



## Neuropathic Pain Therapeutic Class Review (TCR)

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May 21, 2019

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Post-herpetic Neuralgia (PHN)	Diabetic Peripheral Neuropathy (DPN)	Neuropathic Pain	Fibromyalgia	Other Indications
capsaicin OTC <sup>1</sup>	generic	--	--	X	--	Treatment of mild to moderate pain
duloxetine (Cymbalta®) <sup>2</sup>	generic*, Eli Lilly	--	X	X	X	Major depressive disorder; generalized anxiety disorder; chronic musculoskeletal pain
gabapentin (Neurontin®) <sup>3</sup>	generic, Pfizer	X	--	--	--	Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy; adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 to 12 years
gabapentin (Gralise®) <sup>4</sup>	Depomed	X	--	--	--	--
gabapentin enacarbil (Horizant®) <sup>5</sup>	Xenoport	X	--	--	--	Treatment of moderate-to-severe primary restless legs syndrome in adults
gabapentin/lidocaine/menthol <sup>†</sup> (Active-PAC with Gabapentin™) <sup>6</sup>	Pharmaceutica North America	X	--	--	--	Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy; adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 to 12 years
gabapentin/lidocaine/menthol <sup>†</sup> (SmartRx Gaba Kit™) <sup>7</sup>	MAS Management Group	X	--	--	--	Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy

**FDA-Approved Indications (continued)**

Drug	Manufacturer	Post-herpetic Neuralgia (PHN)	Diabetic Peripheral Neuropathy (DPN)	Neuropathic Pain	Fibromyalgia	Other Indications
gabapentin/ methyl salicylate/ menthol/ capsaicin <sup>†</sup> (SmartRx Gaba-V Kit <sup>™</sup> ) <sup>§</sup>	MAS Management Group	X	--	--	--	Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy
lidocaine 1.8% (Ztlido <sup>™</sup> ) <sup>§</sup>	Scilex	X	--	--	--	--
Lidocaine 5% <sup>‡</sup> (Lidoderm <sup>®</sup> , DermacinRx <sup>®</sup> PHN Pak <sup>™</sup> , Lidopure Patch <sup>™</sup> , LMR Plus <sup>™</sup> , Neurcaine <sup>™</sup> 5% Kit <sup>®</sup> , Zilacaine <sup>™</sup> ) <small>10,11,12,13, 14,15</small>	Endo, generic; Puretek, Shoreline	X	--	--	--	--
milnacipran (Savella <sup>®</sup> ) <sup>16</sup>	Allergan	--	--	--	X (in adults)	--
pregabalin (Lyrica <sup>®</sup> ) <sup>17</sup>	generic, Pfizer	X	X	X (associated with spinal cord injury)	X	Partial onset seizures as adjunctive therapy in adults and pediatric patients 1 month and older
pregabalin ER <sup>§</sup> (Lyrica CR <sup>®</sup> ) <sup>18</sup>	Pfizer	X	X	--	--	--
tapentadol ER <sup>¶</sup> (Nucynta ER <sup>®</sup> ) <sup>19</sup>	Depomed	--	X (in adults)	--	--	--

OTC = over-the counter; ER = extended-release

\* A duloxetine 40 mg strength from Lupin was FDA-approved via an Abbreviated New Drug Application (ANDA).<sup>20</sup> It is approved for major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathy (DPN), and chronic musculoskeletal pain.

† While approved indications for gabapentin component are listed, the product packaged as a kit is intended for treatment of PHN. The topical kit component is intended for temporary relief of pain associated skin irritations or muscle or joint pain.

‡ DermacinRx PHN Pak and Neurcaine 5% Kit include lidocaine patch co-packaged with an emollient cream. Lidopure includes a lidocaine patch co-packaged with kinesiology tape (Xrylix<sup>™</sup>). LMR Plus includes a lidocaine patch co-packaged with menthol gel. Zilacaine includes a lidocaine patch co-packaged with a gel dressing (Nuvazil<sup>™</sup>) to flatten, soften, and fade new hypertrophic scars or keloids. Ztlido (lidocaine 1.8%) was FDA-approved via the 505(b)(2) pathway, in which approval relied, at least in part, on data not developed by the applicant.<sup>21,22</sup>

§ Efficacy for the management of fibromyalgia has not been established for pregabalin ER (Lyrica CR).

¶ Immediate-release tapentadol (Nucynta<sup>®</sup>) is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternatives are inadequate, but does not have an indication specific to DPN.

Capsaicin (Qutenza® Kit) 8% patch, manufactured by Acorda, is indicated for the management of neuropathic pain associated with postherpetic neuralgia.<sup>23</sup> Administration by a healthcare professional in an office/clinic setting is required.

Products packaged as kits are discussed in the FDA Indications and Dosages sections, and components are addressed in the Pharmacology section. For other information regarding these products, please refer to the primary component throughout the text (e.g., gabapentin, lidocaine).

Pregabalin (Lyrica, Lyrica CR) is a Schedule V controlled substance.

## OVERVIEW

Neuropathic pain can be caused by a number of different diseases (e.g., diabetes mellitus, herpes zoster, human immunodeficiency virus [HIV] infection), medical interventions (e.g., chemotherapy, surgery), and injuries. It has recently been defined as the pain that evolves as a result of direct injury or disease to the nervous system, specifically the somatosensory system.<sup>24</sup>

Neuropathic pain is commonly associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). This review will have a concentration on PHN, DPN, neuropathic pain in general, and fibromyalgia.

