Health Resources Commission

DRAFT

Drugs for Neuropathic Pain

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Produced by:
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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In the fall of 2007 the Oregon Health Resources Commission (HRC) appointed a Pharmaceutical Subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, a PhD, RPh, and a PharmD. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria. The EPC's report, "Drugs for Neuropathic Pain" was completed in October 2007, circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The Drugs for "Neuropathic Pain" report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Drugs for Neuropathic Pain* is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:
www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml
You may request more information including copies of the draft report, and minutes of subcommittee meetings, from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
Alison Little, MD
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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

Health Resources Commission

– "Clinical outcomes are the most important indicators of comparative effectiveness"
– "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Clinical Overview

Neuropathic pain (NP) is defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system."[1] NP is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching, or shooting. NP is also commonly associated with hyperalgesia (increased pain intensity evoked by normally painful stimuli), paresthesia, and dysesthesia. NP can occur because of dysfunction or disease of the nervous system at the peripheral and/or central level. NP can be very severe and disabling, with significant functional, psychological, and social consequences. Regardless of the underlying cause of NP, common treatment goals are to decrease pain and/or improve function. NP is often classified by etiology or by the presumed site of neurologic involvement (central or peripheral). However, both peripheral and central nervous system lesions may contribute to most types of chronic NP.

While estimates of prevalence vary widely up to 3% of the population may complain of NP at some time. NP is most commonly associated with painful diabetic neuropathy, post-herpetic neuralgia (PHN), or lumbar nerve root compression. Diabetic neuropathy occurs in approximately 10% of persons with diabetes. Prevalence of diabetic neuropathy increases with age, worsening glycemic control, and duration of diabetes.

PHN is defined as pain persisting or recurring at the site of acute herpes zoster 3 or more months after the acute episode. It occurs in up to 25% of patients following an episode of shingles. Symptomatic spinal stenosis and lumbar disc herniation with nerve root compression occur in approximately 3% and 4% of patients with low back pain, respectively. Other causes of NP include cancer-related pain, spinal cord injury, post-stroke pain, HIV-associated neuropathy, and phantom limb pain. Uncommon but potentially debilitating NP conditions include trigeminal neuralgia (incidence 4/100,000 population). In the U.S., health care and disability-related costs associated with NP are estimated at almost $40 billion annually

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

The subcommittee's task was to evaluate

Scope and Key Questions

Scope

Table 1. lists the drugs included in this review. The objective of this study is to review evidence on comparative effectiveness of gabapentin, pregabalin, duloxetine, venlafaxine, and topical lidocaine (patch or ointment), including the comparative effectiveness of these medications compared to other medications for NP (defined in this review as tricyclic antidepressants, other antiepileptic medications [carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid and derivatives], selective serotonin reuptake inhibitors, and

dextromethorphan). The medications gabapentin, pregabalin, duloxetine, and lidocaine patch were chosen as the main focus of this review because they have been approved by the US Food and Drug Administration (FDA) for treatment of diabetic neuropathy or PHN. Venlafaxine was chosen because it is similar in structure and mechanism of action to duloxetine and lidocaine ointment chosen because of its similarities to the lidocaine patch. The other drugs included in this review have been used but are not FDA-approved for treatment of neuropathic pain, with the exception of carbamazepine, which was approved for trigeminal neuralgia based on trials published in the 1960's. Simple analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids were not included in this review.

Table 1. Included drugs

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

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

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

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

Key Questions

KQ1. What is the comparative effectiveness of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine versus each other for neuropathic pain?

KQ2. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, or topical lidocaine versus other drugs (other antiepileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

KQ3. What are the comparative harms of pregabalin, gabapentin, SNRIs, and topical lidocaine for neuropathic pain?

KQ4. What are the comparative harms of pregabalin, gabapentin, SNRIs, or topical lidocaine versus other drugs (other antiepileptics, tricyclic antidepressants (including tertiary versus secondary amines), selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

KQ5. What are the comparative effectiveness and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine plus a tricyclic antidepressant or another antiepileptic versus monotherapy with a tricyclic antidepressant or another antiepileptic?

