Drug Class Review

Neuropathic Pain

Final Update 1 Report
Executive Summary

June 2011

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

The purpose of the Executive Summary is to summarize key information contained in the Drug Effectiveness Review Project report "Drug class review: Neuropathic Pain", dated June 2011. The full report can be accessed at the following web address: http://derp.ohsu.edu/about/final-document-display.cfm. Readers are advised to review the full 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. They are not intended to provide any legal or business advice. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Original Report: October 2007

Update 1 Authors
Shelley Selph, MD
Susan Carson, MPH
Rongwei Fu, PhD
Sujata Thakurta, MPA:HA
Allison Low, BA
Marian McDonagh, PharmD

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

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" and can occur because of dysfunction or disease of the nervous system at the peripheral and/or central level. 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) and is characterized by continuous or intermittent spontaneous pain, typically characterized by patients as burning, aching, or shooting. Neuropathic pain is also commonly associated with hyperalgesia (increased pain intensity evoked by normally painful stimuli), paresthesia, and dysesthesia. Up to 3% of the general population reports neuropathic pain at some time, and neuropathic pain is most commonly associated with painful diabetic neuropathy, postherpetic neuralgia, or lumbar nerve root compression.

Scope and Key Questions

The goal of this report is to compare the effectiveness and safety of the drugs shown in Table 1 in the treatment of neuropathic pain.

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

Drug	Trade name(s)	Labeled indications for neuropathic pain	Recommended daily dosing for neuropathic pain
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] Effexor XR®	None	NA
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.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

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

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. 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. Dossiers were screened for studies or data not found through other searches.

We assessed the internal validity (quality) of all studies using predefined criteria based on study design (see www.ohsu.edu/drugeffectiveness). We also determined the quality of studies to be *good, fair, or poor* based on predefined criteria. 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.

RESULTS

Overview

Overall, 128 studies were included in this report (55 were identified in searches conducted for Update 1). 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. Of the included studies, 14 were direct comparisons of drugs in this review. The remainder was placebo-controlled, observational, or systematic reviews.

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

In patients with 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 (low- to moderate-strength evidence), pregabalin was found to be superior to topiramate (low-strength evidence), and 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.

Direct evidence for patients with other types of neuropathic pain found that in patients with cancer-related neuropathic pain, no difference in pain relief was shown with low-dose gabapentin (400 mg or 800 mg) plus opioids compared with 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; 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, and 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.

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.

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

For patients with diabetic neuropathy and postherpetic neuralgia, moderate evidence showed that there was 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), there were 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), and 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), and 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 cause 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.

For patients with other types of neuropathic pain, direct evidence was insufficient to evaluate comparative harms. 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.

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?

No evidence was found that assessed 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 low-strength evidence suggested that combinations of duloxetine and pregabalin; lidocaine patch and pregabalin; or gabapentin with imipramine, nortriptyline, or venlafaxine had a potential benefit compared to monotherapy therapy, 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.

SUMMARY

The main findings of this review are summarized in Table 2. 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.

Table 2. 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 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

Key question	Strength of evidence	Conclusion
	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

CONCLUSION

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.