### Postherpetic Neuralgia

Postherpetic Neuralgia (PHN) is a long-lasting pain disorder that causes pain from stimuli that are not normally painful. There are a number of oral medications available to treat neuropathic pain. The most recent 2004 (reaffirmed 2008) American Academy of Neurology treatment guidelines advise that tricyclic antidepressants (TCAs), gabapentin, pregabalin (Lyrica), opioids, and lidocaine transdermal patches (Lidoderm) can be used as the first option in treating PHN.<sup>25</sup> Notably, these guidelines were retired in February 2018; pregabalin ER (Lyrica CR) and **Ztlido lidocaine patches** were not available at the time that this practice guideline was published.

### Diabetic Peripheral Neuropathic Pain and Neuropathic Pain

Diabetic peripheral neuropathy (DPN), a common complication of diabetes, typically presents as diabetic peripheral neuropathic pain (DPNP). The etiology, though not completely understood, is thought to be multifactorial. The most common symptoms associated with DPNP are pain or loss of feeling in the toes, feet, legs, and arms. DPNP can affect many aspects of life and severely limit the patient's daily functions. Loss of sensation in the periphery may lead to muscle weakness and loss of reflexes, especially in the ankles, which can lead to gait disturbances. Patients with DPNP may be unaware of pressure or injury, leading to blisters or sores appearing on numb areas of the foot or leg. These areas may go unnoticed for extended periods of time, increasing the risk for infection and, possibly, amputation.<sup>26,27,28,29,30</sup>

Diagnosis of DPNP is based on the presence of symptoms and a physical exam. A comprehensive foot exam is performed to assess skin appearance and integrity, muscles, bones, circulation, and sensation of the feet. Pin prick sensation, vibration perception, 10-g monofilament pressure sensation, and assessment of ankle reflexes are commonly performed tests used to screen, diagnose, and assess DPNP. General treatment measures include glycemic control, foot care, and the treatment of pain.

Both duloxetine (Cymbalta) and pregabalin (Lyrica, Lyrica CR) are approved specifically for DPN. Tapentadol ER (Nucynta ER) is indicated for the management of neuropathic pain associated with DPN in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.<sup>31</sup>

According to a 2015 peripheral neuropathy review by the Mayo Clinic, first-line treatment of diabetic peripheral neuropathy includes gabapentin (Neurontin, generics) or pregabalin (Lyrica, generics), tricyclic antidepressants, or duloxetine (Cymbalta, generic).<sup>32</sup> The choice of first-line agents should be based on patient comorbidities. If a first-line agent fails, they advise a trial of another first-line agent after tapering off the original medication. Second- and third-line agents include opioid analgesics.<sup>33</sup> Duloxetine is not recommended for patients with hepatic insufficiency or where drug interactions are a factor; caution should also be used in patients with delayed gastric emptying. Pregabalin ER (Lyrica CR) was not available at the time that this practice guideline was published.

According to the 2011 American Academy of Neurology (AAN) guidelines for the management of diabetic neuropathic pain, treatments include pregabalin (Level A recommendation) which is established as effective and amitriptyline, duloxetine, venlafaxine, gabapentin, valproate, opioids (morphine sulfate, oxycodone controlled-release, or tramadol), or topical capsaicin (all Level B recommendations) which are probably effective.<sup>34</sup> Effective treatments for painful diabetic neuropathy are available, but many have adverse effects that limit their usefulness, and few studies have adequate information on treatment effects on function and quality of life. Pregabalin ER (Lyrica CR) was not available at the time that this practice guideline was published.

The 2017 position statement by the American Diabetes Association (ADA) recommends that either pregabalin or duloxetine as initial pharmacologic treatments for neuropathic pain in diabetes.<sup>35</sup> Gabapentin may also be used initially to account for patients' socioeconomic status, comorbidities, and potential drug interactions. Off-label use of tricyclic antidepressants may be used with caution due to their higher adverse effect profile, but opioids are not recommended as first- or second-line agents. Pregabalin ER (Lyrica CR) was not available at the time that this practice guideline was published. The 2018 Standards of Care in Diabetes from the ADA also state that either pregabalin or duloxetine are recommended as initial pharmacologic treatments for neuropathic pain in diabetes.<sup>36</sup>

## **Fibromyalgia**

Fibromyalgia is a chronic disorder characterized by pain, fatigue, and sleep disturbances.<sup>37,38,39</sup> It predominantly affects women and is difficult to treat. A multidisciplinary approach should be utilized. In 2010, the American College of Rheumatology (ACR) updated the diagnostic criteria for fibromyalgia. Although the presence of widespread pain is still needed for diagnosis, a specific number of tender points is no longer required. Rather, a widespread pain index (WPI) and symptom severity scale (SS), which includes somatic symptoms, waking unrefreshed, cognition, and fatigue, is employed.<sup>40</sup> Symptoms must have been present for at least 3 months and cannot be explained by another medical condition. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia. Laboratory tests for thyroid stimulating hormone (TSH) and erythrocyte sedimentation rate (ESR) are recommended to rule out hypothyroidism and polymyalgia rheumatica, respectively, as they have similar symptomatology.