KQ6. Are there differences in effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions?

Results

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

KQ1. What is the comparative effectiveness of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine versus each other for neuropathic pain?

Direct Evidence

There were no head-to-head trials comparing gabapentin, pregabalin, an SNRI, or topical lidocaine to each other in this DERP report.

Indirect Evidence

Gabapentin (12 placebo-controlled trials), pregabalin (8 trials), and duloxetene (3 trials) were consistently more effective than placebo for pain relief or improvement in function. Trials of topical lidocaine and venlafaxine versus placebo were inconsistent or showed no clear benefit.

In adjusted indirect analyses pregabalin was moderately superior to duloxetine for the proportion of patients experiencing at least moderate improvement or >50% improvement in pain scores (RR=1.45, 95% CI 1.12 to 1.87). There was no significant difference between gabapentin and duloxetine (RR=1.22, 95% CI 0.95 to 1.56). There were no significant differences between gabapentin and pregabalin in the likelihood of achieving pain relief (RR=0.84, 95% CI 0.64 to 1.11), average pain relief (WMD=-0.50 on a 0 to 10 scale, 95% CI -2.91 to +1.91), the SF-36 McGill Pain Questionnaire (Total score), or SF-36 Bodily Pain or Mental Health scores. The only statistically significant difference between gabapentin versus pregabalin was observed on the SF-36 Vitality score. Gabapentin was superior to pregabalin by less than 10 points (WMD=+9.32, 95% CI, +2.67 to +15.97). However, this finding should be interpreted cautiously because it is based on an analysis that included only one trial of gabapentin and two trials of pregabalin. Selective outcomes reporting bias may have occurred for some outcomes, as statistically significant SF-36 subscale scores appeared to be preferentially reported.

There were no differences between venlafaxine and either gabapentin, pregabalin, or duloxetine on average pain scores or the likelihood of achieving significant pain relief. However, analyses involving venlafaxine only included two trials of that medication. No trial included in the indirect analyses was rated poor-quality, or evaluated patients with HIV-associated neuropathic pain or trigeminal neuralgia.

Summary

Adjusted indirect analyses of placebo-controlled trials found gabapentin, duloxetine, and venlafaxine similarly effective for pain relief and improvement in function compared to one another. Pregabalin was moderately superior to duloxetine for the proportion of patients experiencing significant pain relief, but there were no differences between pregabalin and gabapentin or venlafaxine**.** There were no suitable data from placebo-controlled trials of topical lidocaine to perform indirect analyses.

KQ 1 Consensus Statements

We considered all of the trials included in this report to be efficacy studies, as none met all criteria for effectiveness studies

The Pharmaceutical Subcommittee agrees by consensus that:

1. There is insufficient evidence to determine a difference in comparative effectiveness between gabapentin, pregabalin, duloxetene, or venlafaxine for neuropathic pain.
2. The studies of lidocaine were of poor quality and no conclusion can be reached for or against the effectiveness of lidocaine for relief of neuropathic pain.

KQ2. What is the comparative effectiveness of pregabalin, gabapentin, SNRIs, or topical lidocaine versus other drugs (other antiepileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

Direct Evidence

Two systematic reviews included head-to-head trials of gabapentin versus tricyclic antidepressants for NP (Table 3).[2,3] One systematic review[2] found no difference between gabapentin versus tricyclic amitriptyline for the proportion of patients experiencing pain relief (RR=1.30, 95% CI 0.91 to 1.85, 2 trials[4,5]). The other systematic review[3] analyzed the same two trials qualitatively, and found inconsistent results, with no difference between drugs in one trial[5] and gabapentin superior by about 0.6 points on a 0 to 4 pain scale in the other.[4] Both head-to-head trials were small (N=25) and relatively short-term (6 weeks and 12 weeks).

