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Drug Class Update: Non-analgesics for Pain

Date of Review: March 2017 **Date of Last Review:** June 2011 (DERP)

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Evaluate recent evidence for alternatives to opiate medications such as antiepileptics, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine in managing chronic and neuropathic pain.

Research Questions:
1. What is the comparative effectiveness of antiepileptics, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and topical lidocaine for chronic non-cancer pain or neuropathic pain?
2. What are the comparative harms of antiepileptics, tricyclic antidepressants, SNRIs, and topical lidocaine for neuropathic pain or chronic pain?
3. Are there differences in effectiveness or harms of antiepileptics, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain?

Conclusions:
Efficacy
- Recent comparative trials do not reveal a clear preference for one class of medications over another for management of neuropathic pain.[1]
- Moderate quality evidence exists to support the use of pregabalin to manage central neuropathic pain.[2]
- Moderate quality evidence shows that duloxetine is an effective agent to manage chronic LBP.[3]
- Low quality evidence supports the safety and efficacy of desipramine and amitriptyline in management of DPN or post herpetic neuropathy (PHN).[4,5]
- Low quality evidence supports the efficacy of carbamazepine in trigeminal neuralgia, DPN, and post-stroke pain.[6]
- Moderate quality evidence shows no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in treatment of diabetic peripheral neuropathy (DPN).[7]
- Moderate quality evidence indicates little or no effect for lamotrigine, oxcarbazepine and topiramate for treatment of neuropathic pain.[1, 3, 4] There is insufficient evidence to demonstrate the efficacy of valproic acid, lacosamide, levetiracetam, and phenytoin in management of neuropathic pain.[2]
- There is insufficient evidence to evaluate the effect of antiepileptics to manage acute nonradicular low back pain (LBP).[3]
- There is insufficient evidence to support the use of topical lidocaine in mixed peripheral neuropathic pain.[10]
- There is insufficient evidence to support the use of milnacipran for management of neuropathic pain.[11]

Safety

- There is insufficient comparative evidence in patients with neuropathic pain or chronic pain to assess comparative safety.
- Moderate quality evidence revealed approximately 80% of participants experienced an adverse event with an antiepileptic, but about 70% of participants receiving placebo did as well. Withdrawals due to adverse events were much higher with antiepileptics than placebo.[2]
- Moderate quality evidence showed that adverse events experienced with gabapentin were significantly higher than with placebo (RR 1.25; 95% CI 1.2 to 1.3). Adverse events noted with gabapentin included somnolence, dizziness, peripheral edema and gait disturbances.[12]
- Low quality evidence showed that 65% of participants experienced at least one adverse event with carbamazepine, and 27% with placebo. For every 5 participants treated, 2 experienced an adverse event who would not have done so with placebo.[6]
- Almost 10% of participants in one low quality lamotrigine trial reported a skin rash (RR 1.4; 95% CI 1.01 -2.0; NNH 27; 95% CI 16-89).[9]
- Low quality evidence demonstrated that participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.[4]

Specific Populations

- There is insufficient evidence to identify differences in effectiveness or harms of antiepileptics, tricyclic antidepressants, SNRIs, and the lidocaine patch based on demographics, socioeconomic status, comorbidities, or drug-drug interactions, when used to treat neuropathic pain.

Recommendations:

- Revise prior authorization (PA) criteria as outlined in **Appendix 6** to restrict use to funded pain conditions and include separate PA criteria for the following medications:
    - Pregabalin
    - Milnacipran
    - Lidocaine Patch
    - Topiramate Extended Release (non-preferred products)
- Add quantity limit of 3 patches/24 hours for topical lidocaine patches which is the maximum approved daily dose to insure safe use.
- After comparison of costs in the executive session, make gabapentin tablets preferred.

Previous Conclusions:

- Overall, there is low to moderate evidence comparing benefits and harms of available drugs for neuropathic pain.
- The majority of available direct comparative evidence is in patients with either diabetic neuropathy or postherpetic neuralgia and included comparisons between amitriptyline or nortriptyline and gabapentin, pregabalin, or lamotrigine.
- There is insufficient comparative effectiveness evidence in patients with other types of neuropathic pain to assess comparative safety. Conclusions for efficacy were largely based from placebo-controlled trials and indirect analyses.
- In patients with diabetic neuropathy and postherpetic neuralgia, there is moderate evidence that there is not a statistically significant difference in response or withdrawal due to adverse events with gabapentin, pregabalin, and lamotrigine compared to tricyclic antidepressants and low strength evidence that there is no difference between oral pregabalin and the lidocaine patch.
- Low strength evidence based on indirect comparisons demonstrates that duloxetine, pregabalin, and gabapentin are superior to lacosamide and lamotrigine and there are no differences between pregabalin, duloxetine, and gabapentin or comparisons of lidocaine and amitriptyline or gabapentin.

Previous Recommendations:

- Include topical analgesics into current neuropathic pain PA criteria including Lidoderm patch and capsaicin 8% patch to restrict use to patients with postherpetic neuralgia who have failed or cannot tolerate oral therapy with gabapentin and TCA's.
- Designate gabapentin ER as a line extension of currently available gabapentin and as a non-preferred agent due no management demonstrated in evidence-based guidelines and alternative therapy with available comparative effectiveness evidence showing efficacy in neuropathic pain.

Background:

Chronic pain is defined by the International Association for the Study of Pain (IASP) as pain that typically last greater than 3 months or past the time of normal tissue healing.[14] A Medical Expenditure Panel survey completed in 2008 estimated that approximately 100 million adults in the United States (U.S.) were affected by chronic pain.[15] The costs of medical care for patients with a primary diagnosis of pain including headache, abdominal pain, chest pain and back pain ranged from $261 to $300 billion.[15] The IASP defines neuropathic pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system.[16] Neuropathic pain can be caused by injury, medical interventions (e.g., chemotherapy, surgery), or different diseases (e.g., diabetes, herpes zoster, or human immunodeficiency virus).[17] Opiates are frequently used to treat patients with persistent non-cancer pain despite minimal evidence to support their use. Multiple studies have been published that describe the harms of long-term opiate therapy in patients with chronic, non-cancer pain.[18] A recent retrospective study of Tennessee Medicaid patients compared the risk of death among chronic non-cancer patients taking long-acting opiates with patients taking an antiepileptic or low dose antidepressant for their analgesic effect.[19] The long-acting opioid group was followed up for a mean 176 days and had 185 deaths while the alternative treatment group was followed up for a mean 128 days and had 87 deaths.[19] The hazard ratio (HR) for mortality in the opioid cohort was 1.64 (95% CI, 1.26-2.12) with a risk difference of 68.5 excess deaths (95% CI, 28.2-120.7) per 10,000 person-years.[19] Given the adverse impact of prolonged long term opiate therapy, there is increased interest in alternative therapies to manage chronic non-cancer pain. The focus of this review will be on the comparative safety and effectiveness of non-analgesics used in practice to manage neuropathic and other forms of chronic pain, such as antidepressants, antiepileptics and topical lidocaine. **Appendix 2** lists the specific medications that were included in this review and identifies their status on the Oregon Health Plan (OHP) preferred drug list (PDL). **Table 1** in **Appendix 5** outlines pain conditions that are funded under the OHP. Skeletal muscle relaxants used to manage low back pain (LBP) will be reviewed separately.

Tricyclic antidepressants (TCAs), which include amitriptyline, imipramine, nortriptyline and desipramine, have been shown to be effective in treating a variety of painful neuropathic conditions like DPN, PHN, polyneuropathy, and post-stroke pain.[20] The analgesic effect of TCAs occurs at a lower dose than doses used to treat depression and with more rapid onset.[21] Studies have shown that the analgesic effects are independent of the presence of any changes in depression or mood state.[21] The primary mechanism of TCA action is through reuptake inhibition of norepinephrine and serotonin, which increases the activation of descending inhibitory pathways in the midbrain and spinal cord and contributes to their analgesic effect.[17] Of the TCAs, secondary amines, including nortriptyline and desipramine, are preferred because they provide pain relief that is comparable to amitriptyline while causing fewer side effects.[17] Serotonin and norepinephrine reuptake inhibitors (SNRIs), duloxetine and venlafaxine, have also shown efficacy in treating peripheral neuropathic pain and other chronic pain conditions.[17] Duloxetine has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of painful DPN, fibromyalgia, and chronic musculoskeletal pain.[22] Venlafaxine has approval for the treatment of depression, anxiety disorder, and panic disorder but does not have FDA approval for pain management.[23] Milnacipran, another SNRI, is approved for the treatment of fibromyalgia, but not for depression or other neuropathic pain conditions.[24] Of note, fibromyalgia is not an OHP-funded condition, so prior authorization (PA) criteria have been developed to restrict use of milnacipran for funded conditions.

The first antiepileptic used in clinical trials to treat a neuropathic pain disorder was carbamazepine. Prior to approval for seizures, carbamazepine was approved by the FDA for trigeminal neuralgia.[25] Carbamazepine acts to stabilize the inactivated state of voltage-gated sodium channels thereby decreasing the excitability of frequency-dependent neuronal activity of A-delta and C-fibers, thus suppressing spontaneous activity.[14] Carbamazepine and its derivative oxcarbazepine have continued to be used for the treatment of trigeminal neuralgia, but have not been shown to be as effective in treating other neuropathic pain disorders.[17] Gabapentin and pregabalin are structural analogs of the neurotransmitter gamma-aminobutyric acid (GABA). However, they do not inhibit GABA receptors; they inhibit calcium influx and consequently decrease the release of excitatory neurotransmitters which modulate pain.[26] Gabapentin and pregabalin have both been shown to be effective when compared with placebo in treating painful DPN, PHN, polyneuropathy, neuropathic cancer pain, central post-stroke pain, and spinal cord injury pain.[17] Other antiepileptic drugs such as topiramate, valproic acid, levetiracetam, zonisamide, tiagabine and lamotrigine have been studied for various neuropathic pain disorders; however, evidence of their effectiveness is lacking.[17] A 2007 systematic review of lamotrigine for acute and chronic pain concluded it does not have a place in the treatment of pain, given other more effective therapies.[15]

Lidocaine is a local anesthetic that blocks abnormal activity in sodium channels located on peripheral neurons in painful regions.[27] Topical lidocaine products are available as a cream, ointment or patch. Only 1-5% of the topical lidocaine dose is absorbed which produces an analgesic effect, but does not cause a complete sensory block.[27] The lidocaine patch is approved for relief of pain associated with PHN.[27] The FDA approval was based on one unpublished trial in a single dose study in 35 PHN patients whose pain intensity was monitored over 12 hours.[27] After reviewing the initial study, the FDA requested more data. Therefore, an additional open label, multiple dose, 2-week treatment trial was conducted in 32 subjects who had responded in the previous study. Statistically significant differences favoring the lidocaine patch over observation were noted in terms of time to exit from the trial (14 versus 3.8 days; $p < 0.001$).[27] A 2014 Cochrane review found insufficient evidence to support the use of topical lidocaine formulations (patch, cream, gel or spray) in mixed peripheral neuropathic pain.[10] This Cochrane review was included in the topical analgesic scan discussed at the January 2016 P and T committee meeting.[28]

A summary of recent head to head trials is included in **Table 2**. The head-to-head trials were primarily of amitriptyline, duloxetine, gabapentin, and pregabalin in patients with painful DPN. The comparative trials do not reveal a clear preference for one class of medications over another. Effectiveness outcomes utilized in these trials included patient pain response, use of rescue analgesics, speed and duration of response, relapse, and functional capacity. Both duloxetine and amitriptyline demonstrated efficacy in DPN.[29] Another study concluded was no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin in treating diabetic patients with DPN.[7] Amitriptyline and nortriptyline were shown to be equivalent for overall adverse effects and discontinuation rates in patients with DPN.[30] Another study showed the efficacy of venlafaxine, pregabalin, and carbamazepine in pain reduction in patients with diabetic neuropathy, and although pregabalin was shown to be superior to carbamazepine and venlafaxine in relieving pain, no significant superiority was shown between carbamazepine and venlafaxine.[31] In patients with DPN inadequately treated with gabapentin, switching to duloxetine instead of pregabalin may have provided better pain reduction.[32]

Dosing recommendations for non-opiate medications used in chronic pain management are outlined in **Appendix 3, Table 1**. Precautions and warnings for these medications are included in **Appendix 3, Table 2**. A summary of evidence supporting the use of these therapies in different pain conditions is described in **Appendix 3, Table 3**.

