Therapeutic Class Overview
Neuropathic Pain and Fibromyalgia Agents

INTRODUCTION

- Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2017*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2019*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2018*).
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or post-herpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine), Gralise (gabapentin ER), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), Savella (milnacipran), and ZTlido (lidocaine 1.8% topical system). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2020, Gralise 2020, Horizant 2016, Lidoderm 2018, Lyrica 2020, Lyrica CR 2020, Neurontin 2020, Nucynta ER 2019, Qutenza 2020, Savella 2017, ZTLido 2018*).
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman 2020[a]*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman et al 2020[b]*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2020[b]*).
  - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in established diabetic neuropathy is uncertain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman et al 2020[b]*).
  - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman et al 2020[b]*).
  - A small proportion of patients with diabetic neuropathy will experience painful symptoms, and in some instances the condition is self-limited. When treatment is necessary, options include antidepressants, anticonvulsants, capsaicin cream, lidocaine patches, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation (*Feldman et al 2020[b]*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw et al 2009*).

  - Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity (*Crofford 2015*).
- The prevalence of fibromyalgia in the general U.S. population is estimated to be 2% to 3% and increases with age *(Goldenberg 2019)*. It is more common in women than in men, with a ratio of approximately 9:1 (*Crofford 2015*).
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw et al 2009, Crofford 2015*).

PHN

- PHN refers to the persistence of the pain of herpes zoster beyond 4 months from the initial onset of the rash. Among patients with acute herpes zoster infection, the major risk factors for PHN are older age, greater acute pain, and greater rash severity. The duration of PHN is highly variable among individuals and may persist for months, years, or life (*Bajwa et al 2019*).
- PHN, as well as acute herpetic neuralgia, can be a severe condition associated with profound psychological dysfunction, including impaired sleep, decreased appetite, and decreased libido (*Bajwa et al 2019*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2019*). Although evidence suggests that antiviral therapy hastens resolution of lesions and acute neuritis of herpes zoster, it is unclear if it decreases the risk of PHN *(Albrecht 2018).*
- A number of treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, opioids, capsaicin, topical lidocaine, intrathecal glucocorticoids, N-methyl-D-aspartate receptor antagonists, botulinum toxin, cryotherapy, and surgery (*Bajwa et al 2019*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cymbalta (duloxetine delayed-release)	✔
Gralise (gabapentin ER)*	-
Horizant (gabapentin enacarbil ER)*	-
Lidoderm (lidocaine transdermal patch)	✔
Lyrica (pregabalin)	✔
Lyrica CR (pregabalin ER)	-
Neurontin (gabapentin)	✔
Nucynta ER (tapentadol ER)	-
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	-
ZTlido (lidocaine topical system)	-

* Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Cymbalta (duloxetine)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)
Adjunctive therapy for adult patients with partial onset seizures					✔					
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✔			
Adjunctive therapy for patients 1 month of age and older with partial onset seizures					✔					
Management of chronic musculoskeletal pain	✔ †									
Management of fibromyalgia in adults	✔				✔					✔
Management of fibromyalgia in adults and pediatric patients 13 years of age and older	✔									
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔				✔	✔		✔ §	✔	
Management of neuropathic pain associated with spinal cord injury					✔					
Management of PHN		✔	✔		✔	✔	✔			
Relief of pain associated with PHN				✔					✔	
Moderate-to-severe primary restless legs syndrome			✔ ‡							
Treatment of generalized anxiety disorder	✔									
Treatment of major depressive disorder	✔									
Management of moderate to severe chronic pain in adults								✔ §		

† This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.
§ Indicated when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Medication is not for: use as an as-needed analgesic; pain that is mild or not expected to persist for an extended period of time; acute pain; or postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

(*Prescribing information: Cymbalta 2020, Gralise 2020, Horizant 2020, Lidoderm 2018, Lyrica 2020, Lyrica CR 2020, Neurontin 2020, Nucynta ER 2019, Qutenza 2020, Savella 2017, ZTlido 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Neuropathic Pain