Four small (N=25 to 70), fair quality, head-to-head trials directly compared a newer versus an older medication for neuropathic pain. Two trials[4,5] of gabapentin versus amitriptyline in patients with diabetic neuropathy were included in the previously mentioned (above) systematic reviews. Also identified was one trial comparing

nortriptyline to gabapentin for postherpetic neuralgia,[6] and one trial comparing imipramine to venlafaxine for various types of neuropathic pain (this trial also included a placebo arm).[7] Qualitatively, results from three small head-to-head trials (N=25 to 76) of gabapentin versus tricyclic antidepressants are inconclusive regarding relative effectiveness.[4,5,6] Two trials (N=25 in both trials) compared gabapentin to amitriptyline for diabetic neuropathy.[4,5] One of these studies found no difference between the two drugs, while the other found that patients randomized to gabapentin experienced greater improvements in measures of pain and paresthesia than those randomized to amitriptyline (difference of about 0.5 points on a 0 to 4 pain scale). However the study that showed no differences used a lower dose of gabapentin (mean 1565 vs. 1785 mg/day), while the amitriptyline mean dose was similar (53 vs. 59 mg/day). The study that found gabapentin more effective was open label while the study that showed no differences was double blinded and there were differences between the two studies in outcome measures, treatment duration and data analysis. The third trial, an 8-week, double-blind, parallel-group trial (N=70) of nortriptyline versus gabapentin (up to 2700mg/day) in a different population (patients with postherpetic neuralgia) found no differences between groups in mean improvement in pain scores (primary outcome), likelihood of experiencing a good or excellent response, or other secondary outcomes (sleep ratings, disability, or proportion of patients responding to treatment).[6]

Quantitatively, there was no difference between gabapentin and tricyclic antidepressants for experiencing >50% pain relief or at least moderate pain relief when the three head-to-head trials of this comparison were pooled (RR=0.99, 95% CI 0.76 to 1.29, I_2=0%).[4,5,6] In a subgroup analysis of two trials, there was also no significant difference between gabapentin versus amitriptyline specifically for diabetic neuropathy (RR=0.91, 95% CI 0.66 to 1.28).[4,5] Results were also similar after excluding data from the single cross-over trial[5] (RR=1.07, 95% CI 0.79 to 1.47).

In one small trial comparing venlafaxine versus imipramine (N=32), about half of enrolled patients had diabetic neuropathy and half had neuropathic pain due to another etiology. Venlafaxine and imipramine were similar in efficacy on a number of pain scales, with no statistically significant difference in the likelihood of achieving pain relief (RR=0.55, 95% CI 0.27 to 1.12).[7]

Indirect Evidence

DERP identified 21 placebo-controlled trials of tricyclic antidepressants, 3 trials of SSRIs, 21 trials of older antiepileptics (7 carbamazepine, 5 valproic acid, 7 lamotrigine 2 oxcarbazepine), 4 trials of topiramate, and 4 trials of dextromethorphan (reported in three articles). Most trials were short term (range 1 week to 18 weeks, median 6 weeks). Forty trials were rated fair quality and 13 were rated poor quality.

Indirect comparisons

In adjusted indirect analyses, gabapentin and duloxetine were both inferior to tricyclic antidepressants (RR=0.54, 95% CI 0.30 to 0.99 for gabapentin and RR=0.45, 95% CI 0.25 to 0.80 for duloxetine). Gabapentin and pregabalin were both superior to other antiepileptics (RR=1.42, 95% CI 1.04 to 1.96 for gabapentin and RR=1.70, 95% CI 1.23

to 2.35 for pregabalin), and gabapentin and pregabalin were also both superior to SSRI's (RR=1.72, 95% CI 1.05 to 2.80 for gabapentin and RR=2.05, 95% CI 1.25 to 3.35 for pregabalin). However, only two trials of SSRI's[8,9] contributed data to the indirect analyses. We found no differences between gabapentin or pregabalin and other antiepileptic drugs in mean improvement in pain scores or the SF-McGill Pain Questionnaire. There were no differences in comparisons involving venlafaxine, but only two trials of venlafaxine[7,10] contributed data to the indirect analysis. Only one trial of dextromethorphan reported usable data for indirect analyses, resulting in wide confidence intervals.[11]

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

Sensitivity and subgroup analyses had little effect on conclusions involving tricyclic antidepressants. However, for some comparisons estimates that were non-significant based on all trials became significant in sensitivity analyses (venlafaxine or pregabalin versus tricyclics). We (DERP) also performed a subgroup analysis based on four placebo-controlled trials of lamotrigine. Pregabalin was superior to lamotrigine for achieving pain relief (RR=1.60, 95% CI 1.16 to 2.20), though results were similar to the estimate for pregabalin versus carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid (RR=1.70, 95% CI 1.23 to 2.35). We (DERP) did not perform subgroup analyses on other individual antiepileptic medications, which were each evaluated in one to three trials and associated with wider confidence intervals than estimates for lamotrigine.