The interpretation of chronic pain trials is difficult due to a number of potential biases. Most of the trials are of short duration and include a small number of subjects.[33] The use of the "last observation carried forward" imputation method can bias results, often generating statistical significance when adverse event withdrawals are high.[33] Furthermore, the use of average pain scores can be misleading compared with responder analysis in which withdrawal is regarded as

non-response.[33] In addition to evaluating the risk of potential biases, it is difficult to compare studies because randomized controlled trials (RCTs) differ substantially in research design. Many older RCTs of TCAs are crossover trials, while newer medications have been assessed using a parallel group research design.[17] Also, recent trials have often used a run-in period and have required pain of at least moderate baseline severity.[17] The outcomes measured have also varied; newer RCTs have used measures such as daily numeric ratings of pain intensity and measures of health-related quality of life that were not collected in many older RCTs.[17] In general, most trials of effective treatments have found that less than 50% of patients achieve satisfactory pain relief.[17]

Utilization of the non-analgesics from July 1, 2016 through September 30, 2016 is described in **Appendix 5**. Because this information is based on claims data, it is not clear which diagnosis is associated with each claim. The antiepileptics and antidepressants may be prescribed for other reasons besides pain. The most commonly prescribed non-analgesic drug that might be used for pain was duloxetine, followed by gabapentin, amitriptyline, and venlafaxine. The requests for lidocaine patch were substantially less than the other 4 agents. In addition to total claims data, the reasons why fee for service clients may not have received medications are also described. Some patients lost eligibility while others may have received insurance coverage from another provider.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews

Overview of Antiepileptics for Neuropathic Pain

A 2013 Cochrane overview assessed the evidence for antiepileptics in treatment of neuropathic pain.[2] Ten Cochrane reviews were included in this assessment. Ninety-one studies including 17,955 subjects were included.[2] Antiepileptics studied for management of neuropathic pain included carbamazepine (n= 15 studies), gabapentin (n=29), lacosamide (n=6), lamotrigine (n=11), oxcarbazepine (n =4), pregabalin (n= 19), topiramate (n= 4), and valproic acid (n=3). Most of the studies were conducted over short durations (i.e., 6 weeks) with small sample sizes. All of the trials were randomized and double-blinded. The efficacy data for each painful condition was analyzed in 3 tiers, according to outcome and freedom from known sources of bias.[2] The first tier met current best standards; at least 50% pain intensity reduction over baseline was assessed as an outcome, the use of last observation carried forward (LOCF) for dropouts was not used, an intention-to-treat (ITT) analysis was completed, and parallel group studies had at least 200 participants lasting 8 weeks or more.[2] The second tier used data from at least 200 participants where one or more of the above conditions were not met.[2] The third tier of evidence related to data from fewer than 200 participants, or with several important methodological problems that limited interpretation.[2] This tier analysis was employed by the other authors in subsequent systematic reviews evaluating the efficacy of pharmacologic agents in neuropathic pain management.

No studies in the Cochrane overview reported top tier results. Second tier (moderate) evidence was available to assess gabapentin and pregabalin for efficacy in DPN and PHN.[2] Trials for gabapentin versus placebo in DPN utilized a wide range of doses from 600 to 3600 mg per day to reduce pain intensity by 50% from baseline (Risk Ratio (RR)1.8; 95% CI 1.4-2.2).[3] The calculated NNT was 5.8 (95% CI 4.3-9.0) based on data pooled from 4 studies with a total of 829 participants.[2] Similar results were noted when pregabalin 600 mg per day was compared to placebo for 50% pain reduction (RR 1.5; 95% CI 1.3-1.8) in 1005 subjects from 4 pooled trials.[2] There was less of an impact on 50% pain reduction observed when pregabalin 300 mg per day was compared to placebo (RR 1.3; 95% CI 1.1-1.6; NNT = 11; 95% CI 6.1-54) than was noted with gabapentin or pregabalin 600 mg.[2]

Relief of PHN with gabapentin required higher daily doses (1800-3600 mg) for at least a 50% reduction in pain intensity compared to placebo (RR = 1.7; 95% CI 1.3-2.2) with a NNT of 8 (95% CI 6-14) in 3 studies comprised of 892 subjects.[2] Pregabalin 300 mg and 600 mg once daily gave similar results relative to placebo in reducing pain intensity by 50% from baseline (RR 2.7; 95% CI 1.9-4.0 and RR 2.8; 95% CI 2.0-3.9, respectively). Estimated NNT for pregabalin 300 mg per day was 6 (95% 4-9) and 4 (95% CI 4-6) for the 600 mg daily dose.[2] There were data from approximately 500 patients pooled for the pregabalin PHN analysis. For relief of central neuropathic pain, the only data available was with pregabalin 600 mg once daily. In 2 studies with a total of 176 patients, pregabalin compared to placebo showed a 50% pain reduction with a RR of 3.6 (95% CI 1.5-8.4) and NNT of 6 (95% CI 4-14).[2]
No second tier evidence was found to evaluate antiepileptics in treatment of trigeminal neuralgia or HIV-related neuropathic pain. For other antiepileptic drugs, there was very little evidence to evaluate efficacy (valproic acid) or low quality evidence subject to a number of biases that overestimated efficacy (carbamazepine).[2] Moderate quality evidence indicated little or no effect for lamotrigine, oxcarbazepine and topiramate in treatment of neuropathic pain.[2] There was insufficient evidence of efficacy for valproic acid, lacosamide, levetiracetam, and phenytoin in treatment of neuropathic pain.[2] Evidence for lacosamide was too unreliable to make any conclusions.[2] There were no effective trials that evaluated levetiracetam or phenytoin in management of neuropathic pain.

Withdrawals due to adverse events were much higher with antiepileptics than placebo except for carbamazepine, where studies were of short duration, and for the low dose of 150 mg daily of pregabalin.[2] Numbers needed to harm (NNH) decreased as doses increased for pregabalin and locasamide. About 80% of participants experienced an adverse event with an antiepileptic, but about 70% of participants receiving placebo did as well.[2]

Carbamazepine for Neuropathic Pain
A 2014 Cochrane systematic review updated a 2011 report which evaluated carbamazepine for acute and chronic pain in adults.[6] The update used higher standards of evidence than the earlier review, which resulted in the exclusion of five studies that were previously included.[6] However, no additional studies were identified for inclusion. Ten studies evaluated trigeminal neuralgia, DPN, and post-stroke pain in 480 subjects.[6] Nine studies used a cross-over design, and one trial used a parallel group design. Most of the studies were of short duration, lasting 4 weeks or less. The studies were graded as low quality due to relatively short trial periods, poorly defined outcomes, incomplete reporting, and small sample size.[6] The evidence for this review was compiled by the same authors as the 2013 Cochrane review of antiepileptic drugs in neuropathic pain. Consequently, the same 3 tiers of evidence were used to evaluate outcomes as previously described. No study provided first or second tier evidence for an efficacy outcome. Third tier (low quality) evidence from 4 trials showed carbamazepine generally provided better pain relief than placebo in trigeminal neuralgia, DPN, and post stroke patients with pain. At least 50% pain reduction from baseline for carbamazepine 100 mg to 2400 mg daily compared to placebo resulted in a RR of 6.5 (95% CI 3.4 -12) with a NNT of 2 (95% CI 2-3).[6] In the 4 studies, 65% of participants experienced at least one adverse event with carbamazepine, and 27% with placebo. Reported adverse events included blood dyscrasias, rash, life threatening cutaneous reactions, and impaired mental and motor function.[6] For every 5 participants treated, 2 experienced an adverse event who would not

have done so with placebo.[6] This systematic review provides low quality evidence to support the use of carbamazepine in treatment of trigeminal neuralgia, DPN, and post-stroke pain.

Oxcarbazepine for Neuropathic Pain

A 2013 Cochrane review focused on the safety and efficacy of oxcarbazepine in treatment of neuropathic pain.[8] Four multi-centered, randomized, placebo-controlled, double-blind trials with a total of 779 participants were eligible for inclusion.[8] All 4 studies were funded by the manufacturer. Three of them investigated oxcarbazepine in people with painful DPN (n=634) and one was a trial of oxcarbazepine for neuropathic pain due to radiculopathy (n=145).[8] The authors graded the evidence as moderate quality due to the large amount of incomplete outcome data leading to possible attrition bias, although they acknowledged the studies were well designed due to adequate blinding and randomization.[8] Results for painful DPN showed that compared to baseline, the proportion of participants who reported a 50% or 30% reduction of pain scores after 16 weeks of treatment was significantly higher in the oxcarbazepine group than the placebo group [50% pain reduction: RR 1.91 ; 95% CI 1.08 - 3.39; NNT 6; 95% CI 4 to 41 and 30% reduction: RR 1.57; 95% CI 1.01 to 2.44 ; NNT 7; 95% CI 4 to 114].[8] However, both results were based on data from a single positive trial (n=146) since the 2 negative trials did not provide data that could be included in a meta-analysis.[8] For participants with neuropathic pain due to radiculopathy, the trial demonstrated no significant efficacy for oxcarbazepine.[8] Although trial reports stated that most adverse effects were mild to moderate in severity, the proportion of events leading to withdrawals was statistically higher in the oxcarbazepine group than in the placebo group both for painful diabetic neuropathy (RR 3.86; 95% CI 2.29 - 6.40) and radiculopathy (RR 2.84; 95% CI 1.55 - 5.23).[8] There was insufficient evidence to determine the efficacy or safety of oxcarbazepine for other kinds of neuropathic pain. The authors concluded more well designed RCTs are needed.[8]

Lamotrigine for Neuropathic Pain

A 2013 Cochrane review updated a previous 2007 report that evaluated lamotrigine for acute and chronic pain.[9] This updated review did not identify any new additional studies but used higher standards of evidence than previous reports.[9] Twelve studies were included involving 1,511 participants with chronic neuropathic pain: central post-stroke pain (n= 1 trial), chemotherapy-induced neuropathic pain (n=1), diabetic neuropathy (n=4), HIV-related neuropathy (n=2), mixed neuropathic pain (n=2), spinal cord injury-related pain (n=1), and trigeminal neuralgia (n=1).[9] Study duration was 2 weeks in one study and at least 6 weeks in the remainder; 8 trials were of 8-week duration or longer.[9] The authors used 3 tiers to evaluate the quality of evidence as previously described. No study provided first-tier evidence for an efficacy outcome. The included studies were rated as second (moderate quality) to third (low quality) tier evidence because of LOCF imputation and small study size.[9] There was no convincing evidence that lamotrigine is effective in treating DPN at doses of 200 mg to 400 mg daily as the relative risk for 50% pain reduction was not significant (RR = 1.1; 95% CI 0.82 to 1.4).[9] Almost 10% of participants in the lamotrigine arm reported a skin rash (RR 1.4; 95% CI 1.01 -2.0; NNH 27; 95% CI 16-89).[9] The authors concluded that given the availability of more effective treatments including antiepileptics and antidepressant medicines, lamotrigine does not have a significant place in therapy based on the available evidence.[9] The adverse effect profile of lamotrigine is also of concern.[9]

Gabapentin for Neuropathic Pain

A 2015 Canadian Agency for Drugs and Technologies in Health (CADTH) report evaluated the clinical efficacy and safety of gabapentin compared with placebo in adults with neuropathic pain.[34] Seven publications including 6 systematic reviews and 1 RCT met criteria for inclusion in the CADTH report. Most of the patients included in the trials had either PHN or DPN while a small proportion (11%) had mixed neuropathic pain or nerve injury pain. For PHN, 1,816 patients were included in placebo controlled trials with gabapentin. Thirty-four percent of patients treated with gabapentin showed substantial benefit (defined as > 50% pain intensity reduction) compared to 21% of patients that received placebo (RR 1.6; 95% CI 1.3 to 1.9) with an NNT of 8 (95% CI 6 to 12). [34] For DPN, 1,277 patients

were included in the placebo controlled gabapentin trials. Thirty-eight percent of patients treated with gabapentin showed substantial benefit compared to 21% of placebo treated patients (RR 1.9; 95% CI 1.5 to 2.3) with an NNT of 6 (95% CI 5 to 9).[34] Withdrawals due to adverse events (AEs) were significantly higher and withdrawals due to lack of efficacy significantly lower with gabapentin compared to placebo for the various conditions considered together (RR 1.4; 95% CI 1.1 to 1.7 for withdrawal due to AEs and RR 0.5 95% CI 0.3 to 0.8 for withdrawal due to lack of efficacy).[34] Also, considering the various conditions together, the adverse events experienced with gabapentin were significantly higher than with placebo (RR 1.25; 95% CI 1.2 to 1.3).[34] Adverse events included somnolence, dizziness, peripheral edema and gait disturbances.