TCAs, a class of drugs not approved for the treatment of fibromyalgia, have been found to be effective in a couple of trials of short duration.<sup>41,42</sup> These drugs are associated with a number of adverse effects,

including anticholinergic effects (e.g., dry mouth and urinary retention), orthostatic hypotension, and cardiac dysfunction. Gabapentin is not approved for the treatment of fibromyalgia, although its effectiveness in the treatment of fibromyalgia is supported by data.<sup>43</sup> Gabapentin has low bioavailability and is not rapidly absorbed; therefore, it requires a dosage regimen of 3 to 4 times daily. The American Pain Society (APS) last produced guidelines for fibromyalgia pain treatment in 2005, prior to any product receiving Food and Drug Administration (FDA) approval for treatment of this condition.<sup>44</sup> However, these guidelines are available for archival purposes only due to their age. FDA-approved drugs for the treatment of fibromyalgia now include duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica). The APS guidelines recommend amitriptyline (and other TCAs) or cyclobenzaprine as the initial pharmacologic option, with selective serotonin reuptake inhibitors (SSRIs), tramadol, and opioids also listed as subsequent options. Amitriptyline and cyclobenzaprine received the highest ranking regarding strength and consistency of evidence at the time. There is no comparative evidence to support the superiority of any of these products for the treatment of fibromyalgia.

## PHARMACOLOGY<sup>45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61</sup>

Drug Mechanism of Action	Mechanism of Action
capsaicin (OTC)	Causes an initial enhanced stimulation of transient receptor potential vanilloid 1 (TRPV1), expressed on nociceptive nerve fibers in the skin; stimulation may result in painful sensations followed by pain relief thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings
duloxetine (Cymbalta)	Potential of serotonergic and noradrenergic activity in the central nervous system (CNS)
gabapentin (Gralise, Neurontin)	Binds to the presynaptic $\alpha$ 2-delta subunit of voltage sensitive calcium channels
gabapentin enacarbil (Horizant)	Prodrug of gabapentin; gabapentin binds to the presynaptic $\alpha$ 2-delta subunit of voltage sensitive calcium channels
lidocaine (Lidoderm, Ztlido)	Stabilizes neuronal membranes by inhibiting the ionic fluxes required for initiation and conduction of impulses
menthol	based on observation, local effects include mild analgesia, cooling sensation, irritant/counter-irritant effect, and vasodilation through an undefined mechanism of action; analgesia may occur directly through interaction with kappa-opioid receptors or indirectly through nociceptor activation and resultant counter-irritant effect
methyl salicylate	inhibits the synthesis of prostaglandins by irreversibly acetylating and inactivating cyclooxygenase
milnacipran (Savella)	Potential of serotonergic and noradrenergic activity in the CNS; exact mechanism in fibromyalgia is unknown
pregabalin (Lyrica, Lyrica CR)	Pregabalin binds to presynaptic $\alpha$ 2-delta subunit of voltage sensitive calcium channels, inhibiting release of pro-nociceptive neurotransmitters in the spinal cord.
tapentadol ER (Nucynta ER)	Centrally-acting synthetic analgesic; exact mechanism of action unknown Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI)

## PHARMACOKINETICS<sup>62,63,64,65,66,67,68,69,70,71,72</sup>

Systemic absorption of the topical agents included in this review is low. No detectable levels of capsaicin metabolites were observed in treated patients. The duration of action of capsaicin cream is about 4 to 6 hours, with maximal pain relief occurring with 2 weeks of continuous therapy.

Lidocaine (Lidoderm, Ztlido) has varied absorption depending on the duration of application and the surface area over which it is applied. Only 3% ( $\pm$  2%) of the applied dose of lidocaine 5% patch (Lidoderm) is expected to be systemically absorbed. At least 95% of lidocaine 5% (Lidoderm) within the transdermal system will remain in a used patch. The lidocaine 1.8% (Ztlido) and 5% adhesive patches (Lidoderm) contain 36 mg and 700 mg of lidocaine, respectively. Bioavailability of the patches differ and equivalent exposure between the patches was demonstrated in a single-dose, crossover study in healthy subjects. Lidocaine is approximately 70% protein bound; although, at higher concentrations, the binding becomes concentration-dependent. Metabolism in the skin is unknown; however, lidocaine is metabolized rapidly by the liver to a number of metabolites which are then renally excreted.

A clinical trial (n=54) demonstrated 87% of patients experienced at least 90% adherence of the lidocaine 1.8% patch (Ztlido) during the 12 hours of administration; the remaining 13% had 75% to < 90% adherence.

Duloxetine is a naphthalene derivative that is converted to naphthol in acidic environments. Even though duloxetine is enteric coated, conversion may occur with delayed gastric emptying, such as with diabetic gastroparesis, which is due to autonomic nerve toxicity.<sup>73</sup> Naphthol is also known to cause ocular toxicity which may be of concern in diabetics.<sup>74</sup>

Drug	Bioavailability (%)	Tmax (hrs)	Half-life (hrs)	Active Metabolites	Excretion (%)
duloxetine (Cymbalta)	N/A	6	12	None	Urine: 70 Feces: 20
gabapentin (Neurontin)	27–60 (not dose proportional)	2–4	5–7	None	Renal
gabapentin (Gralise)	N/A	8	5–7	None	Renal
gabapentin enacarbil (Horizant)	42-65 (fasting state) 75 (fed state)	5 (fasting state) 7.3 (fed state)	5.1–6	Yes	Renal
milnacipran (Savella)	85–90	2–4	6–8	None	Urine: 55
pregabalin (Lyrica)	> 90	0.7-1.5	6	None	Urine: 90–98
pregabalin ER (Lyrica CR)	> 90	5-12	6.3	None	Urine: 90
tapentadol ER (Nucynta ER)	32	3–6	5	None	Renal

N/A = not available

\*Both Gralise and Horizant are not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.