Summary

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

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

Results of indirect analyses should be interpreted cautiously. Conclusions about comparative efficacy of tricyclic antidepressants based on indirect analyses may be unreliable because of funnel plot asymmetry and heterogeneity among placebo-controlled trials. Although estimates were similar after adjusting for potential publication bias and after excluding trials of HIV-related neuropathic pain (which substantially reduced heterogeneity), there were statistically significant discrepancies between direct and indirect estimates of gabapentin versus tricyclic antidepressants for pain relief. Because

there were no head-to-head trials of tricyclic antidepressants versus pregabalin, duloxetine, venlafaxine, or topical lidocaine, we could not contrast results of direct and indirect analyses for these comparisons.
Analyses involving pooled results for the antiepileptic medications carbamazepine, oxcarbazepine, lamotrigine, topiramate, and valproic acid should also be interpreted cautiously, as these medications vary in pharmacologic structure and mechanism of action. However, stratified estimates suggest no clear differences in efficacy, and estimates for individual drugs were too imprecise to be informative in adjusted indirect analyses.

KQ 2 Consensus Statements

We considered all of the trials included in this report to be efficacy studies, as none met all criteria for effectiveness studies
The Pharmaceutical Subcommittee agrees by consensus that:
1. Three fair quality head to head trials found no difference between gabapentin and tricyclic antidepressants for relief of neuropathic pain.
2. There is insufficient evidence to determine comparative effectiveness gabapentin vs. other drugs for neuropathic pain.
3. There is insufficient evidence to determine comparative effectiveness between Pregabalin, SNRI's (duloxetene and venlafaxine) or topical lidocaine vs. other drugs for neuropathic pain.

KQ3. What are the comparative harms of pregabalin, gabapentin, SNRIs, and topical lidocaine for neuropathic pain?

Direct Evidence
We found no head-to-head trials directly comparing harms associated with pregabalin, gabapentin, SNRIs, and topical lidocaine for neuropathic pain.

Indirect Evidence
Four systematic reviews evaluated adverse events associated with newer drugs for neuropathic pain versus placebo (Table 21).[3,12,13,14] All four reported estimates for withdrawal due to adverse events, which may be a surrogate for more serious adverse events. However, data from systematic reviews are of limited usefulness for assessing comparative risks because none attempted formal indirect analyses.
One systematic review reported a number needed to cause one withdrawal due to adverse events) of 17.8 (95% CI, 12 to 30) for gabapentin or pregabalin (13 trials).[12] A second systematic review, which pooled results from trials of gabapentin, pregabalin, and oxcarbazepine, reported an odds ratio for withdrawal due to adverse events of 2.98 (95% CI, 1.75 to 5.07), or a number needed to harm of about 11.[14] However, nearly 70% of the withdrawals due to adverse events occurred in two trials of oxcarbazepine, which reported odds ratios of 4.50 (95% CI 1.68 to 12.06) and 4.13 (95% CI 1.57 to 10.87). From data reported in the systematic review, we re-calculated a pooled odds ratio of 1.78 (95% CI 0.78 to 4.04) for the three trials of gabapentin and pregabalin, or a NNH of