Milnacipran for Neuropathic Pain

A 2015 Cochrane review updated an earlier 2012 report that assessed the analgesic efficacy and associated adverse events of milnacipran for chronic neuropathic pain in adults.[11] Twenty-seven studies were identified, but only 1 short-term, low quality study of 40 participants met inclusion criteria for the updated review.[11] The subjects had a history of LBP with pain radiating to the legs or buttocks. The study was rated low quality due to inadequate details describing randomization, concealment of allocation, and blinding. The study found no difference in pain scores between milnacipran 100 mg to 200 mg daily or placebo after 6 weeks.[11] Adverse event rates were similar between treatments in this trial. There is insufficient evidence to support the use of milnacipran in managing neuropathic pain.

Desipramine for Neuropathic Pain

A 2014 Cochrane review examined 5 studies that treated 177 participants with DPN or PHN.[4] Four studies used a cross-over design, and one used a parallel group design.[4] Desimpramine doses ranged from 100 mg to 150 mg once daily following titration. Comparators were placebo in 3 studies, fluoxetine, clomipramine (one study each), and amitriptyline (2 studies), and treatment ranged from 2 to 6 weeks.[4] All studies had one or more source of potential bias. The review used the same methods to evaluate the quality of evidence as previous systematic reviews evaluating management of neuropathic pain. No study provided first or second tier evidence for any outcome. No data were available on the proportion of people with at least 50% or 30% reduction in pain, so pooling of data was not possible.[4] Third tier (low quality) evidence in individual studies indicated some improvement in pain relief with desipramine compared with placebo.[4] These data were derived primarily from group mean data and completer analyses in small, short duration studies so major bias was possible. There were too few participants in comparisons of desipramine with another active treatment to draw any conclusions.[4] All studies reported some information about adverse events, but reporting was inconsistent and fragmented. Very low quality evidence demonstrated that participants taking desipramine experienced more adverse events, and a higher rate of withdrawal due to adverse events, than did participants taking placebo.[4] Reported adverse effects included syncope, jitteriness, hypotension, tremor, confusion, and sedation. This review found little evidence to support the use of desipramine to treat neuropathic pain. There was very low quality evidence of benefit and harm, but this came from studies that were methodologically flawed and potentially subject to major bias.[4]

Amitriptyline for Neuropathic Pain

The most recent Cochrane review evaluating the safety and efficacy of amitriptyline in neuropathic pain was published in 2015.[35] The review included 15 studies from a previous 2012 review and 2 new studies. Types of neuropathy included painful DPN (n = 5 studies), PHN (n=5), spinal cord injury (n =2), cancer-related pain (n=2), mixed neuropathic pain (n =1), HIV neuropathy (n=1), and post-stroke pain (n=1).[35] Eight cross-over studies with 302 participants had a median of 36 participants, and 9 parallel group studies with 1,040 participants had a median of 84 participants.[35] Study quality analysis was completed using a 3 tier rating as previously described. Most studies were at high risk of bias due to small sample size.[35] There was no first-tier or second-tier evidence for amitriptyline in treatment for any neuropathic pain condition. Only third-tier (low quality) evidence was available. Combining results from the DPN, PHN and mixed neuropathic

pain trials (n=382, 4 trials), benefit for amitriptyline was found compared with placebo (RR 2.0; 95% CI 1.5 to 2.8), with an NNT of 6 (95% CI 4 to 10).[35] More participants who received amitriptyline experienced at least one adverse event compared to placebo (55% vs. 36%, respectively; RR 1.5; 95% CI 1.3 to 1.8).[35] The NNH for one additional harmful outcome was 5.2 (95% CI 3.6 to 9.1).[35] Serious adverse events were rare. Adverse events and early study withdrawal rates were not different, but were rarely reported.[35] This systematic review was unable to find high or moderate quality evidence to support the use of amitriptyline in management of neuropathic pain. Low quality evidence supports the efficacy of amitriptyline in management of DPN, PHN and mixed neuropathic pain.

Duloxetine for Treating Painful Neuropathy or Chronic Pain

A 2014 Cochrane review updated a 2010 assessment of the benefits and harms of duloxetine in treating painful neuropathy and chronic pain.[36] The reviewers identified 18 trials which included 6,407 subjects. The different types of pain included DPN (n=8 studies), fibromyalgia (n=6), depression with painful physical symptoms (n=3) and central neuropathic pain (n=1). The reviewers graded the evidence as moderate quality, although significant attrition and imputation methods increased risk of bias. In addition, nearly every study was sponsored by the drug manufacturer.[36] Duloxetine 60 mg once daily was shown to be effective compared to placebo in treatment of painful DPN, with a RR for ≥ 50% pain reduction at 12 weeks of 1.73 (95% CI 1.44 to 2.08).[36] The estimated NNT was 5 (95% CI 4 to 7).[36] Duloxetine 60 mg once daily was also effective when compared to placebo for 50% pain reduction from baseline in patients with painful conditions and depression (RR 1.37, 95% CI 1.19 to 1.59; NNT 8, 95% CI 5 to 14).[36] When compared to placebo in 48 patients with central neuropathic pain, duloxetine showed no effect in improving pain over 12 weeks as measured on a 1-10 VAS (Mean Difference = -1.0, 95% CI -2.05 to 0.05).[36] In all conditions, adverse events were common in both treatment and placebo arms but more common in the treatment arm, with a dose-dependent effect.[36] The most common adverse effects included nausea, headache, dry mouth, constipation, sedation or dizziness. Most adverse effects were minor, but 16% of participants stopped the drug due to adverse effects.[36] Serious adverse events were rare. Moderate quality evidence supports the use of duloxetine 60 mg once daily in management of DPN.

Noninvasive Treatments for Low Back Pain

A 2016 AHRQ report of noninvasive treatments for LBP evaluated systematic reviews of pharmacologic treatments for nonradicular or radicular LBP.[3] Most of the trials enrolled patients with pain symptoms of at least moderate intensity (> 5 on a 0-10 numeric rating scale for pain).[3] Pain intensity was the most commonly reported outcome, followed by back-specific function. Pharmacological treatments included nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opiates, muscle relaxants, antiepileptics, and antidepressants.[3] For LBP, one systematic review found no differences in pain between TCAs and placebo (4 trials; Standardized Mean Difference (SMD) = -0.10; 95% CI -0.51 to 0.31; I^2 = 32%).[3] Moderate quality evidence showed antidepressants were associated with high risk of adverse events compared with placebo, although there was no difference in the risk of serious adverse effects.[3] Three placebo-controlled trials of moderate quality evaluated duloxetine in management of chronic LBP and found duloxetine was associated with lower pain intensity (differences: 0.58 to 0.74 on a 0-10 scale) and better function (differences 0.58 to 0.74 on the Brief Pain Inventory-Interference on a 0 -10 scale) than placebo.[3] No studies compared TCAs with duloxetine. There was insufficient evidence to evaluate the effect of antiepileptics on controlling acute nonradicular LBP.[3]

New Guidelines

International Association for the Study of Pain

In 2015 IASP funded a neuropathic pain guideline update supported by evidence compiled through a systematic review and meta-analysis.[37] Evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification.[38] The target population included patients of any age with neuropathic pain associated with diabetes, herpes, surgery, amputation, stroke, spinal cord injury, HIV, or multiple sclerosis. Low back pain and trigeminal neuralgia were not assessed in this publication. The primary effect measurements were 30% or 50% pain reduction from baseline. A total of 229 reports published from January 1966 through April 2013 met inclusion criteria developed by the 5 reviewers. Approximately half of the trials were conducted in patients with DPN or PHN. The NNT for most of the positive trials ranged from 4 to 10 patients, which reinforces the modest effect in pain reduction observed with these drugs.[37] Previous IASP recommendations supported the use of TCAs, pregabalin, gabapentin and lidocaine patches as first line agents.[20] This recent update now includes duloxetine as a first line agent and no longer recommends lidocaine patches as first line therapy due the weak quality of evidence.[37] **Table 1** summarizes the recent IASP recommendations.

Table 1. IASP recommendations of drugs that can be used to manage neuropathic pain[37]

	Total Daily Dose	**Recommendations**	**Quality of Evidence**
Strong Recommendations for Use			
Gabapentin	1200-3600 mg in 3 divided doses	First line	High
Pregabalin	300- 600 mg in 2 divided doses	First line	High
Duloxetine	60 -120mg once daily	First line	High
Venlafaxine	150-225mg once daily	First line	High
Tricyclic Antidepressants*	25-150mg once daily or in 2 divided doses	First line	Moderate
Weak Recommendations for Use			
Lidocaine Patches	One to three patches to the region of pain once a day for up to 12 h	Second line – peripheral neuropathic pain only (not central pain)	Low
Inconclusive Recommendations for Use			
Carbamazepine			
Lacosamide			
Lamotrigine			
Oxcarbazepine			
Topiramate			
***** Amitriptyline and imipramine are not recommended at doses greater than 75 mg/day in adults aged 65 years and older because of major anticholinergic and sedative side-effects and potential risk of falls.[13]			

National Institute for Health and Care Excellence (NICE)

The NICE guidelines were updated in December 2014 and are similar to the IASP recommendations.[39] The guideline development group tasked with making recommendations categorized neuropathic pain into 3 broad types: central neuropathic pain, peripheral neuropathic pain and trigeminal neuralgia. The reviewers identified 115 studies with a total of 18,087 subjects for inclusion in the review. Quality of evidence was rated according the GRADE classification.[40] Primary outcomes measures included 30% or 50% reduction in pain intensity. The treatment recommendations are as follows:

- First line drugs include amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain, except for trigeminal neuralgia.[39]
- If initial treatment is not tolerated, try one of the remaining 3 drugs and consider switching again if the second and third drugs tried are also not effective or not tolerated.[39]
- Carbamazepine is recommended as initial treatment for trigeminal neuralgia.[39]
- Treatments that should not be used include lacosamide, lamotrigine, levetiracetam, oxcarbazepine or topiramate.[39]

Randomized Controlled Trials:

A total of 229 citations were manually reviewed from the initial literature search. After further review, 218 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 11 trials are summarized in the table below.