- Pregabalin demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- Tapentadol ER demonstrated superiority over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores, responder rates, and Patient Global Impression of Change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- Duloxetine demonstrated consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory (BPI), Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberg et al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberg et al 2014*). Another head-to-head trial found no significant differences between high-dose duloxetine or pregabalin monotherapy and combination duloxetine/pregabalin therapy, as measured by BPI Modified Short Form (BPI-MSF) average pain (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Derry et al 2019, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, Quilici et al 2009, Wernicke et al 2007[a], Wiffen et al 2017*). In a meta-analysis by Quilici et al, limited available clinical trial data suitable for indirect comparison demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain (*Quilici et al 2009*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, 1 of 12 weeks duration and the other of 16 weeks duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores compared to placebo, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score (*Lyrica prescribing information 2019*, *Siddall et al 2006, Vranken et al 2008*).
- The efficacy of capsaicin 8% in diabetic peripheral neuropathy was assessed in a placebo-controlled trial *(Simpson et al 2016)*. The primary endpoint, percentage reduction in average daily pain score from baseline through 8 weeks, was significantly improved with capsaicin 8%. Patients treated with capsaicin also had significant improvements in median time to treatment response and in sleep interference scores through week 8.

Fibromyalgia

- From the agents included in this review, the agents that have several randomized controlled trials (RCTs) and meta-analyses demonstrating their efficacy in the treatment of fibromyalgia include duloxetine, pregabalin, and milnacipran (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Russell et al 2008, Vitton et al 2004, Welsch et al 2018*).
  - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with the tricyclic antidepressant, amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the SNRIs, duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).
  - In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve ≥ 30% reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
  - Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the occurrence of key symptoms of fibromyalgia syndrome and the specific AEs that are associated with each drug (*Hauser et al 2010*).
  - A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
  - A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving > 30% improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee et al 2016*).
  - A systematic review and meta-analysis of 18 randomized trials involving 7903 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction and provided no clinically relevant benefit over placebo in improving health-related quality of life or in reducing fatigue. Dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Welsch et al 2018*).
  - Duloxetine is approved for treatment of fibromyalgia in patients age 13 years and older. Pediatric approval was supported by findings of a 13-week, placebo-controlled RCT (N = 184) of patients age 13 to 17 years with juvenile fibromyalgia *(Upadhyaya et al 2019)*. The primary outcome, mean change in BPI average pain severity, was not statistically different between groups; however, significantly more duloxetine- vs placebo-treated patients had a treatment response of ≥ 30% reduction (52% vs 36%) and ≥ 50% reduction (40% vs 24%) on BPI average pain severity.

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).
- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 75% to < 90% adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater (< 75% adhered) *(ZTlido prescribing information 2018)*.
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in

PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin was also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).

- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, short-form McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3,600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).
- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported ≥ 50% reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1,800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (n = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with ≥ 50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirms these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN support the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*). Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).
- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of pregabalin in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2020*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial *(Huffman et al 2017).*

CLINICAL GUIDELINES

Diabetic Neuropathy

- The 2011 American Academy of Neurology (AAN) guidelines, which were reaffirmed in 2016 [update in progress 2020], recommend the following:
  - If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment (*Bril et al 2011*).
  - Amitriptyline, venlafaxine, and duloxetine should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another. Combination therapy with venlafaxine and gabapentin may be utilized for a better response.
  - Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another.
  - With regards to other pharmacologic options, capsaicin and isosorbide dinitrate spray should be considered for treatment, while lidocaine patch may be considered.
- The 2020 American Diabetes Association (ADA) guideline acknowledges the lack of quality of life outcomes and recommends that treatment decisions follow a trial-and-error approach (*ADA 2020*).
  - Pregabalin, duloxetine, and tapentadol ER have been approved for relief of diabetic peripheral neuropathy; however, none of these agents affords complete relief, even when used in combination.
  - Either pregabalin or duloxetine is recommended as initial pharmacologic therapy for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker.
  - Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin are not approved for the treatment of painful diabetic peripheral neuropathy, but may be effective and can be considered as treatment options.
- In general, other published guidelines support recommendations from the AAN and ADA concerning the use of the neuropathic pain and fibromyalgia agents in the management of diabetic neuropathy (*Dworkin et al 2007, Handelsman et al 2015, Pop-Busui et al 2017*).