about 29. Systematic reviews that reported results separately for gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine were limited by sparse data or heterogeneity. Neither venlafaxine nor topical lidocaine were associated with increased withdrawal due to adverse events compared to placebo in two systematic reviews.[12,13]
Randomized trials were a source of adverse event reporting. Overall withdrawals and withdrawals due to adverse events, dizziness or vertigo, or somnolence were the most frequently reported adverse events. Dry mouth was reported in 7 of 8 trials of pregabalin but infrequently reported for the other drugs. Ataxia or gait disturbance was reported in 3 trials of pregabalin and 2 trials of gabapentin.
"Serious" adverse events were reported by 6 trials of pregabalin (range 0% to 3.6%), 5 of gabapentin (range 0% to 2.6%), 3 of duloxetine (2.6% to 5.1%), 1 of venlafaxine (9% to 12%), and 2 of lidocaine patch (0% in both trials). However, only three trials defined the term "serious." Seven others trials reporting serious adverse events reported no cases. From pooled estimates involving the remaining trials, we found no differences between gabapentin, pregabalin, duloxetine, or venlafaxine versus placebo for risk of serious adverse events, though most estimates were fairly imprecise and could be affected by selecting outcomes reporting bias. In general, estimates of adverse events for different drugs were similar or associated with overlapping confidence intervals, with no obvious differences between medications. However, gabapentin was the only newer medication for NP not associated with a statistically significant increased rate of withdrawals due to adverse events compared to placebo (RR=1.29, 95% CI, 0.90 to 1.85, I_2=0%).
In a stratified analysis, pregabalin 150 mg/day was associated with a lower risk of withdrawal due to adverse events compared to placebo than trials evaluating pregabalin 300 to 600 mg/day (RR=1.07, 95% CI 0.59 to 1.97, I_2=0%, [4 trials] versus RR=2.49, 95% CI 1.77 to 3.52, I_2=3%, [8 trials]; p=0.040 for difference in pooled estimates).

Indirect comparisons
1. Indirect analyses of placebo-controlled trials found no differences between gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine for neuropathic pain in rates of overall withdrawals
2. Gabapentin was associated with a lower likelihood of withdrawal due to adverse events compared to pregabalin 150 to 600 mg/day (RR=0.58, 96% CI 0.34 to 0.98). Results were similar when gabapentin was compared to pregabalin 300 to 600 mg/day.
3. Gabapentin and pregabalin 150 to 600 mg/day were each associated with greater risk of somnolence compared to venlafaxine (RR=2.62, 95% CI 1.35 to 5.06 and RR=2.82, 95% CI 1.46 to 5.45, respectively).
4. Pregabalin was also associated with a greater risk of dry mouth compared to venlafaxine (RR=2.52, 95% CI 1.22 to 5.19).
5. Gabapentin was associated with a higher risk of dizziness or somnolence compared to pregabalin 150 mg/day (RR=2.12, 95% CI 1.06 to 4.26), but there was no difference when compared to pregabalin 150 to 600 mg/day (RR=0.93, 95% CI 0.56 to 1.55).

As is the case with all indirect comparisons, results should be interpreted cautiously because of clinical diversity across the different sets of trials in populations, interventions (average doses or methods of dose titration), and duration of exposure. In addition, assessment of harms was a secondary outcome in all of the trials. Very few trials reported

pre-defined criteria for different harms, few trials used active methods to assess harms, and assessment and reporting of harms in general was poorly standardized.

Summary
In adjusted indirect analyses, gabapentin was associated with a lower likelihood of withdrawal due to adverse events compared to pregabalin at comparable doses. We found no differences between gabapentin and pregabalin in rates of overall withdrawals, somnolence/sedation, or dizziness. Gabapentin and pregabalin are associated with more somnolence/sedation compared to venlafaxine. Pregabalin is also associated with more dry mouth than venlafaxine. There are no clear differences between duloxetine and either gabapentin, pregabalin, or venlafaxine for any adverse event assessed, though analyses were limited by small numbers of trials of duloxetine. There was insufficient data to perform indirect analyses on harms associated with topical lidocaine.

KQ 3 Consensus Statements:

We considered all of the trials included in this report to be efficacy studies, as none met all criteria for effectiveness studies
The Pharmaceutical Subcommittee agrees by consensus that:
1. Indirect analysis showed a lower likelihood of withdrawal due to adverse events with gabapentin vs. pregabalin at comparable doses, but no difference in overall rates of withdrawal, somnolence/sedation or dizziness between the two drugs.
2. There is insufficient evidence to differentiate between duloxetene and either gabapentin, pregabalin or venlafaxine for any adverse events.
3. Gabapentin and pregabalin are associated with more somnolence/sedation compared to venlafaxene.

