mp. (0)
30 Aventyl.mp. (1)
31 exp Imipramine/ (986)
32 Tofranil.mp. (48)
33 exp Doxepin/ (139)
34 (Sinequan or Silenor).mp. (11)
35 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (3813)
36 3 and 35 (0)
37 3 and 23 (0)
38 36 or 37 (0)
39 (Serotonin Uptake adj2 (Inhibit$ or block$)).mp. (1976)
40 Duloxetine.mp. (242)
41 Cymbalta.mp. (1)
42 Venlafaxine.mp. (761)
43 Effexor.mp. (11)
44 Desvenlafaxine.mp. (24)
45 Pristiq.mp. (0)
46 40 or 41 or 42 or 43 or 44 or 45 (1009)
47 3 and 39 (0)
48 3 and 46 (0)

49 (Lidocaine adj5 (transderm$ or patch$ or skin or cutaneous$)).mp. (218)
50 lidoderm.mp. (2)
51 49 or 50 (218)
52 3 and 51 (0)
53 47 or 48 (0)
54 22 or 38 or 52 or 53 (5)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2010>
Search Strategy:
---
1 Complex regional pain syndrome.mp. (24)
2 Reflex sympathetic Dystrophy.mp. (23)
3 1 or 2 (34)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2010>
Search Strategy:
---
1 Complex regional pain syndrome.mp. [mp=title, full text, keywords] (8)
2 Reflex sympathetic dystrophy.mp. (7)
3 1 or 2 (11)

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to July Week 4 2010>
Search Strategy:
---
1 desvenlafaxine.mp. (67)
2 Pristiq.mp. (4)
3 1 or 2 (67)
4 limit 3 to (english language and humans) (62)

Search for milnacipran was exploratory. We did not find any new studies on this drug and hence it was not included.

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to August Week 4 2010>
Search Strategy:
---
1 milnacipran.mp. (340)
2 savella.mp. (2)
3 levetiracetam.mp. (1143)
4 keppra.mp. (75)
5 lacosamide.mp. (90)
6 vimpat.mp. (4)
7 1 or 2 or 3 or 4 or 5 or 6 (1561)
8 (neuropath$ adj5 (pain$ or ache$ or discomfort$ or agony or agoniz$)).mp. (8322)
9 neuropath$.mp. (77060)
10 8 or 9 (77060)
11 7 and 10 (65)
12 limit 11 to (english language and humans) (40)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2010>

Search Strategy:

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1 milnacipran.mp. (80)
2 savella.mp. (0)
3 levetiracetam.mp. (184)
4 keppra.mp. (14)
5 lacosamide.mp. (24)
6 vimpat.mp. (0)
7 1 or 2 or 3 or 4 or 5 or 6 (290)
8 (neuropath$ adj5 (pain$ or ache$ or discomfort$ or agony or agoniz$)).mp. (697)
9 neuropath$.mp. (2965)
10 8 or 9 (2965)
11 7 and 10 (13)
12 limit 11 to (english language and humans) [Limit not valid; records were retained] (13)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2010>
Search Strategy:

---

1 milnacipran.mp. (36)
2 savella.mp. (1)
3 levetiracetam.mp. (20)
4 keppra.mp. (1)
5 lacosamide.mp. (2)
6 vimpat.mp. (0)
7 1 or 2 or 3 or 4 or 5 or 6 (57)
8 (neuropath$ adj5 (pain$ or ache$ or discomfort$ or agony or agoniz$)).mp. (95)
9 neuropath$.mp. (431)
10 8 or 9 (431)
11 7 and 10 (6)
12 limit 11 to (english language and humans) [Limit not valid; records were retained] (6)

Appendix D. Excluded studies

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

2=ineligible outcome, 3=ineligible intervention, 4=ineligible population, 5=ineligible publication type, 6= ineligible study design