## CONTRAINDICATIONS/WARNINGS<sup>75,76,77,78,79,80,81,82,83,84,85</sup>

Capsaicin (OTC) has no contraindications. Capsaicin should not be used near eyes, mucus membranes, or near skin with abrasions, irritation, infection, or inflammation. If irritation does occur, flush the affected area with water. Inhalation of airborne capsaicin following patch removal or removal of clothing covering capsaicin cream can cause coughing or sneezing. Blood pressure may increase transiently during and after capsaicin administration and should be monitored. Patients should be prepared to treat acute pain during and following capsaicin application with local cooling or appropriate analgesics. Treated areas may become heat-sensitive following application.

Lidocaine transdermal systems (Lidoderm, **Ztlido**) are contraindicated in patients with a known history of sensitivity to local amide anesthetics, or to any other component of the product.

Used lidocaine patches (Lidoderm) will still contain residual lidocaine (at least 665 mg for Lidoderm; **not specified for Ztlido**). To avoid accidental exposure of children, pets, and others, proper storage and disposal of lidocaine patches is highly recommended. Use of lidocaine with external heating sources, such as heating pads or electric blankets, should be avoided. Extended duration of application of lidocaine-containing patches (Lidoderm, **Ztlido**), application of more than the recommended number of patches, use in smaller patients, or use in patients with impaired elimination may lead to increased blood concentrations of lidocaine and serious adverse effects. Lidocaine patches should only be applied to intact skin.

Skin reactions at the application site of the lidocaine patch (Lidoderm, **Ztlido**) may develop during or immediately after treatment. Reactions are typically mild and resolve within a few hours, and include blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, and abnormal sensation.

**Although not reported, there is a potential for cross-sensitivity of lidocaine 1.8% patch (Ztlido) in patients allergic to PABA derivatives.**

In 2008, the FDA informed healthcare professionals that the Agency analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of 11 drugs used to treat epilepsy, as well as psychiatric disorders and other conditions.<sup>86</sup> The FDA's analysis stated that patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as 1 week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the 11 drugs. Gabapentin and pregabalin were among the drugs that were included in the analysis. The relative risk for suicidality was higher in patients with epilepsy compared to patients who were given 1 of the drugs in the class for psychiatric or other conditions.

Healthcare professionals should closely monitor all patients currently taking or starting any antiepileptic drug, including gabapentin (Neurontin, Gralise), gabapentin enacarbil (Horizant), and pregabalin (Lyrica, Lyrica CR), for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts, behavior, or depression.

Duloxetine (Cymbalta) and milnacipran (Savella) also have boxed warnings regarding the risk of suicide. Like other antidepressants, including serotonin-norepinephrine reuptake inhibitors (SNRIs), these agents increase the risk compared to placebo of suicidal thinking and behavior (suicidality) in children,



adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Healthcare professionals considering the use of any antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Milnacipran is not approved for use in pediatrics and duloxetine is not indicated to treat neuropathic pain in pediatric patients.

Concomitant use of duloxetine with monoamine oxidase inhibitors (MAOIs) is also contraindicated.

Treatment with SNRIs, including duloxetine and milnacipran, has been associated with increases in blood pressure compared to placebo. Blood pressure should be measured prior to initiating treatment and periodically throughout treatment. Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine, especially during the first week of therapy or after dose increases. The risk of decreased blood pressure may be greater in patients taking concomitant medications that induce orthostatic hypotension or are potent CYP1A2 inhibitors and in patients taking duloxetine at doses above 60 mg daily. Consider discontinuation of duloxetine in patients with symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reaction has been reported with SNRI (duloxetine) treatment, particularly with concomitant use of serotonergic drugs, including triptans, tricyclic antidepressants (TCAs), fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's wort, and drugs that impair metabolism of serotonin, including MAOIs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

SNRIs, including duloxetine and milnacipran, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may increase this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding.

Duloxetine and milnacipran have been known to affect urethral resistance. If symptoms of urinary hesitation develop, consideration should be given to the possibility that it might be drug-related.

Duloxetine and milnacipran should not be prescribed for patients with substantial alcohol use or evidence of chronic liver disease. Elevated transaminases, bilirubin, and other liver function markers have occurred when SNRIs have been given to such patients. There have been reports of hepatic failure in patients treated with either duloxetine or milnacipran.

Duloxetine should not be used within 2 weeks of stopping an MAOI. Additionally, when converting from an MAOI to duloxetine, there must be a washout period of 7 to 14 days.

Due to the risk of serotonin syndrome, milnacipran is also contraindicated with concomitant use with MAOIs for the treatment of psychiatric disorders. If treatment with an MAOI is absolutely necessary, milnacipran should be discontinued 5 days prior to initiating an MAOI or 14 days should elapse before discontinuation of an MAOI and initiation of milnacipran.

Heart rate should be measured at baseline prior to the initiation of milnacipran treatment and periodically thereafter. For patients who experience a sustained increase in heart rate while receiving milnacipran, dose reduction or discontinuation of milnacipran may be clinically warranted.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a multi-organ hypersensitivity reaction, has occurred with gabapentin, including gabapentin enacarbil. Some cases have been fatal or life threatening. Manifestations of DRESS typically include fever, rash, and/or lymphadenopathy in conjunction with other organ system abnormalities, including hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis.