KQ4. What are the comparative harms of pregabalin, gabapentin, SNRIs, or topical lidocaine versus other drugs (other antiepileptics, tricyclic antidepressants (including tertiary versus secondary amines), selective serotonin reuptake inhibitors [SSRIs], or dextromethorphan) for neuropathic pain?

Direct Evidence
There was insufficient evidence from four small (N=25 to 70), fair quality, head-to-head trials directly comparing a newer versus an older medication for neuropathic pain to determine whether one medication or another is associated with fewer harms.[4-7]

Indirect evidence
Systematic Reviews
Five systematic reviews reported pooled estimates for risk of withdrawal due to adverse events for newer medications for neuropathic pain versus placebo (Table 24).[2,12,13,14,15] The systematic reviews are of limited usefulness for assessing comparative harms of gabapentin, pregabalin, SNRIs, or topical lidocaine versus other antiepileptics, tricyclic antidepressants, SSRIs, or dextromethorphan for neuropathic pain because none attempted to perform formal indirect analyses. Versus placebo, estimates for tricyclic

antidepressants were relatively consistent across three systematic reviews, with numbers needed to cause one withdrawal due to adverse events ranging from 15 to 17. The systematic review reporting estimates from the most trials of tricyclic antidepressants (21 trials of any neuropathic pain condition) estimated a number needed to cause one withdrawal due to adverse event of 15 (95% CI 10 to 25).[12] Among the antiepileptic drugs, topiramate appeared associated with a greater likelihood of withdrawal due to adverse events compared to carbamazepine, though estimates for topiramate were based on two trials.[12] Estimates of numbers needed to cause a minor harm (an adverse event not resulting in discontinuation of the medication) were similar for tricyclic antidepressants, carbamazepine, and SSRI's in three systematic reviews (each versus placebo).

Randomized Trials

Overall withdrawals and withdrawals due to adverse events, dizziness or vertigo, somnolence were the most frequently reported adverse events.

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

In stratified analyses, lamotrigine was associated with no increased risk of adverse event withdrawal or total withdrawal compared to placebo Carbamazepine/oxcarbazepine, topiramate, and valproic acid were all associated with a similar increased risk for adverse event withdrawal versus placebo. Topiramate and carbamazepine/oxcarbazepine were associated with an increased risk of total withdrawals compared to placebo, but valproic acid was not. An analysis of trials of tricyclic antidepressants stratified by use of active placebo (benztropine) or inert placebo found no clear differences in estimates of adverse events.

Indirect comparisons

For adjusted indirect analyses, we pooled data for all tricyclics because there were few differences between tertiary and secondary amine drugs in stratified analyses. Antiepileptic medications were stratified based on differences observed between drugs in risk of withdrawal due to adverse events or total withdrawals. Indirect analyses on adverse events for SSRIs or dextromethorphan was not performed because of insufficient data (one or two small trials) for meaningful results, and no trials of topical lidocaine reported poolable data on adverse events. For total withdrawals, gabapentin and pregabalin were both superior to carbamazepine, oxcarbazepine, and topiramate (RR=0.55, 95% CI 0.38 to 0.81 and RR=0.55, 95% CI 0.36 to 0.85, respectively). Gabapentin was also superior to carbamazepine, oxcarbazepine, topiramate, and valproic acid for withdrawals due to adverse events (RR=0.31, 95% CI 0.26 to 0.65). Pregabalin was inferior to lamotrigine for withdrawal due to adverse events (RR=2.75, 95% CI 1.26 to 6.03). We found no other statistically significant differences between gabapentin,