Excluded studies	Exclusion code
Head-to-head trials	
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.	4
Baron R, Mayoral V, Leijon G, et al. Efficacy and safety of 5% lidocaine (lignocaine) medicated plaster in comparison with pregabalin in patients with postherpetic neuralgia and diabetic polyneuropathy: interim analysis from an open-label, two-stage adaptive, randomized, controlled trial. Clinical Drug Investigation. 2009;29(4):231-241.	6
Jann S, Muscia F, Sterzi R. Randomized, open label trial on the efficacy and tollerability of oxcarbazepione versus gabapentin in the treatment of neuropathic pain. Journal of the Peripheral Nervous System : JPNS. 2007;12(2):160-161.	5
Park JH, Lee SH, Kim ST. Pharmacologic management of trigeminal nerve injury pain after dental implant surgery. International Journal of Prosthodontics. Jul-Aug 2010;23(4):342-346.	6
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.	6
Turkington RW. Depression masquerading as diabetic neuropathy. JAMA. Mar 21 1980;243(11):1147-1150.	6
Active-control trials	
Backonja M, Wallace M, Blonsky E, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: A randomized, double-blind study. . Lancet Neurol. 2008 7(12):1106-1112.	3
Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. Pain. Apr 2009;142(3):209-217.	4
Gatti A, Sabato AF, Occhioni R, et al. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. European Neurology. 2009;61(3):129-137.	6
Giannopoulos S, Kosmidou M, Sarmas I, et al. Patient compliance with SSRIs and gabapentin in painful diabetic neuropathy. Clinical Journal of Pain. Mar-Apr 2007;23(3):267-269.	6
Ho KY, Huh BK, White WD, et al. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. Clinical Journal of Pain. Jan 2008;24(1):51-55.	3
Irving G, Backonja M, Dunteman E, et al. A Multicenter, Randomized, Double-Blind, Controlled Study of NGX-4010, a High-Concentration Capsaicin Patch, for the Treatment of Postherpetic Neuralgia. Pain Med. 2011 12(1):99-109.	3
Kadiroglu AK, Sit D, Kayabasi H, et al. The effect of venlafaxine HCl on painful peripheral diabetic neuropathy in patients with type 2 diabetes mellitus. Journal of Diabetes & its Complications. Jul-Aug 2008;22(4):241-245.	6
Kvarnstrom A, Karlsten R, Quiding H, Gordh T. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiologica Scandinavica. 2004;48(4):498-506.	3
Nalamachu S, Crockett RS, Mathur D. Lidocaine patch 5% for carpal tunnel syndrome:	4

Excluded studies	Exclusion code
how it compares with injections: a pilot study. Journal of Family Practice. Mar 2006;55(3):209-214.	
Ruessmann HJ, German Society of out patient diabetes centres AND. Switching from pathogenetic treatment with alpha-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients. Journal of Diabetes & its Complications. May-Jun 2009;23(3):174-177.	6
Solak O, Metin M, Esme H, et al. Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain. European Journal of Cardio-Thoracic Surgery. Jul 2007;32(1):9-12.	6
Placebo-controlled trials	
Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. Epilepsia. 1999;40 Suppl 6:S57-59; discussion S73-54.	5
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.	5
Bongardt S, Bain S, Tzschaschel B, Sommerville K. Lacosamide reduces pain in a randomized, controlled trial of subjects with diabetic neuropathic pain. Poster presented at 12th World Congress on Pain (WCP) of The International Association for The Study of Pain (IASP). August 17-22, 2008. Glasgow, UK.	6
Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. Journal of Clinical Oncology. Jul 15 2004;22(14):2909-2917.	4
Carlsson KC, Hoem NO, Moberg ER, Mathisen LC. Analgesic effect of dextromethorphan in neuropathic pain. Acta anaesthesiologica Scandinavica. 2004;48(3):328-336.	3
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.	5
Eisenberg E, Lurie Y, Brecker C, Daoud D, Ishay A. Lamotrigine in the treatment of painful diabetic neuropathy: A randomized, placebo-controlled study. Progress in Pain Research and Management. 2000;16:857-862.	5
Estanislao L, Carter K, McArthur J, Olney R, Simpson D, Lidoderm HIVNG. A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. Journal of Acquired Immune Deficiency Syndromes: JAIDS. Dec 15 2004;37(5):1584-1586.	3
Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. Journal of Orofacial Pain. 2004;18(2):131-137.	4
Hidvégi T, Bretschneider M, Bongardt S, Koch B. Lacosamide in subjects with painful distal diabetic neuropathy: results of a multi-center, open-label, follow-on trial. Poster presented at American Pain Society (APS) 25th Annual Scientific Meeting. May 3-6, 2006. San Antonio,USA.	6
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Appendix E. Strength of evidence

Table 1: Strength of the body of evidence in patients with diabetic neuropathy and postherpetic neuralgia