Gabapentin and pregabalin may cause somnolence/sedation and dizziness. Patients should be cautioned when driving or operating a car or other complex machinery until sufficient experience is gained to assess the ability to perform these tasks.

Gabapentin and pregabalin (Lyrica, Lyrica CR) should be gradually withdrawn over at least a 1-week period to minimize the potential of increased seizure frequency. A gradual reduction in the dose of SNRIs, including duloxetine and milnacipran, rather than abrupt cessation is also recommended, whenever possible.

Peripheral edema is a concern with pregabalin products. There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Gabapentin can also cause angioedema and anaphylaxis after the first dose or at any time during treatment with the same symptoms and difficulty breathing. Immediate medical care should be sought if these signs and symptoms are experienced. Exercise caution when prescribing pregabalin to patients with a history of angioedema or who are already taking medications associated with angioedema, such as angiotensin-converting enzyme (ACE) inhibitors.

Tapentadol ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma, paralytic ileus, and in patients concurrently using MAOIs or patients who have used MAOIs in the past 14 days.

Tapentadol ER is a Schedule II controlled substance. It has a boxed warning regarding abuse potential, life-threatening respiratory depression, accidental exposure, interaction with alcohol, and risk of concomitant use with benzodiazepines or other central nervous system (CNS) depressants. Concomitant prescribing should occur when alternative treatment options are inadequate; dosages and durations should be limited to the minimum required; and patients should be monitored carefully for signs and symptoms of respiratory depression and sedation.

Tapentadol ER is cautioned in patients with a history of seizures. Serotonin syndrome could result from other medications that exhibit serotonergic activity.

Gabapentin is not a scheduled drug but recent post-marketing reports point to misuse and abuse. The patient's drug abuse history must be evaluated prior to prescribing gabapentin, and the patient must be observed for signs and symptoms.

## **Medication Guide/Risk Evaluation and Mitigation Strategies (REMS)**

Tapentadol ER (Nucynta ER) has been placed into the "Extended-Release and Long-Acting Opioid Analgesics" REMS program. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.<sup>87</sup> Other agents do not require a REMS program, but duloxetine, gabapentin, milnacipran, pregabalin, and pregabalin ER prescriptions are dispensed with a medication guide.

## DRUG INTERACTIONS<sup>88,89,90,91,92,93,94,95,96,97,98</sup>

No drug interactions have been reported with capsaicin.

Lidocaine-containing patches (Lidoderm, **Ztlido**) should be used with caution in patients receiving Class I antiarrhythmics (e.g., tocainide and mexiletine) since the toxic effects are additive and potentially synergistic. In addition, caution should also be exercised when using lidocaine-containing patches with other products containing local anesthetics.

Duloxetine (Cymbalta) should not be used concomitantly within 2 weeks of stopping an MAOI. Additionally, when converting from an MAOI to duloxetine, there must be a washout period of 7 to 14 days.

Milnacipran (Savella) should not be started in a patient being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome.

Duloxetine is a moderate inhibitor of CYP2D6 and is also affected by inhibitors of CYP2D6 and CYP1A2 (increased duloxetine levels), and may impact the metabolism of other drugs metabolized by CYP2D6. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine and thioridazine should not be co-administered. Drugs that raise the gastric pH may lead to early release of duloxetine when given concomitantly. Duloxetine is highly protein bound and administration with another highly protein bound drug may increase free concentrations of the other drug.

Antacids may reduce the bioavailability of gabapentin (n=16) by approximately 20%. It is recommended that gabapentin be taken at least 2 hours following antacids containing aluminum and magnesium administration.

The development of a potentially life-threatening serotonin syndrome may occur with duloxetine and milnacipran (Savella) treatment, particularly with concomitant use of serotonergic drugs, including triptans, and with drugs which impair metabolism of serotonin, including MAOIs. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Concomitant use of these agents with a triptan requires careful observation of the patient, particularly during treatment initiation and dosage increases. Concomitant treatment with duloxetine and milnacipran with serotonergic or anti-dopaminergic agents, including antipsychotics, should be discontinued immediately if signs of serotonin syndrome and/or neuroleptic malignant syndrome emerge. These symptoms may include mental status changes, autonomic instability, neuromuscular aberrations, and/or gastrointestinal symptoms. Supportive symptomatic treatment should be initiated immediately. In addition, there is an increased risk of serotonin syndrome in patients treated with linezolid or intravenous methylene blue while on duloxetine therapy. Duloxetine should not be taken concomitantly unless acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits are judged to outweigh the risks. The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first.

Milnacipran inhibits the reuptake of norepinephrine; therefore, concomitant use of milnacipran with epinephrine and norepinephrine may be associated with paroxysmal hypertension and possible arrhythmia.

Given the primary CNS effects of duloxetine and milnacipran, caution should be used when either is taken in combination with other centrally-acting drugs, including those with a similar mechanism of action.

In a drug-drug interaction study, an increase in euphoria and postural hypotension was observed in patients who switched from clomipramine to milnacipran.

Use of milnacipran concomitantly with digoxin may be associated with potentiation of adverse hemodynamic effects. Postural hypotension and tachycardia have been reported in combination therapy with intravenously administered digoxin. Co-administration of milnacipran and intravenous digoxin should be avoided.

Because milnacipran inhibits norepinephrine reuptake, co-administration with clonidine may inhibit clonidine's anti-hypertensive effect.