PHN

- According to the 2010 European Federation of Neurological Societies guideline on the pharmacological treatment of neuropathic pain, tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line treatment for PHN. Topical lidocaine may be considered first line in the elderly, especially if there are concerns regarding AEs of oral medications. Capsaicin cream and opioids may be considered a second-line choice; capsaicin patches are promising, but the long-term effects of repeated applications on sensation are unclear *(Attal et al 2010).*

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies, and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane 2017*).
- According to the 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

SAFETY SUMMARY

- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors (MAOIs) is contraindicated with duloxetine, milnacipran, and tapentadol ER.
  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All SNRIs are not approved for use in pediatric populations. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.

- Duloxetine may increase the risk of bleeding events due to interference with serotonin reuptake. Concomitant use with aspirin and other antithrombotics may increase risk of bleeding.
- Tapentadol ER has a boxed warning for the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system depressants that can cause profound sedation, respiratory depression, coma, and death.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- Tapentadol ER should not be abruptly discontinued in patients who may be physically dependent on opioids. Rapid discontinuation in these patients may result in withdrawal symptoms, uncontrolled pain, and suicide. Mixed agonist/antagonist or partial agonist analgesics should not be used concomitantly with tapentadol ER.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.
- Gabapentin, gabapentin enacarbil, pregabalin, and pregabalin ER carry warnings regarding the risk of respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment.
- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions. Methemoglobinemia has been reported in association with local anesthetic use.
- Topical capsaicin carries warnings for severe irritation with unintended exposure, pain associated with application, and temporary reductions in sensory function.
- The following monitoring parameters are recommended with treatment:
  - Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin.
  - Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, MAOIs, linezolid, and methylene blue).
  - Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored for 72 hours after initiating tapentadol ER treatment and monitored throughout treatment due to an increased risk of respiratory depression.
  - Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
  - Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
  - Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.
- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with central nervous system-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.
  - Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine delayed-release)	Capsule	Oral	Once daily	Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency
Gralise (gabapentin ER)	Tablet	Oral	Once daily	Administer with evening meal

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Reduce dose in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Twice daily	Administer with food Reduce dose in CrCl < 60 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	Apply for up to 12 hours within a 24-hour period Caution in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min Administer after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	Reduce dose in CrCl < 60 mL/min
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	Schedule II controlled substance Do not use in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment Reduce dose in moderate hepatic impairment
Qutenza (capsaicin)	Patch	Transdermal	30-minute (DPN) or 60-minute (PHN) application of up to 4 patches every 3 months	Only administered by physicians or health care professionals
Savella (milnacipran)	Tablet	Oral	Twice daily	Reduce dose in CrCl < 30 mL/min Caution in patients with moderate renal impairment or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; DPN = diabetic peripheral neuropathy; ESRD = end-stage renal impairment; PHN = postherpetic neuralgia
See the current prescribing information for full details

CONCLUSION

- Included in this review are the neuropathic pain and fibromyalgia agents, duloxetine, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, tapentadol ER, capsaicin, and milnacipran. In general, these agents are FDA-approved for the treatment of diabetic peripheral neuropathic pain, PHN, and/or fibromyalgia.
- Clinical trials support the use of the neuropathic pain and fibromyalgia agents for their FDA-approved indications. Available data demonstrate that neuropathic pain and fibromyalgia agents provide relief from pain; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are rare, and consistent benefit of one agent over another has not been demonstrated.
- According to the available literature, tricyclic antidepressants and duloxetine demonstrate an ability to provide pain relief in patients with painful diabetic neuropathy. While pregabalin and valproate have both demonstrated usefulness in the management of diabetic neuropathy, available literature suggests that the utility of gabapentin is less certain. There is minimal evidence evaluating the use of topical lidocaine and capsaicin for the management of painful diabetic neuropathy. Strong opioids have demonstrated efficacy compared to placebo; however, prescribers may consider this

as last line therapy due to concerns regarding long-term safety, including addiction potential and misuse (*Attal et al 2010, Feldman et al 2020[b], Schwartz et al 2011*).
  - Of the neuropathic pain and fibromyalgia agents included in the review, capsaicin, duloxetine, pregabalin, pregabalin ER, and tapentadol ER are approved for the management of diabetic neuropathy.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo (*Bajwa et al 2019*).
  - Of the neuropathic pain and fibromyalgia agents included in this review, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin are approved for the management or relief of pain associated with PHN.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg 2018*).

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