Table 2. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Boyle J et al.[7]

RCT, DB, PG

4 weeks</td>
<td>Pregablin 150 mg BID x 14 days followed by 300 mg BID x 14 days

Vs

Amitriptyline 25 mg BID x 14 days followed by 25 mg qam and 50 mg qhs x 14 days

Vs

Duloxetine 60mg qam x 14 days followed by 60 mg BID x 14 days

Vs

Placebo</td>
<td>Adults ≥ 18 y with DPN with LANSS score > 12 in T1 and T2 DM

N=83</td>
<td>Subjective pain as assessed by the VAS and BPI on Day 1, Day 14 and Day 28</td>
<td>Individual treatments effect on VAS and BPI compared to placebo[7]
<table>
<tr><th>Intervention</th><th>Mean Score on Visual Analog Scale (SE)</th><th>BPI Severity (SE)</th></tr>
<tr><td>Placebo</td><td>16.8 (2.0)</td><td>3.1 (0.4)</td></tr>
<tr><td>Pregablin 150mg BID</td><td>13.5* (2.1)</td><td>2.3* (0.4)</td></tr>
<tr><td>Pregablin 300mg BID</td><td>13.2 (1.7)</td><td>2.4 (0.4)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Placebo</td><td>29.6 (2.3)</td><td>3.5 (0.4)</td></tr>
<tr><td>Amitriptyline 25 mg BID</td><td>22.3 **(2.1)</td><td>2.7*(0.4)</td></tr>
<tr><td>Amitriptyline 25mg QAM and 50mg QHS</td><td>23.6 (2.4)</td><td>2.6 (0.4)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Placebo</td><td>23.3 (2.5)</td><td>3.4 (0.5)</td></tr>
<tr><td>Duloxetine 60mg Daily</td><td>16.3** (2.3)</td><td>2.5** (0.4)</td></tr>
<tr><td>Duloxetine 60mg BID</td><td>13.2***(2.2)</td><td>2.2 * (0.4)</td></tr>
<tr><td colspan="3">p < 0.05, ** p < 0.01, ***p< 0.001</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Kaur, H et al.[29]

RCT, DB, CO

6 wks for each drug</td>
<td>Amitriptyline 10, 25 or 50 mg QHS for 6 wks

Vs
Duloxetine 20, 40 or 60 mg QHS for 6 wks</td>
<td>Adults > 18- 75 y with T2 DM and with DPN > 1 month

N = 58</td>
<td>Reduction in the median pain score from baseline as assessed by VAS (numeric scale of 0-100)</td>
<td>Median VAS scores for each drug at baseline and 6 weeks[29]

<table>
<tr><th>Median VAS Pain Score</th><th>Amitriptyline</th><th>Duloxetine</th></tr>
<tr><td>Baseline</td><td>68</td><td>80</td></tr>
<tr><td>Week 6</td><td>50</td><td>30</td></tr>
<tr><td>P value (baseline to 6 weeks</td><td>P < 0.001</td><td>P < 0.001</td></tr>
</table>
</td>
</tr>
<tr>
<td>Razazian N et al.[31]

RCT, DB, PG

4 wks</td>
<td>Pregabalin 75 mg daily x 7 days followed by 75 mg Q12h x 3 wks

Vs

Venlafaxine 75 mg daily x 7 days followed by 150mg daily x 3 wks
Vs

Carbamazepine 100 mg q12h x 7 days followed by 200 mg q12h x 3 wks</td>
<td>Adults ≥ 18 y with T1 or T2 DM with DPN > 3 months and VAS > 40mm

N = 257

33 (~ 13%) patients withdrew due to adverse effects</td>
<td>Mean subjective pain scores as analyzed by VAS on days 2, 7, 14, and 35.</td>
<td>Mean VAS scores in treatment groups over time[31]

<table>
<tr><th></th><th>Baseline</th><th>Day 2</th><th>Day 7</th><th>Day 14</th><th>Day 35</th><th>p-value**</th></tr>
<tr><td>Carbamazepine</td><td>74.5</td><td>69.4</td><td>63.4</td><td>40.2</td><td>39.6</td><td>0.0001</td></tr>
<tr><td>Pregablin</td><td>82.3</td><td>80.2</td><td>69.7</td><td>35.6</td><td>33.4</td><td>0.0001</td></tr>
<tr><td>Venlafaxine</td><td>74.5</td><td>70.2</td><td>65.5</td><td>48.0</td><td>46.6</td><td>0.0001</td></tr>
<tr><td>p-value*</td><td>0.0001</td><td>0.0001</td><td>0.007</td><td>0.0001</td><td>0.0001</td><td></td></tr>
</table>
*One way ANOVA - pregabalin compared to carbamazepine and venlafaxine
**Repeated measurement ANOVA
</td>
</tr>
<tr>
<td>Tanenberg RJ et al.[41]

Phase 4, MC, OL, randomized, noninferiority

12 wks</td>
<td>Duloxetine 30 mg daily x 1 wk followed by 60 mg daily

Vs

Pregablin 50 mg po TID x 1 wk followed by 100 mg TID
*(Germany, Puerto Rico, US)

*Canada: Pregablin 75 mg BID x 1 wk followed by 150 mg BID

*Dosing varied by country depending on the prescribing recommendations for each nation</td>
<td>Adults > 18 y with T1 or T2 DM and DPN treated with gabapentin 900 mg/day > 5 weeks with an inadequate response to therapy (daily pain score > 4 on a scale of 1-10)

N = 407</td>
<td>To determine whether duloxetine is noninferior to pregabalin in the treatment of pain associated with DPN. Evaluated by improvement in the weekly mean of a daily 24-hour pain diary on a 0-10 point scale (0 = no pain; 10 = worst possible pain) from baseline to week 12.

(125 (31%) patients withdrew due to adverse effects, lack of efficacy, withdrawal of consent, protocol violation, or loss to follow up)</td>
<td>Changes in weekly mean of daily pain diary ratings in the ITT population[41]

<table>
<tr><th></th><th>Duloxetine</th><th>Pregabalin</th><th>Treatment Difference</th></tr>
<tr><td>Mean change in daily pain score</td><td>-2.6</td><td>-2.1</td><td>0.49
95% CI = -0.05 to 1.04
p = 0.08</td></tr>
</table>

Noninferiority would be declared if the mean improvement for duloxetine was no worse than the mean improvement for pregabalin, within statistical variability, by a margin of 0.8 unit.
</td>
</tr>
<tr>
<td>Tesfaye S et al.[32]

MC, RCT, DB, PG

8 wks initial therapy followed by additional 8</td>
<td>Phase 1: Initial therapy
Duloxetine 60 mg daily x 8 wks (Groups 1, 2)

Vs

Pregabalin 300 mg daily x 8 wks (Groups 3, 4)</td>
<td>Age > 18 y with T1 or T2 DM DPN > 3 mo not responding to standard doses of duloxetine or pregabalin and pain score ≥ 4 on BPI-MSF</td>
<td>24-hour average pain change in between high dose monotherapy or combination therapy as evaluated on BPI-MSF from baseline to week 8 or week 16</td>
<td>Phase 1 and Phase 2: Pain Reduction in BPI-MSF 24 hour average pain[32]

<table>
<tr><th></th><th>Number</th><th>Number (%) of responders</th><th>P value</th></tr>
<tr><td colspan="4">≥ 50% reduction in BPI-MSF</td></tr>
<tr><td>Duloxetine 60 mg /day (week 8)</td><td>375</td><td>151 (40.3)</td><td>-</td></tr>
<tr><td>Pregabalin 300 mg/day (week 8)</td><td>374</td><td>104 (27.8)</td><td>-</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>wks for non-responders</td>
<td>Phase 2: Nonresponders - Combination/high-dose therapy

Duloxetine 120 mg daily (Group 1)
Vs
Duloxetine 60 mg daily Pregabalin 300 mg daily (Groups 2, 3)
Vs
Pregabalin 600 mg daily (Group 4)</td>
<td>Phase1 : Initial therapy
n = 804

Phase 2: Non-responders: Combination/high dose therapy
n = 343</td>
<td></td>
<td>
<table>
<tr><td colspan="3">Comparison: Duloxetine vs pregabalin</td><td>< 0.001</td></tr>
<tr><td>Combination Therapy -Duloxetine 60 mg/day and Pregabalin 300 mg/day (week 16)</td><td>165</td><td>86 (52.1)</td><td>-</td></tr>
<tr><td>High Dose Monotherapy – Duloxetine 120 mg/day OR Pregabalin 600 mg/day (week 16)</td><td>163</td><td>64 (39.3)</td><td>-</td></tr>
<tr><td colspan="3">Comparison: combination vs high dose therapy</td><td>0.068</td></tr>
<tr><td colspan="4">≥ 30% reduction in BPI-MSF</td></tr>
<tr><td>Duloxetine 60 mg /day (week 8)</td><td>375</td><td>195 (52.0)</td><td>-</td></tr>
<tr><td>Pregabalin 300 mg/day (week 8)</td><td>374</td><td>138 (36.0)</td><td>-</td></tr>
<tr><td colspan="3">Comparison: Duloxetine vs pregabalin</td><td><0.001</td></tr>
<tr><td>Combination Therapy -Duloxetine 60 mg/day and Pregabalin 300 mg/day (week 16)</td><td>165</td><td>102 (61.8)</td><td>-</td></tr>
<tr><td>High Dose Monotherapy – Duloxetine 120 mg/day OR Pregabalin 600 mg/day (week 16)</td><td>163</td><td>91 (55.8)</td><td>-</td></tr>
<tr><td colspan="3">Comparison: combination vs high dose therapy</td><td>0.565</td></tr>
</table>
</td>
</tr>
<tr>
<td>Mishra S et al.[41]

RCT, DB, PC

4 wks</td>
<td>Amitriptyline 50 mg daily x 1 wk followed by 75 mg daily x 1 wk, followed by 100 mg daily x 2 weeks

Vs

Gabapentin 900 mg daily x 1 wk; 1200 mg daily x 1 wk; 1800 mg daily in divided doses x 2 wks

Vs
Pregabalin 150 mg daily x 1 wk; 300 mg daily x 1 wk; 300mg BID x 2 weeks

Vs

Placebo</td>
<td>Adults with cancer related neuropathic pain

N = 120</td>
<td>Change in VAS value as compared to baseline measured each week for 4 weeks</td>
<td>Comparison of pain score in different groups at different time periods.[41]
<table>
<tr><td></td><td>Mean VAS</td><td>P value</td></tr>
<tr><td>Amitriptyline – week 1</td><td>7.8</td><td></td></tr>
<tr><td>Amitriptyline – week 2</td><td>7</td><td></td></tr>
<tr><td>Amitriptyline – week 3</td><td>4.9</td><td></td></tr>
<tr><td>Amitriptyline – week 4</td><td>3.2</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Gabapentin – week 1</td><td>7.5</td><td></td></tr>
<tr><td>Gabapentin – week 2</td><td>6.2</td><td></td></tr>
<tr><td>Gabapentin – week 3</td><td>5</td><td></td></tr>
<tr><td>Gabapentin – week 4</td><td>3.07</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Pregabalin – week 1</td><td>7.8</td><td></td></tr>
<tr><td>Pregabalin – week 2</td><td>6.2</td><td></td></tr>
<tr><td>Pregabalin – week 3</td><td>4.2</td><td></td></tr>
<tr><td>Pregabalin – week 4</td><td>2.5</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Placebo – week 1</td><td>7.47</td><td></td></tr>
<tr><td>Placebo – week 2</td><td>6</td><td></td></tr>
<tr><td>Placebo – week 3</td><td>4.3</td><td></td></tr>
<tr><td>Placebo – week 4</td><td>3.4</td><td></td></tr>
<tr><td colspan="3"></td></tr>
<tr><td colspan="2">Comparison: Pregabalin to Amitriptyline Week 3</td><td>p = 0.003</td></tr>
<tr><td colspan="2">Comparison: Pregabalin to Amitriptyline Week 4</td><td>p = 0.024</td></tr>
<tr><td colspan="2">Comparison: Pregabalin to Gabapentin Week 4</td><td>P = 0.042</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Liu WQ et al.[42]

Randomized, OL, flexible dosing

6 mos</td>
<td>Amitriptyline monotherapy 10, 25, or 50 mg (at baseline and 3 months), 10, 25, 50, or 100 mg (at 6 months)

Vs

Amitriptyline adjuvant therapy 10, 25, or 50 mg (at baseline and 3 months), 10, 25, 50, or 100 mg (at 6 months)

Vs

Nortriptyline monotherapy 12.5, 25, 50, or 100 mg (at baseline, 3, and 6 months)

Vs

Nortriptyline adjuvant therapy 12.5, 25, 50, or 100 mg (at baseline, 3, and 6 months)

Vs
No pharmacological therapy (control)</td>
<td>Adults with peripheral neuropathy due to different etiologies enrolled in a tertiary care neuromuscular clinic.