Pregabalin (Lyrica, Lyrica CR) is predominantly excreted unchanged in the urine; it undergoes negligible metabolism in humans (less than 2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins. Its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.

Concomitant use of alcohol can increase plasma levels of tapentadol ER (Nucynta ER). Alcohol should be avoided while on tapentadol ER. MAOIs should not be taken within 14 days of using tapentadol ER. Concurrent use of tapentadol ER and other CNS depressants, including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol, can increase the risk of respiratory depression, hypotension, profound sedation, or coma. The concomitant use of tapentadol ER with mixed agonist/antagonists (e.g., butorphanol, nalbuphine, and pentazocine) and partial agonists (e.g., buprenorphine) may precipitate withdrawal symptoms, and anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

## ADVERSE EFFECTS<sup>99,100,101,102,103,104,105,106,107,108,109</sup>

Drug	Pruritus	Dermatitis	Burning	Nausea	Dysgeusia	Headache
capsaicin OTC	nr	nr	reported	nr	nr	nr
lidocaine (Lidoderm, Ztlido)	reported	reported	reported	reported	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences

Drug	Weight Change	Nausea	Diarrhea	Somnolence	Dizziness	Dry Mouth	Constipation	Edema	Tremor
duloxetine (Cymbalta)	-0.6 kg	24	9	12	10	11	11	nr	2
gabapentin (Neurontin)	reported	3.9	5.7	21.4	28	4.8	3.9	8.3	reported
gabapentin (Gralise)	reported	nr	3.3	4.5	10.9	2.8	1.4	3.9	reported
gabapentin enacarbil (Horizant)	reported	4-9	nr	10-14	17-30	reported	nr	6-7	nr
milnacipran (Savella)	-0.8 kg	35-39	reported	reported	10-11	5	15-16	reported	2
pregabalin (Lyrica)	0-9	4.9	reported	0.5-23	8-30	2-7	0-6	4-12	1-2
pregabalin ER (Lyrica CR)	3.7-9	3-3.4	1-1.4	0.5-15.8	3.4-24	0.5-3.7	0-2.7	0.4-1.4	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Data for the placebo group are indicated in parentheses. nr = not reported.

Gabapentin has an 8.3% incidence of nystagmus compared to 4% for placebo. Agitation has been reported as an adverse effect in post-marketing experience with gabapentin.

There have been reports of peripheral edema and angioedema; these included postmarketing cases of angioedema with respiratory compromise requiring emergency treatment in patients during initial and chronic treatment with pregabalin (Lyrica, Lyrica CR). Caution is advised with the use of pregabalin in those with concurrent use of a thiazolidinedione's and with the diagnosis of heart failure as an exacerbation can occur. In clinical trials, pregabalin ER (Lyrica, Lyrica CR) has been associated with blurred vision. See the *Contraindications/Warnings* section of this review for additional information.

Cases of acute pancreatitis and Takotsubo cardiomyopathy have been reported with both duloxetine (Cymbalta) and milnacipran (Savella).

The most common ( $\geq 10\%$ ) adverse reactions reported with tapentadol ER (Nucynta ER) were nausea, constipation, dizziness, headache, and somnolence.

## SPECIAL POPULATIONS<sup>110,111,112,113,114,115,116,117,118,119,120</sup>

### Pediatrics

Safety and effectiveness in pediatric patients for the topical products in this review have not been established.

The use of pregabalin ER (Lyrica CR), milnacipran (Savella), duloxetine (Cymbalta), and tapentadol ER (Nucynta ER) have not been adequately studied in children.

Gabapentin (Neurontin) is indicated for treatment of partial seizures in children 12 years of age and older with epilepsy and as adjunctive therapy for treatment of partial seizures in children 3 to 12 years of age with epilepsy. The safety and effectiveness of gabapentin (Gralise, Horizant, Neurontin) in the management of postherpetic neuralgia in patients less than 18 years of age have not been studied.

Pregabalin (Lyrica) is indicated for the adjunctive treatment of partial-onset seizures in children  $\geq 1$  month of age; however, the safety and effectiveness of pregabalin (Lyrica) in the management of postherpetic neuralgia, diabetic peripheral neuropathy, neuropathic pain associated with spinal cord injury, or fibromyalgia in patients less than 18 years of age have not been studied.

### Pregnancy

Capsaicin (OTC) and lidocaine 5% patch (Lidoderm) are Pregnancy Category B. Labeling for lidocaine 1.8% patch (Ztlido) complies with the Pregnancy and Lactation Labeling Rule (PLLR) and advises that there is limited data for use in pregnant women to inform of drug-related risks to the fetus.

Duloxetine (Cymbalta) and milnacipran (Savella) are Pregnancy Category C. Neonates exposed to SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Gabapentin (Neurontin) and pregabalin (Lyrica, Lyrica CR) labeling complies with the Pregnancy and Lactation Labeling Rule (PLLR). There are no adequate and well-controlled studies of gabapentin or pregabalin use in pregnant women; however, developmental toxicity, including fetal structural abnormalities, have been reported in animal studies at higher than recommended human dose equivalents. Previously, both were considered Pregnancy Category C.

Although classified as Pregnancy Category C, gabapentin (Gralise, Horizant) has not been evaluated for use during pregnancy.

Tapentadol ER (Nucynta ER) is Pregnancy Category C. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A boxed warning instructs that prolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which can be life-threatening if not recognized and treated properly.