pregabalin, or SNRIs versus other antiepileptic medications or tricyclic antidepressants in risk of total withdrawals or withdrawal due to adverse events. For specific adverse events, there were no differences for any comparison between gabapentin, pregabalin, duloxetine, venlafaxine, or topical lidocaine versus tricyclic antidepressants or other antiepileptic medications except for somnolence/sedation and dizziness. Both gabapentin and pregabalin were associated with increased risk of somnolence compared to other antiepileptic medications (RR=1.92, 95% CI 1.00 to 3.70 for gabapentin and RR=2.07, 95% CI 1.08 to 3.98 for pregabalin) or tricyclic antidepressants (RR=2.52, 95% CI 1.60 to 3.99 for gabapentin and RR=2.72, 95% CI 1.72 to 4.30 for pregabalin). Gabapentin and pregabalin were also associated with increased risk of dizziness compared to tricyclic antidepressants (RR 2.21, 95% CI 1.14 to 4.28 for gabapentin and RR=2.07, 95% CI 1.05 to 4.11 for pregabalin).

As with other indirect analyses in this report, results should be interpreted cautiously because of clinical diversity across the different sets of trials. In all trials, assessment of harms was a secondary outcome. Few trials reported pre-defined criteria for different harms, used active methods to assess harms, or described standardized methods for assessment and reporting of harms.

Summary

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

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KQ 4 Consensus Statements

We considered all of the trials included in this report to be efficacy studies, as none met all criteria for effectiveness studies

The Pharmaceutical Subcommittee agrees by consensus that:

1. There is insufficient evidence from direct comparisons (4 small trials) to determine comparative harms of gabapentin vs. tricyclic antidepressants.
2. Indirect evidence suggests that pregabalin and gabapentin are associated with a higher incidence of somnolence/sedation compared to other antiepileptic drugs and tricyclic antidepressants, and a higher incidence of dizziness/vertigo compared to tricyclic antidepressants. However it was difficult to judge reliability of harms data due to poor reporting of methods used to define and ascertain adverse events and because estimates for commonly reported adverse events ranged widely. Quality of evidence for comparisons involving tricyclics and "other antiepileptics" rated poor to fair. Evidence for comparisons involving SSRI's (duloxetene and venlafaxine) and dextromethorphan rated poor.
3. There is insufficient evidence to determine comparative harms of pregabalin, gabapentin, SNRI's (duloxetene and venlafaxine) or topical lidocaine vs. other drugs for neuropathic pain.

KQ5. What are the comparative effectiveness and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine plus a tricyclic antidepressant or another antiepileptic versus monotherapy with a tricyclic antidepressant or another antiepileptic?

There were no randomized trials or controlled observational studies identified evaluating benefits and harms of dual therapy with pregabalin, gabapentin, an SNRI, or topical lidocaine plus a tricyclic antidepressant or another antiepileptic medication versus monotherapy with a tricyclic antidepressant or another antiepileptic medication.

KQ 5 consensus Statements

We considered all of the trials included in this report to be efficacy studies, as none met all criteria for effectiveness studies

The Pharmaceutical Subcommittee agrees by consensus that:

1. There were no published studies on this topic.

KQ6. Are there differences in effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions?

No studies were identified that were designed to assess differences in effectiveness or harms of medications for neuropathic pain based on demographics, co-morbidities, or drug-drug interactions. One higher-quality systematic review reported estimates for pain relief for different medications versus placebo, stratified by underlying neuropathic pain

condition. (Table 2)[12] However, with the exception of peripheral pain or painful polyneuropathy, data for specific neuropathic pain conditions were sparse.

For peripheral pain and painful polyneuropathy, gabapentin and pregabalin both appeared less effective compared to tricyclic antidepressants for pain relief. However, formal indirect analyses were not performed by the authors of the systematic review.

Three head-to-head trials of gabapentin versus tricyclic antidepressants specifically evaluated patients with diabetic neuropathy or post-herpetic neuralgia. There were no differences between gabapentin and tricyclics in likelihood of achieving at least moderate pain relief or >50% pain relief for either condition (RR=0.91, 95% CI 0.66 to 1.28 for diabetic neuropathy, 2 trials and RR=1.00, 95% CI 0.61 to 1.64 for postherpetic neuralgia, 1 trial).