N = 228</td>
<td>Quantitative adverse effects and discontinuation rates.</td>
<td>
<table>
<tr><th>Drug</th><th colspan="4">Amitriptyline</th><th colspan="4">Nortriptyline</th></tr>
<tr><th>Inter-vention</th><th colspan="2">Monotherapy N=42</th><th colspan="2">Adjuvant N= 47</th><th colspan="2">Monotherapy N = 50</th><th colspan="2">Adjuvant N = 56</th></tr>
<tr><th>Time</th><th>3 mos</th><th>6 mos</th><th>3 mos</th><th>6 mos</th><th>3 mos</th><th>6 mos</th><th>3 mos</th><th>6 mos</th></tr>
<tr><td>Number of Dropouts</td><td>6</td><td>16</td><td>7</td><td>13</td><td>12</td><td>13</td><td>11</td><td>15</td></tr>
<tr><td>Dry Mouth</td><td>5</td><td>5*</td><td>7</td><td>8</td><td>7</td><td>11*</td><td>10</td><td>12</td></tr>
<tr><td>Sedation</td><td>19</td><td>22</td><td>24</td><td>26</td><td>20</td><td>20</td><td>22</td><td>23</td></tr>
<tr><td>Dizziness</td><td>6</td><td>6</td><td>8</td><td>8</td><td>8</td><td>8</td><td>12</td><td>12</td></tr>
<tr><td>Fatigue</td><td>7</td><td>9</td><td>6</td><td>7</td><td>4</td><td>6</td><td>4</td><td>5</td></tr>
<tr><td>Weight Gain</td><td>9*</td><td>11*</td><td>10*</td><td>12*</td><td>1</td><td>1</td><td>4</td><td>6</td></tr>
</table>
*A significant difference with ANOVA testing between amitriptyline and nortriptyline cohorts ($P < 0.05$).
</td>
</tr>
<tr>
<td>Holbech JV et al.[42]

RCT,DB, PC,CO, MC

5 weeks for each of the 4 arms</td>
<td>Imipramine 75 mg daily (age > 70 y, 25 mg daily) x 5 wks

Vs

Pregabalin 150 mg BID (age > 70, 75mg BID) x 5 wks

vs

Imipramine 75 mg daily + Pregabalin 300 mg daily x 5 wks

Vs

Placebo x 5 wks</td>
<td>Adults > 20-85 y with painful polyneuropathy > 6 m of different etiologies with a pain rating of ≥ 4 on a NRS scale of 0-10

N = 73 randomized to medication

48 patients completed the trial</td>
<td>Effect on median weekly pain scores from baseline to week 5 using a NRS from 0 to 10. Modified ITT and PP analysis completed.</td>
<td>
Primary Outcome Measure- Total Pain Intensity from baseline to week 5[42]
<table>
<tr><th></th><th>Mean Baseline NRS</th><th>Mean Week 5 NRS</th><th>NRS Change</th><th>Treatment effect: NRS mean difference (95% CI)</th><th>P</th></tr>
<tr><td>ITT Population</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Combination vs:
Imipramine
Pregabalin
Placebo</td><td>6.4</td><td>4.4</td><td>-2.0</td><td>
-0.59 (-1.02 to -0.15)
-1.19 (-1.63 to -0.75)
-1.67 (-2.11 to -1.23)</td><td>
0.009
<0.001
<0.001</td></tr>
<tr><td>Imipramine vs:
Pregabalin
Placebo</td><td>6.4</td><td>5.0</td><td>-1.4</td><td>
-0.60 (-1.04 to -0.15)
-1.08 (-1.52 to -0.64)</td><td>
0.008
<0.001</td></tr>
<tr><td>Pregabalin vs:
Placebo</td><td>6.4</td><td>5.4</td><td>-1.1</td><td>
-0.48 (-0.92 to -0.04)</td><td>
0.032</td></tr>
<tr><td>Placebo</td><td>6.4</td><td>4.4</td><td>-2.0</td><td></td><td></td></tr>
<tr><td>PP Population</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Combination vs:
Imipramine
Pregabalin
Placebo</td><td>6.3</td><td>4.4</td><td>-0.8</td><td>
-0.60 (-1.07 to -0.14)
-1.21 (-1.67 to -0.74)
-1.63 (-2.09 to -1.16)</td><td>
0.011
<0.001
<0.001</td></tr>
<tr><td>Imipramine vs:
Pregabalin</td><td>6.3</td><td>5.1</td><td>-2.0</td><td>
-0.60 (-1.07 to -0.14)</td><td>
0.011</td></tr>
</table>
</td>
</tr>
</table>

				Placebo | | | | -1.02 (-1.48 to -0.56) | <0.001 **Pregabalin vs:** Placebo | 6.3 | 5.5 | -1.3 | -0.42 (-0.88 to 0.05) | 0.080 **Placebo** | 6.3 | 5.6 | -.07 | |
Min K, et al.[43] OL, SC, CO Not reported	Oxcarbazepine 150 mg BID and titrated up to 300 mg BID based on clinical response Vs Pregabalin 75 mg BID titrated up to 150 mg BID over 1-2 wks	Adults > 20 y with spinal cord injuries and neuropathic pain with a LANSS score ≥ 12 and VAS ≥ 3 N =55	Degree in pain reduction according to the presence or absence of pain (EPP vs EPA).	**Differences of drug effect according to the presence or absence of evoked pain.**[43] **Change in Variable before and after treatment** | **Evoked Pain Present (n = 36)** | | | **Evoked Pain Absent (n =30)** | | | | Oxcarbaze-pine | Pregabalin | *P* | Oxcarbazepine | Pregabalin | *P* Electrical | 1.5 | 2.6 | 0.063 | 3.8 | 3.4 | 0.195 Burning | 2.3 | 2.1 | 0.819 | 4.8 | 4.3 | 0.680 Pricking | 2.0 | 2.5 | 0.554 | 4.3 | 3.5 | 0.434 Numbness | 1.8 | 2.3 | 0.416 | 3.0 | 2.2 | 0.321 Allodynia | 0.6 | 2.3 | 0.000 | 2.1 | - | - Heat | 0.1 | 2.1 | 0.000 | 2.3 | - | - Pressure | 1.3 | 2.3 | 0.218 | 2.4 | - | -
Solak Y, et al.[44] RCT, CO 14 wks	Gabapentin 300 mg after each dialysis session (three times a wk) Vs Pregabalin 75 mg daily	Adults > 18 y receiving hemodialysis with neuropathic pruritus > 3 months with > 40 on SF-MPQ N = 40	Determine the frequency of neuropathic pruritus as evaluated by SF-MPQ and VAS	**Changes in SF-MPQ and VAS with gabapentin and pregabalin**[44] | **Baseline** | **After Gabapentin** | **P value** | **Baseline** | **After Pregabalin** | **P value** SF-PMQ VAS | 191. ± 3.9 | 9.2 ±4.4 | < 0.001 | 18.6 ± 3.9 | 9.1 ±3.5 | < 0.001 SF-MPQ PPI | 2.9 ±0.9 | 1.3 ±0.8 | < 0.001 | 2.8 ±0.8 | 1.4 ± 0.7 | < 0.001 Pruritus VAS Score | 5.84 ±1.38 | 1.43 ± 2.0 | < 0.001 | 5.8 ± 1.4 | 1.36 ± 2.32 | < 0.001
Raskin P et al[45] RCT, DB PC, MC CO 2 x 6 wk treatment sequences with 2 wk washout in between – total of 14 wks	Pregabalin 50 mg TID x 1 wk increased to 100 mg TID x 6 wks Vs Placebo x 6 wks	Adults > 18 y with T1 or T2 DM and DPN ≥ 4 on a NRS and using NSAIDs N = 301	Change in weekly mean DPN pain score from baseline to week 6	**Weekly Mean Pain Scores from Week 1 through Week 6**[45] | **Mean Pregabalin (95% CI) N = 272** | **Mean Placebo (95% CI) N = 276** | **Mean Difference (95% CI)** | ***P*** Week 1 | 5.10 (4.92-5.29) | 5.27 (5.09-5.45) | -0.17 (-0.32 to -.02) | 0.0293 Week 2 | 5.67 (5.47-5.87) | 5.72 (5.52-5.92) | -0.05 (-0.24 to 0.14) | 0.6014 Week 3 | 5.22 (5.02-5.42) | 5.46 (5.26-5.66) | -.025 (-0.44 to -0.05) | 0.0122 Week 4 | 4.99 (4.79-5.19) | 5.26 (5.06-5.46) | -.027 (-0.47 to -0.08) | 0.0061 Week 5 | 4.88 (4.68-5.08) | 5.05 (4.85-5.25) | -0.17 (-0.36 to 0.03) | 0.0983 Week 6 | 4.90 (4.69-5.10) | 4.95 (4.75-5.16) | -0.05 (-0.26 to 0.15) | 0.5987

Abbreviations: BPI = Brief Pain Inventory; BPI-MSF = Brief Pain Inventory-Modified Short Form; CI = Confidence Interval; CO = Cross Over; DB= Double Blind; DM = Diabetes Mellitus; DPN = Diabetic Peripheral Neuropathy; EPA = Evoked Pain Absent; EPP = Evoked Pain Present; ITT = Intention To Treat; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; MC = Multi-Center; N=number; mos = Months; NSAID = non-steroidal anti-inflammatory agent; NRS = Numeric Rating Scale; OL = Open Label; PC = Placebo Controlled; PG = Parallel Group; PP = Per Protocol; PPI = Present Pain Intensity; RCT = Randomized Clinical Trial; SC= Single Center; SF-PMQ = Short Form of McGill Pain Questionnaire; T1= Type 1; T2 = Type 2; VAS = Visual Analog Scale; wks= weeks; Y = Years

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Appendix 1: Current Preferred Drug List

ANTIEPILEPTICS

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVED OUT
ORAL	TABLET	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	TABLET	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET	EPITOL	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	CARBAMAZEPINE ER	CARBAMAZEPINE	Y	
ORAL	TAB ER 12H	TEGRETOL XR	CARBAMAZEPINE	Y	
ORAL	TAB CHEW	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	CARBAMAZEPINE	CARBAMAZEPINE	Y	
ORAL	ORAL SUSP	TEGRETOL	CARBAMAZEPINE	Y	
ORAL	TABLET DR	DEPAKOTE	DIVALPROEX SODIUM	Y	Y
ORAL	TABLET DR	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	CAP SPRINK	DEPAKOTE SPRINKLE	DIVALPROEX SODIUM	Y	Y
ORAL	CAP SPRINK	DIVALPROEX SODIUM	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DEPAKOTE ER	DIVALPROEX SODIUM	Y	Y
ORAL	TAB ER 24H	DIVALPROEX SODIUM ER	DIVALPROEX SODIUM	Y	Y
ORAL	CAPSULE	GABAPENTIN	GABAPENTIN	Y	
ORAL	CAPSULE	NEURONTIN	GABAPENTIN	Y	
ORAL	TABLET	VIMPAT	LACOSAMIDE	Y	
ORAL	TABLET	LAMICTAL	LAMOTRIGINE	Y	Y
ORAL	TABLET	LAMOTRIGINE	LAMOTRIGINE	Y	Y
ORAL	TAB DS PK	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TAB DS PK	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TAB ER 24	LAMOTRIGINE ER	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TAB RAPDIS	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMICTAL	LAMOTRIGINE	V	Y
ORAL	TB CHW DSP	LAMOTRIGINE	LAMOTRIGINE	V	Y
ORAL	TB ER DSPK	LAMICTAL XR	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMICTAL ODT	LAMOTRIGINE	V	Y
ORAL	TB RD DSPK	LAMOTRIGINE ODT	LAMOTRIGINE	V	Y
ORAL	TABLET	KEPPRA	LEVETIRACETAM	Y	
ORAL	TABLET	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	ROWEEPRA	LEVETIRACETAM	Y	