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; Number of Subjects	Risk of bias (design/ quality)	Consistency	Directness	Precision	Summary effect size (95% Confidence Interval)	High, Moderate, Low, Insufficient
Outcome 1. Gabapentin, pregabalin, lamotrigine vs. amitriptyine/nortriptyline ≥50% pain reduction						
	Moderate	Consistent	Direct	Precise	RR 1.0 (0.84, 0.18)	Moderate
Outcome 2. Venlafaxine vs. carbamazepine in pain reduction on 11-point Likert scale						
	High	1 study	Direct	Imprecise	greater reduction of approximately 1.5 points	Insufficient
Outcome 3. 5% Lidocaine patch vs. oral pregabalin ≥50% pain reduction						
	Moderate	1 study	Direct	Imprecise	RR 1.21 (0.88, 1.67)	Low
Outcome 4. Gabapentin, pregabalin, and lamotrigine vs. tricyclics in withdrawal due to adverse events						
	Moderate	Consistent	Direct	Precise	RR 0.61, (0.33, 1.12)	Moderate
Outcome 5. Venlafaxine vs. carbamazepine in withdrawal due to adverse events						
	Moderate	1 study	Direct	Imprecise	RR 2.00 (0.44, 9.14)	Low
Outcome 6. 5% lidocaine patch vs. pregabalin in withdrawal due to adverse events						
	Moderate	1 study	Direct	Imprecise	RR 4.39 (2.25, 8.69)	Moderate
Outcome 7. Gabapentin and pregabalin vs. tricyclic antidepressants in causing dry mouth						
	Low	Consistent	Direct	Imprecise	RR 0.27 (0.14, 0.56)	Moderate
Outcome 8. Gabapentin and pregabalin vs. tricyclics antidepressants in causing ataxia						
	Moderate	Consistent	Direct	Imprecise	RR 3.70 (1.18, 11.65)	Low

Table 2: Strength of the body of evidence in patients with other types of neuropathic pain

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	Risk of bias (design/ quality)	Consistency	Directness	Precision	Summary effect size	High, Moderate, Low, Insufficient
Outcome 1	**Pain reduction**					
Comparison:	**Gabapentin 400 or 800 mg plus opioids vs. imipramine 10 mg plus opioids for cancer-related neuropathic pain**					
1 52 subjects	Moderate/ Randomized controlled trial/Fair	NA	Direct	Imprecise	Insufficient data to calculate RR No difference between treatments on pain score or use of rescue medication Combination with gabapentin + imipramine + opioids more effective than therapy with either gabapentin + opioids or imipramine + opioids	Low
Comparison:	**Gabapentin 3600 mg vs. amitriptyline 150 mg for spinal cord injury-related neuropathic pain**					
1 38 subjects	Moderate/ Randomized controlled trial/Fair	NA	Direct	Imprecise	Average pain intensity score at week 8 Amitriptyline: 3.46±2.09 Gabapentin: 4.85±2.86 *P*=0.03 Response (30% or more pain reduction) Overall: Amitriptyline: 50%, Gabapentin: 42.9% *P*=NS High CESD-SF group (score ≥10): Amitriptyline: 62.5% Gabapentin: 12.5% *P*=0.042 Insufficient data to calculate relative risks	Low
Comparison:	**Amitriptyline vs. carbamazepine in patients with central poststroke pain**					
1 15 subjects	Moderate/ Randomized controlled trial/Fair	NA	Direct	Imprecise	Patients reporting improvement in pain: Amitriptyline vs carbamazepine RR=1.87 (95% CI 0.90, 4.32) Mean pain score at endpoint: Amitriptyline: 4.2 (SD 1.6) Carbamazepine: 4.2 (SD 1.7) *P*=NS	Low

	Domains pertaining to strength of evidence				Magnitude of effect		Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality)**	**Consistency**	**Directness**	**Precision**	**Summary effect size**		**High, Moderate, Low, Insufficient**
Outcome 2	**Withdrawal due to adverse events**						
Comparison:	**Gabapentin 400 or 800 mg plus opioids vs. imipramine 10 mg plus opioids for cancer-related neuropathic pain**						
1 52 subjects	Moderate/ Randomized controlled trial/Fair	NA	Direct	Imprecise	No withdrawals due to adverse events in either group		Insufficient
Comparison:	**Gabapentin 3600 mg vs, amitriptyline 150 mg for spinal cord injury-related neuropathic pain**						
1 38 subjects	Moderate/ Randomized controlled trial/Fair	NA	Direct	Imprecise	Amitriptyline vs gabapentin: RR=0.88 (95% CI 0.36, 1.57)		Low
Comparison:	**Amitriptyline vs, carbamazepine in patients with central poststroke pain**						
1 15 subjects	Moderate/ Randomized controlled trial/Fair	NA	Direct	Imprecise	Amitriptyline vs carbamazepine: 0/12 vs 3/12 *P*=0.10		Low