## Renal impairment

Duloxetine (Cymbalta) is not recommended for patients with end-stage renal disease (ESRD) or severe renal impairment (estimated creatinine clearance < 30 mL/min).

Dosage adjustments are recommended for gabapentin (Gralise, Horizant, Neurontin) in patients with compromised renal function. Gabapentin has not been studied in pediatric patients with renal insufficiency.

Milnacipran (Savella) dose adjustment is necessary in patients with severe renal impairment.

Pregabalin (Lyrica, Lyrica CR) is excreted primarily by the renal route; therefore, dosage should be adjusted based on renal function as determined by creatinine clearance. Pregabalin is effectively removed from the plasma by hemodialysis. Detailed dosing recommendations based on total daily dose and creatinine clearance are outlined in the labeling. Pregabalin ER (Lyrica CR) is not recommended for patients on hemodialysis.

Tapentadol ER (Nucynta ER) is not recommended in patients with severe renal impairment due to accumulation of a metabolite formed by tapentadol.

## Hepatic Impairment

Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine (Lidoderm, **Ztlido**) because of their inability to metabolize lidocaine normally.

Duloxetine (Cymbalta) and milnacipran (Savella) should not be administered to patients with severe hepatic insufficiency as these products increase the risk of elevation of serum transaminase levels.

Use of tapentadol ER (Nucynta ER) is not recommended in severe hepatic impairment. The dose of tapentadol ER should be reduced in patients with moderate hepatic impairment.



## DOSAGES<sup>121,122,123,124,125,126,127,128,129,130,131</sup>

Drug	Initial Dose	Maximum Dose	Availability
capsaicin*	Apply topically up to 5 applications daily to affected areas	Wash hands with soap and water after applying	0.025%, 0.033%, 0.075%, 0.1% cream 0.15% liquid 8% patch + cleansing gel (Qutenza kit)
duloxetine (Cymbalta)	<b>DPN:</b> 60 mg once daily <b>Fibromyalgia:</b> 30 mg once daily <b>Chronic musculoskeletal pain:</b> 30 mg once daily	60 mg once daily	20 mg, 30 mg, 40 mg (generic only), 60 mg capsules
gabapentin (Neurontin)	300 mg 3 times a day	3,600 mg/day (3 times a day); up to 50 mg/kg/day (pediatric dose)	100 mg, 300 mg, 400 mg capsules 600 mg, 800 mg tablets 250 mg/5 mL solution
gabapentin (Gralise)	300 mg/day	1,800 mg/day (once daily)	300 mg, 600 mg extended-release tablets 30-day starter pack
gabapentin enacarbil (Horizant)	600 mg/day for 3 days	600 mg twice daily	300 mg, 600 mg extended-release tablets
gabapentin/lidocaine/ menthol (Active-PAC with Gabapentin)	<b>gabapentin:</b> 300 mg dose on Day 1, 600 mg/day on Day 2 (divided twice daily), and 900 mg/day on Day 3 (divided 3 times daily) <b>Topical component (Lenzagel):</b> apply to affected area up to 4 times daily	<b>gabapentin:</b> Titrate up as needed for pain relief to a daily dose of 1,800 mg (divided 3 times daily) <b>Topical component (LenzaGel):</b> use up to 4 times daily	gabapentin 300 mg (#90) capsules co-packaged with LenzaGel (lidocaine 4%/menthol 1%) 120 g
gabapentin/lidocaine/ menthol (SmartRx Gaba Kit)	<b>gabapentin:</b> 300 mg dose on Day 1, 600 mg/day on Day 2 (divided twice daily), and 900 mg/day on Day 3 (divided 3 times daily) <b>Topical component (Avaderm):</b> apply to affected area up to 3 to 4 times daily	<b>gabapentin:</b> Titrate up as needed for pain relief to a daily dose of 1,800 mg (divided 3 times daily) <b>Topical component (Avaderm):</b> use up to 4 times daily	SmartRx Gaba Kit: gabapentin 300 mg (#90) capsules co-packaged with Avaderm cream (lidocaine 4%/menthol 1%) 120 g
gabapentin/methyl salicylate/ menthol/capsaicin (SmartRx Gaba-V Kit)	<b>gabapentin:</b> 300 mg dose on Day 1, 600 mg/day on Day 2 (divided twice daily), and 900 mg/day on Day 3 (divided 3 times daily) <b>Topical component (Vitacin):</b> Apply to affected area up to 3 to 4 times daily	<b>gabapentin:</b> Titrate up as needed for pain relief to a daily dose of 1,800 mg (divided 3 times daily) <b>Topical component (Vitacin):</b> Use up to 4 times daily	gabapentin 300 mg (#90) capsules co-packaged with Vitacin cream (methyl salicylate 20%/menthol 5%/capsaicin 0.037%) 120 g

\*Available under various trade names (e.g., Zostrix®, Zostrix HP, Capzasin®)

