Non-Opioid Drugs to Treat Neuropathic Pain

Final Report

Executive Summary

March 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

Background

Neuropathic pain comprises a wide range of heterogeneous conditions. The recent International Association for the Study of Pain's (IASP) taxonomy working group has redefined neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." Neuropathic pain may result from a large variety of insults to the peripheral or central somatosensory nervous system, including trauma, inflammation, ischemia, and metabolic and neoplastic disorders. Common examples of peripheral neuropathic pain include diabetic neuropathy and postsurgical neuralgia. Central neuropathic pain includes central post-stroke pain, pain in multiple sclerosis, and pain after spinal cord injury. The main clinical characteristics of neuropathic pain are continuous or intermittent pain, typically described as burning, aching, or shooting in quality, and abnormal sensitivity of the painful site to normally innocuous stimuli such as light touch by garments, running water, or even wind (allodynia).

Up to 8% of the general population reports neuropathic pain at some time. In the United States, health care and disability-related costs associated with neuropathic pain are estimated at almost $40 billion annually. A number of medications (oral or topical) are available for treating neuropathic pain (Table 1). Pharmacotherapy for neuropathic pain has generally involved the use of antidepressants or anticonvulsants, but even with the current generation of these drugs, effective analgesia is achieved in less than half of this population.

Opioids are the most effective broad-spectrum analgesics available and are considered the cornerstone of therapy for moderate-to-severe acute pain, but their long-term use in neuropathic pain is controversial. Particularly in light of the current opioid misuse epidemic happening in the United States, questions of benefit relative to harms associated with treatment are prominent.

Choosing therapy for neuropathic pain is challenging because of the large number of medications available to treat this condition and the potential differences in effectiveness and harms between medications. The objective of this report is to compare the effectiveness and safety of the drugs shown in Table 1 for neuropathic pain, and to provide evidence for potential alternatives to opioids.

Scope and Key Questions

1. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), memantine, the capsaicin patch, and the lidocaine patch for neuropathic pain?
2. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, and the lidocaine patch for neuropathic pain?
3. What is the comparative efficacy and effectiveness of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, and the lidocaine patch versus opioids for neuropathic pain?
4. What are the comparative harms of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, and the lidocaine patch versus opioids for neuropathic pain?
5. Are there subgroups of patients based on demographics, socioeconomic status, other medications, comorbidities, or pregnancy for which there are differences in benefits and

harms of anticonvulsants, tricyclic antidepressants, SNRIs, memantine, the capsaicin patch, the lidocaine patch, and opioids when used to treat neuropathic pain?

Methods Summary

We followed systematic review methodology developed for DERP and that are in accordance with current guidance for systematic reviews, for example, dual review of inclusion decisions, quality assessments and data abstraction. Detailed methods are available upon request. Literature searches were conducted through November 2017 (with a search for mementine studies in January 2018).

Inclusion Criteria

Populations: Adults with chronic (≥3 months in duration) neuropathic pain

Comparators

- Other neuropathic pain drugs
- Opioids (any, including long-acting, short-acting, tramadol, and codeine)

Study Designs

- Randomized controlled trials of at least 8 weeks duration
- Cohort or case-control study of harms
- Published indirect and network meta-analyses

Table 1. Included Drugs

Generic Name	Trade Name(s)	First Approval
Anticonvulsants		
Brivaracetam	Briviact®	02/18/2016
Eslicarbazepine acetate	Aptiom®	11/08/2013
Perampanel	Fycompa®	10/22/2012
Gabapentin Enacarbil	Horizant®	04/06/2011
Lacosamide	Vimpat®	10/28/2008
Pregabalin	Lyrica®, Lyrica CR®	12/30/2004
Oxcarbazepine	Oxtellar XR®, Trileptal®	01/14/2000
Levetiracetam	Keppra®, Keppra XR™, Roweepra®, Spritam®	11/30/1999
Topiramate	Trokendi XR®, Topamax®, Qudexy XR®	12/24/1996
Lamotrigine	Lamictal®, Lamictal CD®, Lamictal ODT®, Lamictal XR®	12/27/1994
Gabapentin	Gralise®, Neurontin®	12/30/1993
Valproic acid/ Divalproex	Depakote®, Depakote ER®, Depakene®, Depacon®	02/28/1978
Carbamazepine[a]	Carbatrol®, Epitol®, Equetro®, Teril®, Tegretol®, Tegretol® XR	03/11/1968
Phenytoin	Dilantin®, Dilantin®-125, Phenytek®	01/6/1953
N-Methyl-D-aspartate receptor antagonists		
Memantine	Namenda®, Namenda XR®	10/16/2003
Serotonin-norepinephrine reuptake inhibitors		
Levomilnacipran	Fetzima®	07/25/2013
Milnacipran	Savella®	01/14/2009
Desvenlafaxine	Khedezla®, Pristiq®	02/29/2008
Duloxetine	Cymbalta®	08/3/2004
Venlafaxine	Effexor XR®	10/20/1997
Tricyclic antidepressants		
Doxepin	Silenor™	03/17/2010
Protriptyline	Vivactil®	08/24/1995