ORAL	SOLUTION	KEPPRA	LEVETIRACETAM	Y	
ORAL	SOLUTION	LEVETIRACETAM	LEVETIRACETAM	Y	
ORAL	TABLET	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	TABLET	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	TRILEPTAL	OXCARBAZEPINE	Y	
ORAL	ORAL SUSP	OXCARBAZEPINE	OXCARBAZEPINE	Y	
ORAL	CAPSULE	DILANTIN	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTEK	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	CAPSULE	PHENYTOIN SODIUM EXTENDED	PHENYTOIN SODIUM EXTENDED	Y	
ORAL	ORAL SUSP	PHENYTOIN	PHENYTOIN	Y	
ORAL	ORAL SUSP	DILANTIN-125	PHENYTOIN	Y	
ORAL	TAB CHEW	DILANTIN	PHENYTOIN	Y	
ORAL	TAB CHEW	PHENYTOIN	PHENYTOIN	Y	
ORAL	TABLET	TOPAMAX	TOPIRAMATE	Y	
ORAL	TABLET	TOPIRAMATE	TOPIRAMATE	Y	
ORAL	CAPSULE	DEPAKENE	VALPROIC ACID	Y	Y
ORAL	CAPSULE	VALPROIC ACID	VALPROIC ACID	Y	Y
ORAL	SOLUTION	DEPAKENE	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SOLUTION	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)	Y	Y
ORAL	SYRINGE	VALPROIC ACID	VALPROIC ACID (AS SODIUM SALT)		Y
ORAL	TABLET	BRIVIACT	BRIVARACETAM	N	
ORAL	SOLUTION	BRIVIACT	BRIVARACETAM	N	
ORAL	CPMP 12HR	CARBAMAZEPINE ER	CARBAMAZEPINE	N	
ORAL	CPMP 12HR	CARBATROL	CARBAMAZEPINE	N	
ORAL	TABLET	APTIOM	ESLICARBAZEPINE ACETATE	N	
ORAL	TABLET	POTIGA	EZOGABINE	N	
ORAL	TABLET	GABAPENTIN	GABAPENTIN	N	
ORAL	TABLET	NEURONTIN	GABAPENTIN	N	
ORAL	SOLUTION	NEURONTIN	GABAPENTIN	N	
ORAL	SOLUTION	GABAPENTIN	GABAPENTIN	N	
ORAL	TAB ER 24H	GRALISE	GABAPENTIN	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	
ORAL	TABLET ER	HORIZANT	GABAPENTIN ENACARBIL	N	
ORAL	SOLUTION	VIMPAT	LACOSAMIDE	N	
ORAL	TAB ER 24H	KEPPRA XR	LEVETIRACETAM	N	
ORAL	TAB ER 24H	LEVETIRACETAM ER	LEVETIRACETAM	N	
ORAL	TAB SUSP	SPRITAM	LEVETIRACETAM	N	
ORAL	TAB ER 24H	OXTELLAR XR	OXCARBAZEPINE	N	

ORAL	ORAL SUSP	FYCOMPA	PERAMPANEL	N
ORAL	TABLET	FYCOMPA	PERAMPANEL	N
ORAL	SOLUTION	LYRICA	PREGABALIN	N
ORAL	CAPSULE	LYRICA	PREGABALIN	N
ORAL	CAP ER 24H	TROKENDI XR	TOPIRAMATE	N
ORAL	CAP SPR 24	QUDEXY XR	TOPIRAMATE	N
ORAL	CAP SPR 24	TOPIRAMATE ER	TOPIRAMATE	N
ORAL	CAP SPRINK	TOPAMAX	TOPIRAMATE	N
ORAL	CAP SPRINK	TOPIRAMATE	TOPIRAMATE	N

Antidepressants: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Tricyclic Antidepressants

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVED OUT
ORAL	TABLET	AMITRIPTYLINE HCL	AMITRIPTYLINE HCL	Y	Y
ORAL	TABLET	DESIPRAMINE HCL	DESIPRAMINE HCL	Y	Y
ORAL	TABLET	NORPRAMIN	DESIPRAMINE HCL	Y	Y
ORAL	TAB ER 24	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24	KHEDEZLA	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24H	DESVENLAFAXINE ER	DESVENLAFAXINE	V	Y
ORAL	TAB ER 24	DESVENLAFAXINE FUMARATE ER	DESVENLAFAXINE FUMARATE	V	Y
ORAL	TAB ER 24H	PRISTIQ	DESVENLAFAXINE SUCCINATE	V	Y
ORAL	CAPSULE	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	ORAL CONC	DOXEPIN HCL	DOXEPIN HCL	Y	Y
ORAL	CAPSULE DR	CYMBALTA	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	DULOXETINE HCL	DULOXETINE HCL	V	Y
ORAL	CAPSULE DR	IRENKA	DULOXETINE HCL	V	Y
ORAL	TABLET	IMIPRAMINE HCL	IMIPRAMINE HCL	Y	Y
ORAL	TABLET	TOFRANIL	IMIPRAMINE HCL	Y	Y
ORAL	CAPSULE	IMIPRAMINE PAMOATE	IMIPRAMINE PAMOATE	V	Y
ORAL	CAP SA 24H	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	CAP24HDSPK	FETZIMA	LEVOMILNACIPRAN HCL	V	Y
ORAL	TAB DS PK	SAVELLA	MILNACIPRAN HCL		
ORAL	TABLET	SAVELLA	MILNACIPRAN HCL		
ORAL	CAPSULE	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	PAMELOR	NORTRIPTYLINE HCL	Y	Y
ORAL	SOLUTION	NORTRIPTYLINE HCL	NORTRIPTYLINE HCL	Y	Y

ORAL	TABLET	PROTRIPTYLINE HCL	PROTRIPTYLINE HCL	Y	Y
ORAL	CAPSULE	SURMONTIL	TRIMIPRAMINE MALEATE	Y	Y
ORAL	CAP ER 24H	EFFEXOR XR	VENLAFAXINE HCL	Y	Y
ORAL	CAP ER 24H	VENLAFAXINE HCL ER	VENLAFAXINE HCL	Y	Y
ORAL	TAB ER 24	VENLAFAXINE HCL ER	VENLAFAXINE HCL	V	Y
ORAL	TABLET	VENLAFAXINE HCL	VENLAFAXINE HCL	Y	Y

Topical Analgesics

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVED OUT
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	OINT. (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	CREAM (G)	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDOCAINE	LIDOCAINE	N	
TOPICAL	ADH. PATCH	LIDODERM	LIDOCAINE	N	

Appendix 2: Abstracts

Boyle J. Eriksson ME. Gribble L. Gouni R. Johnsen S. Coppini DV. Kerr D. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes Care. 35(12):2451-8, 2012 Dec.
OBJECTIVE: Chronic diabetic peripheral neuropathic pain (DPNP) is difficult to treat, with treatment regimens often inadequate at controlling pain and limited by side effects and drug tolerance. Secondary parameters, such as quality of sleep and mood, may also be important for successful DPNP management. The objectives of this study were to compare the analgesic efficacy of pregabalin, amitriptyline, and duloxetine, and their effect on polysomnographic sleep, daytime functioning, and quality of life in patients with DPNP.
RESEARCH DESIGN AND METHODS: This was a double-blind, randomized, parallel group investigation of type 1 and 2 diabetic subjects with DPNP. Each treatment group had a single-blind, 8-day, placebo run-in followed by 14 days of lower-dose and 14 days of higher-dose medication. At the end of each dose titration period, subjective pain, sleep, and daytime functioning were assessed during a 2-day residential period.
RESULTS: All medications reduced pain when compared with placebo, but no one treatment was superior to any other. For sleep, pregabalin improved sleep continuity ($P < 0.001$), whereas duloxetine increased wake and reduced total sleep time ($P < 0.01$ and $P < 0.001$). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there was a significantly higher number of adverse events in the pregabalin treatment group.
CONCLUSIONS: There was no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin. However, there were significant differences in the secondary parameters, which may be of relevance when deciding the optimal treatment for DPNP.

Holbech, J. V., et al. (2015). Imipramine and pregabalin combination for painful polyneuropathy: a randomized controlled trial. Pain 156(5): 958-966.
Monotherapy with first-line drugs for neuropathic pain often fails to provide sufficient pain relief or has unacceptable side effects because of the need for high doses. The aim of this trial was to test whether the combination of imipramine and pregabalin in moderate doses would relieve pain more effectively than monotherapy with either of the drugs. This was a randomized, double-blind, placebo-controlled, crossover, multicenter trial consisting of four 5-week treatment periods in patients with painful polyneuropathy. Treatment arms were imipramine 75 mg/d vs pregabalin 300 mg/d vs combination therapy vs placebo. Patients with polyneuropathy and symptoms for more than 6 months, age 20 to 85 years, pain intensity >4 on a 0- to 10-point numeric rating scale (NRS) and pain at least 4 days a week were included in the trial. A total of 262 patients were screened for participation, 73 patients were randomized, and 69 patients were included in the data analysis. The effect on average pain in comparison with placebo was: combination (-1.67 NRS points, $P < 0.001$), imipramine (-1.08 NRS points, $P < 0.001$), and pregabalin (-0.48 NRS points, $P = 0.03$). The combination therapy had significantly lower pain scores than both monotherapies: combination vs imipramine ($P = 0.009$), combination vs pregabalin ($P < 0.001$). During combination therapy, the dropout rate was higher and the patients reported a higher rate and severity of side effects. Combination of moderate doses of the tricyclic antidepressant imipramine and pregabalin could be considered as an alternative to high-dosage monotherapy. However, the trial also emphasized that balance between efficacy and safety is an issue.

Kaur H. Hota D. Bhansali A. Dutta P. Bansal D. Chakrabarti A. A comparative evaluation of amitriptyline and duloxetine in painful diabetic neuropathy: a randomized, double-blind, cross-over clinical trial. Diabetes Care. 34(4):818-22, 2011 Apr.
OBJECTIVE: To compare the efficacy and safety of duloxetine and amitriptyline in painful diabetic neuropathy (PDN).
RESEARCH DESIGN AND METHODS: In this randomized, double-blind, cross-over, active-control trial, 58 patients received amitriptyline and duloxetine orally once daily at bedtime, each for 6 weeks with optional dose uptitration fortnightly. Single-blinded placebo washout was given for 2 weeks between the two

treatments and a single-blinded placebo run-out phase of 4 weeks was given at the end of the treatment period. Pain relief was measured by the patient's global assessment of efficacy, using a visual analog scale (0-100) as a primary end point, and overall improvement and adverse events were assessed as secondary outcome measures. Median pain score reductions of >50%, 25- 50%, and <25% were considered good, moderate, and mild responses, respectively.
RESULTS: There was a significant improvement in pain with both treatments compared with their baseline values ($P < 0.001$ for both). Good, moderate, and mild pain relief was achieved in 55, 24, and 15% of patients, respectively, on amitriptyline and 59, 21, and 9% of patients, respectively, on duloxetine. There were no significant differences in various other outcome measures between the groups. Of the reported adverse events, dry mouth was significantly more common with amitriptyline than duloxetine (55 vs. 24%; $P < 0.01$). Although, numerically, more patients preferred duloxetine, overall this was not statistically significant (48 vs. 36%; $P = 0.18$).
CONCLUSIONS: Both duloxetine and amitriptyline demonstrated similar efficacy in PDN. A large, multicentric clinical trialin other populations could possibly demonstrate the superiority of either drug.

Liu, W. Q., et al. (2014). Equivalency of tricyclic antidepressants in open-label neuropathic pain study. Acta Neurologica Scandinavica 129(2): 132-141.
OBJECTIVES: To compare adverse effects, tolerability and efficacy of the tricyclic antidepressants (TCAs) amitriptyline and nortriptyline in management of neuropathic pain due to peripheral neuropathy (PN).
MATERIALS & METHODS: We performed a prospective open-label flexible-dosing comparison of monotherapy or adjuvant therapy using amitriptyline or nortriptyline in PN-associated neuropathic pain. Primary outcomes were quantitative adverse effects and discontinuation rates. Secondary outcomes assessed changes in pain severity, quality of life, disability, sleep efficacy, mood and anxiety, and global improvement. Assessments occurred at 3 and 6 months after initiation. Our hypothesis was that nortriptyline would have better tolerance than amitriptyline.
RESULTS: A total of 228 PN patients were enrolled approximately equally for monotherapy and adjuvant therapy. Adverse effects and discontinuation rates were similar between amitriptyline and nortriptyline interventions. Weight gain was more common with amitriptyline, while nortriptyline use was associated with greater prevalence of dry mouth. Secondary outcome measures were similar in both groups, demonstrating improvement from baseline.
CONCLUSIONS: Amitriptyline and nortriptyline are equivalent for overall adverse effects and discontinuation rates. Either TCA should be equally considered for use in neuropathic pain due to PN. When used as monotherapy or as part of adjuvant therapy, either TCA can be expected to provide approximately 23-26% visual analog scale pain reduction if tolerated. Discontinuations due to inefficacy or adverse effects can be anticipated in 26-37% of patients initiated on either TCA for PN-associated neuropathic pain.