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

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

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

Evidence on efficacy of neuropathic pain medications for HIV-associated neuropathic pain and trigeminal neuralgia is quite limited. Two trials of amitriptyline for HIV-associated neuropathic pain both found no benefit over placebo in the proportion of patients experiencing at least moderate improvement or >50% improvement in pain score.[16,17] Six-placebo-controlled trials evaluated neuropathic pain medications for trigeminal neuralgia. However, results may not be reliable because five [100-103, 120] of the six trials were rated poor-quality, with four of the trials (all of carbamazepine[100-103]) published in 1966 or 1968.

Table 2 Efficacy of different medications for different types of neuropathic pain, NNT to achieve >50% pain relief (hierarchy of outcomes)[18]

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

Summary

Direct evidence on effectiveness or harms of drugs used to treat neuropathic pain based on demographics, co-morbidities, or drug-drug interactions is very limited. For diabetic neuropathy, two head-to-head trials of gabapentin versus amitriptyline found no clear differences between drugs. For post-herpetic neuralgia, one head-to-head trial of gabapentin versus nortriptyline also found no clear differences. Adjusted indirect estimates of comparative efficacy of different neuropathic pain medications for diabetic neuropathy found pregabalin superior to duloxetine, venlafaxine, or SSRIs for achieving significant pain relief. Pregabalin, gabapentin, duloxetine, and venlafaxine were all inferior to tricyclic antidepressants. However, indirect analyses involving tricyclic antidepressants should be interpreted with caution because the discrepancy between direct and indirect estimates of gabapentin versus tricyclic antidepressants for pain relief was highly statistically significant.

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

KQ 6 Consensus Statements:

We considered all of the trials included in this report to be efficacy studies, as none met all criteria for effectiveness studies

The Pharmaceutical Subcommittee Agrees by Consensus that:

1. Direct evidence (two fair quality trials) found no difference in effectiveness (efficacy) in diabetic neuropathy for gabapentin vs. amitriptyline.
2. Indirect evidence (adjusted indirect analysis) of comparative effectiveness (efficacy) for diabetic neuropathy found pregabalin superior to duloxetene, venlafaxine, or SSRI's for achieving significant pain relief.
3. There is insufficient evidence to determine comparative effectiveness or harms for other neuropathic pain conditions.

Conclusions:

Critical Policy

– "Clinical outcomes are the most important indicators of comparative effectiveness"

– "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Limitations of the data base:

1. Neuropathic Pain includes a diverse group of clinical conditions
2. This report covers a diverse group of drug classes
3. The overall quality of the studies in this review were poor-fair
4. Limited comparative evidence is published
5. Pooling of data was not possible in many cases due to heterogeneity

[See Conclusions Below:]

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The Pharmaceutical Subcommittee Concludes:

1. There is insufficient evidence to determine a difference in comparative effectiveness between gabapentin, pregabalin, duloxetene, or venlafaxine for neuropathic pain.
2. Three fair quality head to head trials found no difference between gabapentin and tricyclic antidepressants for relief of neuropathic pain.
3. There is insufficient evidence to determine comparative effectiveness of gabapentin vs. other drugs for neuropathic pain.
4. There is insufficient evidence to determine comparative effectiveness between Pregabalin, SNRI's (duloxetene and venlafaxine) or topical lidocaine vs. other drugs for neuropathic pain.
5. There is insufficient evidence from direct comparisons (4 small trials) to determine comparative harms of gabapentin vs. tricyclic antidepressants.
6. There is insufficient evidence to determine comparative harms of pregabalin, gabapentin, SNRI's (duloxetene and venlafaxine) or topical lidocaine vs. other drugs for neuropathic pain.
7. Direct evidence (two fair quality trials) found no difference in effectiveness (efficacy) in diabetic neuropathy for gabapentin vs. amitriptyline.
8. Indirect evidence (adjusted indirect analysis) of comparative effectiveness (efficacy) for diabetic neuropathy found pregabalin superior to duloxetene, venlafaxine, or SSRI's for achieving significant pain relief.
9. There is insufficient evidence to determine comparative effectiveness or harms for other neuropathic pain conditions.

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