Imipramine	Tofranil®	05/22/1984
Amitriptyline	Generic	11/21/1977
Nortriptyline	Pamelor®	08/01/1977
Desipramine	Norpramin®	11/20/1964
Topical analgesics		
Capsaicin	Qutenza®	11/16/2009
Lidocaine	Lidoderm®	03/19/1999

[a] An injectable form of carbamazepine (Carnexiv™) is available.
Discontinued drugs and formulations are not listed in the table.

Results

Overview

This systematic review evaluated non-opioid drugs to treat neuropathic pain. We included 13 randomized controlled trials (RCTs), 10 of pregabalin versus other included drugs and 1 systematic review with a network meta-analysis. We found only 1 trial of opioids and none on serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, the lidocaine patch or memantine. For details of included studies, please see the full report.

Key Findings

Neuropathic Pain Drugs compared with Opioids

- Nortriptyline and morphine SR were not found different on pain or adverse event outcomes after 2 weeks at the highest tolerated dose in a small, fair-quality RCT.

Comparisons of Anticonvulsant Drugs

- Pregabalin compared with gabapentin or gabapentin enacarbil in painful diabetic neuropathy
  - Pregabalin and gabapentin were not different in pain control or adverse events in 2 small, fair-quality RCTs.
  - A fair-quality trial of pregabalin and 3 doses of gabapentin enacarbil (or placebo) found inconclusive results - **gabapentin enacarbil 1200 mg daily and 3600 mg daily reduced pain significantly more than pregabalin (-2.55 vs. -1.66, P=0.02; -2.54 vs. -1.66, P=0.01)** while 2400 mg daily was not significantly different. Adverse events were frequent and similar between treatments.

Comparisons of Anticonvulsant Drugs with Antidepressant Drugs

- Pregabalin compared with duloxetine in painful diabetic neuropathy
  - Evidence was mixed, depending on the outcome measured. For reduction in pain of at least 50%, duloxetine was superior to pregabalin in a good-quality, 8-week RCT **(40.3% versus 27.8%, P<0.001)** (strength of evidence: low). However, there was no difference in mean change in pain (using visual analog scale of 0-100) in a fair-quality, 12-week trial. Adverse event withdrawals were infrequent in both trials.
- Pregabalin compared with amitriptyline
  - An unpublished fair-quality trial found no difference in pain control between treatments (strength of evidence: low). There was no difference in adverse event outcomes.
- Gabapentin compared with amitriptyline
  - Gabapentin reduced pain scores more than amitriptyline in a fair-quality, 12-week study in patients with diabetic neuropathy **(-1.9 vs. -1.3, P=0.026).**
  - There was no difference in pain control or adverse event withdrawals at 6 months in a fair-quality study of cancer patients with neuropathic pain.

Comparisons of Anticonvulsant Drugs with Topical Analgesics

- Capsaicin patch compared with pregabalin
  - Capsaicin patch and pregabalin were not significantly different in pain response at 8 weeks in a fair-quality trial in patients with peripheral neuropathy (strength of evidence: moderate). In the subgroup of patients with **post-traumatic nerve injury, significantly more had achieved 30% or more improvement in pain with capsaicin patch (53% vs. 41%, RR 1.31, 95% CI 1.02 to 1.68)**.
  - **Significantly fewer patients withdrew due to adverse events with capsaicin than with pregabalin (0% vs. 8.5%, RR 0.04, 95% CI 0.005 to 0.29)** (strength of evidence: low).

Conclusions

This systematic review evaluated non-opioid drugs to treat neuropathic pain. The strength of evidence for most outcomes within this report was low or insufficient, as data came from single studies and were imprecise. Most comparisons failed to show significant differences in outcomes related to pain control or adverse events between treatments. Studies failed to report on the use of rescue analgesia, and outcomes were reported differently across studies. Key findings, or outcomes for which there was data to assess the strength of evidence, are summarized below.

Pregabalin and gabapentin were not found to be different in either pain control or adverse events. Findings indicate that gabapentin enacarbil may be better for pain than pregabalin, but further studies are needed. Evidence was mixed in comparing pregabalin with duloxetine, with one study finding duloxetine to be superior in reducing pain, but another showing no difference in mean change in pain. Additional larger, head-to-head studies are needed. Gabapentin was found to reduce pain scores significantly more than amitriptyline. Capsaicin patch and pregabalin were not significantly different in pain response in patients with peripheral neuropathy (strength of evidence: moderate), but significantly fewer patients withdrew due to adverse events with capsaicin than with pregabalin (strength of evidence: low).

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