Min, K., et al. (2016). Symptom-Based Treatment of Neuropathic Pain in Spinal Cord-Injured Patients: A Randomized Crossover Clinical Trial. American Journal of Physical Medicine & Rehabilitation **95**(5): 330-338.
OBJECTIVE: The objective of this study was to identify the differences in medication effect according to pain characteristics in spinal cord-injured patients.
METHODS: This study is a prospective, randomized, crossover study. Fifty-five patients and 66 locations of neuropathic pain were included. Pain was classified into four spontaneous characteristics and three evoked pain characteristics. Oxcarbazepine (Na channel blocker) and pregabalin (calcium channel alpha2-delta ligand medication) were tried. Patients were divided into two groups: evoked pain present and evoked pain absent. Overall average visual analog scale was obtained.
RESULTS: Oxcarbazepine was significantly more effective for patients without evoked pain than in those with it for electrical, burning, and pricking pain. The effect of pregabalin was not different regarding the presence or absence of evoked pain for all pain categories, except burning pain. In patients with evoked pain, pregabalin was shown to be significantly more effective for electrical pain, allodynia, and heat hyperalgesia than oxcarbazepine. In the evoked pain absent group, oxcarbazepine showed greater improvement than pregabalin but was not significant.

CONCLUSIONS: In summary, the phenotype of neuropathic pain was associated with the efficacy of different pharmacologic treatments. Symptom-based treatment, therefore, can lead to more efficient analgesia.

Mishra S. Bhatnagar S. Goyal GN. Rana SP. Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. American Journal of Hospice & Palliative Medicine. 29(3):177-82, 2012 May.
Neuropathic pain is difficult to diagnose and difficult to treat with certainty. So the aim of the study was to evaluate comparative clinical efficacy of pregabaline with amitriptyline and gabapentin in neuropathic cancer pain. A total of 120 patients with cancer having severe neuropathic cancer pain were enrolled in the study after taking approval from Institutional Ethics Committee and divided in to 4 groups: group AT-amitriptyline, group GB-gabapentin, group PG-pregabalin, and group PL-placebo. Oral morphine was used for rescue analgesic for continued pain. Pain score (Visual Analogue scale) and secondary outcome measures such as intensity of lancinating, dysesthesia, and burning on numerical rating scale, Global satisfaction score (GSS), Eastern Co-operative Oncology Group scoring (ECOG), and adverse effects were assessed. At the end of study there was significant decrease in pain score in group PG as compared to the other groups; group AT (P = .003), group GB (P = .042), and group PL (P = .024). Percentage of patients with lancinating pain and dysesthesia were significantly less in group PG as compared to groups GB and PL. All the patients in group PL needed rescue morphine. After 4 visits, maximum improvement in ECOG scoring and GSS scoring was observed in group PG patients. Our results suggested that all antineuropathic drugs are effective in relieving cancer-related neuropathic pain. There was statistically and clinically significant morphine sparing effect of pregabaline in relieving neuropathic cancer pain and neuropathic symptoms as compared to other antineuropathic drugs.

Razazian, N., et al. (2014). Evaluation of the efficacy and safety of pregabalin, venlafaxine, and carbamazepine in patients with painful diabetic peripheral neuropathy. A randomized, double-blind trial. Neurosciences **19**(3): 192-198.
OBJECTIVE: To evaluate the efficacy and safety of carbamazepine, pregabalin, and venlafaxine in patients with painful diabetic neuropathy (PDN).
METHODS: Our study was performed as a randomized, double-blind, parallel-group clinical trial between December 2012 and December 2013 at Kermanshah University of Medical Sciences, Kermanshah, Iran. Two hundred and fifty-seven patients with clinically definite PDN were randomized to receive, carbamazepine, venlafaxine, or pregabalin. The primary outcome was subjective pain as assessed by the visual analogue scale (VAS). Secondary outcomes consisted of sleep, mood, and work interference assessments, and a percentage of patients achieving at least 50% reduction in pain intensity.
RESULTS: Means of VAS scores for carbamazepine, pregabalin, and venlafaxine treatment groups at the baseline (74.5, 82.3, and 74.5) and endpoint (39.6, 33.4, and 46.6) revealed significant reduction, although pregabalin was more efficacious than carbamazepine, and venlafaxine. Improvements in means scores of sleep, mood, and work interferences were identified in all treatment groups.
CONCLUSION: This study showed the efficacy of venlafaxine, pregabalin, and carbamazepine in pain reduction in patients with diabetic neuropathy, although pregabalin was shown to be superior to carbamazepine, and venlafaxine in relieving pain, no significant superiority was shown between carbamazepine, and venlafaxine.

Solak Y. Biyik Z. Atalay H. Gaipov A. Guney F. Turk S. Covic A. Goldsmith D. Kanbay M. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study. Nephrology. 17(8):710-7, 2012 Nov.
AIM: Pruritus is common in dialysis patients. Peripheral neuropathy is also prevalent in this patient population. However, the role of neuropathy in the genesis of uraemic itch has not been adequately studied to date. Therefore, we aimed to investigate the effects of gabapentin and pregabalin on uraemic pruritus along with neuropathic pain in patients receiving haemodialysis.

METHODS: This is a 14 week long randomized, prospective, cross-over trial. Haemodialysis patients with established neuropathy and/or neuropathic pain were included. Fifty patients were randomly assigned to gabapentin 300 mg after each haemodialysis session and pregabalin 75 mg daily. After 6 weeks of treatment, cross-over was performed and patients received the other drug for another 6 weeks. Short Form of McGill Pain Questionnaire and Visual Analogue Scale were used to evaluate pain and pruritus, respectively. At each week's visit, patients were interrogated in terms of adverse effects of study drugs. Baseline laboratory data and demographic characteristics were recorded from patient charts.
RESULTS: Forty (12 males, 28 females) out of 50 patients completed the study. Mean age was 58.2 +/- 13.7. Overall, 29 out of 40 patients (72.5%) had pruritus symptoms at baseline evaluation. Fifteen patients (37.5%) were diabetic. Thirty-one out of 40 patients (77.5%) had electromyography (EMG)-proven peripheral neuropathy. Twenty three patients (57.5%) had both EMG-proven neuropathy and pruritus. Gabapentin and pregabalin improved both neuropathic pain and pruritus significantly. There was no difference between the study drugs in terms of efficacy against pain and pruritus.
CONCLUSION: Treatment of neuropathic pain with either pregabalin or gabapentin effectively ameliorates uraemic itch.

Tanenberg RJ. Irving GA. Risser RC. Ahl J. Robinson MJ. Skljarevski V. Malcolm SK. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. Mayo Clinic Proceedings. 86(7):615-26, 2011 Jul.
OBJECTIVE: To determine whether duloxetine is noninferior to (as good as) pregabalin in the treatment of pain associated with diabetic peripheral neuropathy.
PATIENTS AND METHODS: We performed a 12-week, open-label study of patients with diabetic peripheral neuropathic pain who had been treated with gabapentin (>= 900 mg/d) and had an inadequate response (defined as a daily pain score of >= 4 on a numerical rating scale [0-10 points]). The first patient was enrolled on September 28, 2006, and the last patient visit occurred on August 26, 2009. Patients were randomized to duloxetine monotherapy (n=138), pregabalin monotherapy (n=134), or a combination of duloxetine and gabapentin (n=135). The primary objective was a noninferiority comparison between duloxetine and pregabalin on improvement in the weekly mean of the diary-based daily pain score (0- to 10-point scale) at end point. Noninferiority would be declared if the mean improvement for duloxetine was no worse than the mean improvement for pregabalin, within statistical variability, by a margin of -0.8 unit.
RESULTS: The mean change in the pain rating at end point was -2.6 for duloxetine and - 2.1 for pregabalin. The 97.5% lower confidence limit was a -0.05 difference in means, establishing noninferiority. As to adverse effects, nausea, insomnia, hyperhidrosis, and decreased appetite were more frequent with duloxetine than pregabalin; insomnia, more frequent with duloxetine than duloxetine plus gabapentin; peripheral edema, more frequent with pregabalin than with duloxetine; and nausea, hyperhidrosis, decreased appetite, and vomiting, more frequent with duloxetine plus gabapentin than with pregabalin.
CONCLUSION: Duloxetine was noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin

Tesfaye, S., et al. (2013). Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain 154(12): 2616-2625.
This multicentre, double-blind, parallel-group study in diabetic peripheral neuropathic pain addressed whether, in patients not responding to standard doses of duloxetine or pregabalin, combining both medications is superior to increasing each drug to its maximum recommended dose. For initial 8-week therapy, either 60 mg/day duloxetine (groups 1, 2) or 300 mg/day pregabalin (groups 3, 4) was given. Thereafter, in the 8-week combination/high-dose therapy period, only nonresponders received 120 mg/day duloxetine (group 1), a combination of 60 mg/day duloxetine and 300 mg/day pregabalin (groups 2, 3), or 600 mg/day pregabalin (group 4). Primary outcome (Brief Pain Inventory Modified Short Form [BPI-MSF] 24-hour average pain change after combination/high-dose therapy) was analyzed comparing combination (groups 2, 3 pooled) with high-dose monotherapy (groups 1, 4 pooled). Secondary end points included response rates, BPI-MSF severity items, and comparison of duloxetine and pregabalin in BPI-MSF average pain. Eight hundred four patients were evaluated for initial therapy and

339 for combination/high-dose therapy. There were no significant differences between combination and high-dose monotherapy regarding BPI-MSF average pain (mean change: combination: -2.35; high-dose monotherapy: -2.16; P = 0.370) and most secondary end points, which, however, consistently favoured combination therapy. Fifty-percent response rates were 52.1% for combination and 39.3% for high-dose monotherapy (P = 0.068). In exploratory analyses of the initial 8-week therapy uncorrected for multiple comparisons, 60 mg/day duloxetine was found superior to 300 mg/day pregabalin (P < 0.001). Both drugs and their combination were well tolerated. Although not significantly superior to high-dose monotherapy, combination therapy was considered to be effective, safe, and well tolerated.

Raskin, Philip MD; Huffman, Cynthia MD; Yurkewicz, Lorraine PhD; Pauer, Lynne MS; Scavone, Joseph M. MSc, PharmD; Yang, Ruoyong PhD; Parsons, Bruce MD, PhD Pregabalin in Patients With Painful Diabetic Peripheral Neuropathy Using an NSAID for Other Pain Conditions: A Double-Blind Crossover Study. Clinical Journal of Pain. 32(3):203-210, March 2016

Objectives: To evaluate pregabalin's efficacy and safety versus placebo to reduce pain in patients with diabetic peripheral neuropathy (DPN) using a concomitant nonsteroidal anti-inflammatory drug.

Materials and Methods: In a randomized, double-masked, 14-week, 2-period, crossover study, patients with painful DPN using a nonsteroidal anti-inflammatory drug for non-DPN-related pain received 150 to 300 mg/d pregabalin or placebo (period 1); 14-day washout; then, the opposite therapy (period 2). Endpoints included weekly change in DPN pain score, sleep interference, adverse events, and patient-reported outcomes.

Results: Patients with similar baseline characteristics were randomized (period 1) to 1 of the 2 following possible sequences: pregabalin->placebo (n=154) or placebo->pregabalin (n=147). Results of the primary efficacy measure, mean weekly DPN pain at endpoint, showed no significant difference between pregabalin and placebo. However, 1 sensitivity analysis (mixed-model repeated measures) found greater pain score reductions with pregabalin than placebo at weeks 2 to 4 and overall (all P<0.05). One secondary endpoint analysis, mean treatment difference in DPN-related sleep interference, favored pregabalin over placebo (P=0.0009). Other sensitivity and secondary analyses were nonsignificant. Treatment-emergent adverse events were consistent with the known safety profile of pregabalin.

Discussion: Pregabalin (vs. placebo) showed overall improvements in sleep, pain reduction in 1 sensitivity analysis, and was well tolerated. Potential factors that may have confounded the ability to detect a treatment difference in DPN pain reduction (high placebo response, carryover effect, short washout period, or pregabalin dose) are discussed in the context of future studies.

Source: Clinical Journal of Pain. 32(3):203-210, March 2016.

Appendix 3: Drug Information

Table 1. Dosing Recommendations for Non-analgesics Used to Manage Pain [46,47]

Medication	Starting Dose		Titration	Maximum Dosage	Duration of Adequate Trial
Tricyclic Antidepressants (TCA)					
Amitriptyline	12.5 mg QHS		Increase up to 25-50 mg Daily every 3-7 days	150 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Nortriptyline	10 mg QHS		Increase by 10 to 25 mg Daily every 3-7 days	150 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Imipramine	50 mg QHS		Increase 25 mg Daily every 3 to 7 days	200 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Desipramine	25 mg QHS		Increase 25 mg Daily every 3 to 7 days	200 mg Daily	6-8 weeks with ≥ 2 weeks at maximum dose
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)					
Duloxetine	30 mg po Daily		Increase to 60 mg Daily after 1 week	120 mg Daily	4 weeks
Venlafaxine	37.5 mg Daily or BID		Increase by 75 mg each week	225 mg Daily	4-6 weeks
Milnacipran	12.5 mg Daily		Increase by 12.5 mg BID over 7 days to 50 mg BID	100 mg BID	4 weeks
Antiepileptics					
Gabapentin	100-300 mg QHS OR 100-300 mg TID		Increase by 100-300 mg TID every 1-7 days	1800-3600 mg per day in divided doses	4-8 weeks
Pregabalin	50 mg TID or 75 mg BID		Increase to 300 mg Daily after 3-7 days, then by 150 mg Daily over 3-7 days to 450 mg per day	600 mg Daily	4 weeks
Carbamazepine	100 mg BID		Increase by 100-200 mg as needed for pain control	600 mg BID	Attempt to reduce dose or discontinue use every 3 months
Topiramate	50 mg BID		Increase by 25 mg every 7 days	50 mg BID	4 weeks
Topical Agents					
Lidocaine 5% Patch	Maximum of 3 patches Daily for a max of 12 hours		None needed	Maximum of 3 patches Daily for a maximum of 12-18 hours	Immediate
Lidocaine Gel/Cream/Topical Solution (4%)	Apply 5 gms/6 in to affected area TID to QID		None needed	17-20 gms of ointment per day	Immediate

Abbreviations: BID = twice daily; gms = grams; in = inches; mg = milligrams; QHS = daily at bedtime; QID = four times a day; TID = three times a day

Table 2. Summary of Warnings and Precautions for Non-opiates Used to Manage Chronic Pain[46,47]

Warning/Precaution	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Milnacipran	Carbamazepine	Topiramate	Gabapentin, Pregabalin	Topical Lidocaine
CNS Depression (Confusion, Sedation, dizziness)	X	X	X		X	X	X	
Dry Mouth	X		X	X	X		X	
Blurred Vision	X				X		X	
Urinary Retention	X			X				
Constipation	X	X		X	X		X	
Orthostatic Hypotension	X	X						X
Use with Caution in Glaucoma	X	X	X	X				
Hypertension		X	X	X	X			
Cardiac Disease (MI, stroke, arrhythmia)	X		X	X	X			X
Peripheral Edema							X	
Nausea		X	X	X	X			
Local Erythema/Rash					X			X
Seizure Disorder	X	X	X	X				
SIADH/Hyponatremia		X		X	X			
Bone Marrow Depression*					X			
Stevens-Johnson Syndrome*					X	X		
Nonvertebral Bone Fracture	X							
Increased Risk of Suicidal Thoughts*	X	X	X					
Use with Caution in Hepatic Impairment	X	X	X	X	X	X		
Use with Caution in Renal Impairment	X	X	X	X			X	
Withdrawal Syndrome with Abrupt Discontinuation	X	X	X		X			

***Bold warnings indicate a black box warning associated with the adverse effect**

Table 3. Evidence for Efficacy for Non-opiate Medications in Specific Neuropathic/Chronic Pain Conditions [46,47]

Condition	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Milnacipran	Carbamazepine	Topiramate	Gabapentin	Pregabalin	Topical Lidocaine
Diabetic Neuropathy	X	X*	X			X	X	X*	X
Postherpetic Neuropathy	X						X*	X*	X*
Painful Polyneuropathy	X		X				X	X	X
Phantom Limb Pain							X		
Chemotherapy Induced Neuropathy		X			X		X	X	
HIV Neuropathy	X								
Central Post Stroke Pain	X	X						X	
Spinal Cord Injury Pain		X					X	X*	
Fibromyalgia	X	X*		X*				X*	
Migraine Headache Prophylaxis	X		X		X	X			
Chronic Musculoskeletal Pain	X	X*							
Trigeminal Neuralgia					X*				

***Drug has FDA approval for specific condition**

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 16, 2016

1. *carbamazepine.mp. or Carbamazepine/ 9087*
2. *divalproex.mp. or Valproic Acid/ 7559*
3. *Antiepileptics/ or Analgesics/ or gabapentin.mp. 56374*
4. *vimpat.mp. 17*
5. *lacosamide.mp. 435*
6. *lamotrigine.mp. 4030*
7. *levetiracetam.mp. 2169*
8. *oxcarbazepine.mp. 1360*
9. *phenytoin.mp. or Phenytoin/ 5464*
10. *valproic acid.mp. or Valproic Acid 8869*
11. *brivaracetam.mp. 82*
12. *esclicarbazepine.mp. 2*
13. *Epilepsies, Partial/ or ezogabine.mp. 4889*
14. *Antiepileptics/ or Analgesics/ or gabapentin.mp 56374*
15. *lacosamide.mp. 435*
16. *levetiracetam.mp. 2169*
17. *oxcarbazepine.mp. 1360*
18. *perampanel.mp. 133*
19. *pregabalin.mp. or Pregabalin/ 2041*
20. *topiramate.mp. 3614*
21. *amitriptyline.mp. or Amitriptyline/ 3124*
22. *Antidepressive Agents/ or desimpramine.mp. 25544*
23. *desvenlafaxine.mp. or Desvenlafaxine Succinate/ 277*
24. *doxepin.mp. or Doxepin/ 488*
25. *duloxetine.mp. or Duloxetine Hydrochloride/ 1731*
26. *imipramine.mp. or Imipramine/ 3366*
27. *levomilnacipran.mp. 34*
28. *milnacipran.mp. 524*
29. *nortriptyline.mp. or Nortriptyline/ 1176*
30. *protriptyline.mp. or Protriptyline/ 72*
31. *trimipramine.mp. or Trimipramine/ 148*
32. *venlafaxine.mp. or Venlafaxine Hydrochloride/ 3186*
33. *Lidocaine topical.mp. 286*
34. *Chronic pain.mp. or Chronic Pain/ 22185*
35. *1 or 2 or 3 or 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 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 -10241*
36. *35 and 34 2457*
37. *limit 36 to (english language and humans and humans and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews -year to 2012 current)) 229*

Appendix 5. Fee for Service Utilization of Selected Non-Analgesic Pain Medications (7/1/17 – 9/30/16)

Table 1. Lidocaine Patch

Drug	Total Claims	Paid Claims	Another Drug in PDL Class Paid	No Drugs within PDL Class Paid	Disposition of Claims Not Paid Within PDL Class				
					Patient Enrolled in CCO/IHS/Other*	Patient Lost Eligibility	PA Approved	PA Denied	PA Not Requested
Lidocaine	172	20 (12%)	5 (3%)	147 (85%)	60/24/13 (Total =97)	19	2	2	27

*CCO =Coordinated Care Organization, IHS = Indian Health Service

Table 2. Antiepileptics

Drug	Total Claims	Paid Claims	Another Drug in PDL Class Paid	No Drugs within PDL Class Paid	Disposition of Claims Not Paid Within PDL Class				
					Patient Enrolled in CCO/IHS/Other*	Patient Lost Eligibility	PA Approved	PA Denied	PA Not Requested
Gabapentin	1918	1917 (99%)	0	1 (1%)	1	0	0	0	0
Lyrica (Pregabalin)	205	78 (38%)	34 (17%)	(45%)	48/7/15 (Total = 70)	12	2	4	5

*CCO =Coordinated Care Organization, IHS = Indian Health Service

Table 3. Antidepressants

Drug	Total Claims	Paid Claims	Another Drug in PDL Class Paid	No Drugs within PDL Class Paid	Disposition of Claims Not Paid Within PDL Class				
					Patient Enrolled in CCO/IHS/Other*	Patient Lost Eligibility	PA Approved	PA Denied	PA Not Requested
Duloxetine	10369	10299 (99.4%)	21 (0.2 %)	49 (0.4%)	32/7/1 (Total = 40)	7	0	0	2
Amitriptyline	7359	7338 (99.7%)	5 (0.06%)	16 (0.2%)	8/0/1 (Total = 9)	6	0	0	1
Venlafaxine	5439	5432 (99.8%)	2 (0.03%)	5 (0.09%)	2/0/0 (Total = 2)	3	0	0	0
Imipramine	380	379 (99.8%)	0	1 (0.2%)	0/0/0	1	0	0	0

*CCO =Coordinated Care Organization, IHS = Indian Health Service

Appendix 6. Prior Authorization Criteria

Lidocaine Patch

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

90 days to 12 months (criteria specific)

Requires PA:

- Lidocaine Patch

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (refer to Table 1 for examples).	**Yes:** Go to # 3	**No:** Pass to RPh. Deny; not funded by the OHP
3. Is this a request for renewal of a previously approved prior authorization for lidocaine patch?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 4
4. Is the prescription for Lidoderm patch greater than 3 patches/day?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 90 days
Renewal Criteria		

Approval Criteria		
1. Does the patient have documented improvement from lidocaine patch?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness.

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Lidocaine Patch
Funded	
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	
Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	

P&T Review: *3/17 (DM)*
Implementation: *4/1/17*

Milnacipran

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days

Requires PA:

- Milnacipran

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Approve for 90 days	**No:** Pass to RPh. Deny; not funded by the OHP

Table 1. OHP Funded or Non-Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Milnacipran
Funded	
Diabetic Neuropathy	
Postherpetic Neuropathy	
Painful Polyneuropathy	
Spinal Cord Injury Pain	

Chemotherapy Induced Neuropathy	
Non-funded	
Fibromyalgia	X

P&T Review: *3/17(DM)*
Implementation: *4/1/17*

Pregabalin

Goal(s):
- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:
- 90 days to lifetime (criteria-specific)

Requires PA:
- Pregabalin

Covered Alternatives
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
5. Is this a request for renewal of a previously approved prior authorization for pregabalin?	**Yes**: Go to **Renewal Criteria**	**No**: Go to # 2
6. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
7. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to # 4
8. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to # 5	**No:** Pass to RPh. Deny; not funded by the OHP.
9. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days
Renewal Criteria		
2. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin
Funded	
Diabetic Neuropathy	X
Postherpetic Neuropathy	X
Painful Polyneuropathy	X
Spinal Cord Injury Pain	X
Chemotherapy Induced Neuropathy	X
Non-funded	
Fibromyalgia	X

P&T Review: *3/17 (DM)*
Implementation: *4/1/17*

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7

Approval Criteria	
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."

P&T Review: *3/17 (DM); 7/16 (DM); 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*