## Dosages (continued)

Drug	Initial Dose	Maximum Dose	Availability
lidocaine (Ztlido)	Apply up to 3 patches to affected area once daily for up to 12 hours within a 24-hour period	3 patches per day	1.8% patch (Ztlido)
lidocaine (Lidoderm, DermacinRx PHN Pak, Lidopure, LMR Plus, Neurcaine 5% Kit, Zilacaine)	Apply up to 3 patches to affected area once daily for up to 12 hours within a 24-hour period	3 patches per day	5% patch (Lidoderm) DermacinRx PHN Pak and Neurcaine 5% Kit: 5% lidocaine patch co-packaged with emollient combination number 102 Lidopure: 5% lidocaine patch co-packaged with kinesiology tape (Xrylix) LMR Plus: 5% lidocaine patch co-packaged with menthol 6% roll-on gel (Sore No More) Zilacaine: 5% lidocaine patch co-packaged with silicone scar gel dressings (Nuvazil)
milnacipran (Savella)	12.5 mg daily, titrated up to 50 mg twice daily over the course of 1 week	100 mg twice daily	12.5 mg, 25 mg, 50 mg, 100 mg tablets 4-week titration pack
pregabalin (Lyrica)	<b>DPN:</b> 150 mg/day in 3 divided doses <b>PHN:</b> 150 mg/day in 2 to 3 divided doses <b>Fibromyalgia:</b> 150 mg/day in 2 divided doses <b>Neuropathic pain associated with spinal cord injury:</b> 150 mg/day in 2 divided doses	<b>DPN:</b> 300 mg/day <b>PHN:</b> 300 to 600 mg/day <b>Fibromyalgia:</b> 300 to 450 mg/day <b>Neuropathic Pain associated with spinal cord injury:</b> 300 to 600 mg/day	25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg capsules 20 mg/mL oral solution
pregabalin ER (Lyrica CR)	<b>DPN/PHN:</b> 165 mg once daily, after an evening meal Swallow tablet whole; do not split, crush, or chew	<b>DPN/PHN:</b> 330 mg once day within 1 week, after an evening meal <b>PHN:</b> Maximum dose of 660 mg once day, after an evening meal	82.5 mg, 165 mg, and 330 mg extended-release tablets
tapentadol ER (Nucynta ER)	Initially 50 mg twice daily (approximately every 12 hours); Titrate to response and tolerance within therapeutic range of 100 to 250 mg twice daily	500 mg/day	50 mg, 100 mg, 150 mg, 200 mg, 250 mg extended-release tablets

\*One lidocaine 1.8% patch (Ztlido) provides equivalent lidocaine exposure to one lidocaine 5% patch (Lidoderm).

The lidocaine transdermal patches (Lidoderm, Ztlido) may be cut into smaller sizes prior to the removal of the release liner. Used patches should be folded on the adhesive side and discarded out of the reach of children and pets. The patches may not stick wet; avoid contact with water, such as bathing,

swimming, or showering. Patients should wash their hands after handling the patches. Avoid contact with eyes.

## CLINICAL TRIALS

### Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Due to paucity of data, placebo-controlled trials have been included for some categories. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

### Postherpetic Neuralgia (PHN)

#### *capsaicin versus placebo*

A large, double-blind, vehicle-controlled study of 143 patients with chronic PHN was performed to evaluate the efficacy of capsaicin 0.075% cream.<sup>132</sup> Patients with PHN of 6 months' duration or longer were enrolled. All efficacy variables, including the physician's global evaluation of reduction in PHN pain, changes in pain severity on the categorical scale, visual analogue scale (VAS) for pain severity, visual analogue scale for pain relief, and functional capacity scale, showed significant improvement at nearly all time points throughout the study for capsaicin patients. In contrast, the group receiving vehicle cream remained essentially unchanged. There were no serious adverse effects observed or reported throughout the trial.

To establish the effects of capsaicin on daily activities in patients with painful diabetic neuropathy, 277 men and women with painful peripheral polyneuropathy and/or radiculopathy were enrolled in an 8-week, double-blind, vehicle-controlled study with parallel randomized treatment assignments.<sup>133</sup> Participants were unresponsive or intolerant to conventional therapy and were experiencing pain that interfered with functional activities and/or sleep. Either capsaicin 0.075% cream or vehicle cream was applied to the painful areas 4 times daily. A visual analogue scale of pain intensity and baseline measurements of the pain's interference with the ability to walk, work, participate in recreational activities, use shoes and socks, sleep, and eat were recorded at onset and at 2-week intervals. Statistically significant differences were seen in the percentage of patients with improvement in pain (69.5% capsaicin versus 53.4% vehicle patients;  $p=0.012$ ), improvement in walking (26.1% versus 14.6%, respectively;  $p=0.029$ ), improvement in working (18.3% versus 9.2%, respectively;  $p=0.019$ ), improvement in sleeping (29.5% versus 20.3%, respectively;  $p=0.036$ ), and improvement in participating in recreational activities (22.8% versus 12.1%, respectively;  $p=0.037$ ).

A multicenter study established the efficacy of capsaicin 0.075% cream in relieving the pain associated with diabetic neuropathy.<sup>134</sup> Capsaicin or vehicle cream was applied to painful areas 4 times daily for 8 weeks in 252 patients randomly assigned to 1 of 2 groups. Pain intensity and relief were recorded at 2-week intervals using physician's global evaluation and visual analog scales. Analysis at the final visit showed statistical significance favoring capsaicin for the following: pain improvement by the physician's global evaluation scale (69.5% versus 53.4%, respectively), decrease in pain intensity (38.1% versus 27.4%, respectively), and improvement in pain relief (58.4% versus 45.3%, respectively). With the exception of transient burning, sneezing, and coughing, capsaicin was well tolerated.

### ***gabapentin (Gralise) versus placebo***

An 11-week, multinational, double-blind, randomized, placebo-controlled, phase 3 trial assessed the safety and efficacy of extended-release gabapentin.<sup>135</sup> Adult patients with PHN were randomized 1:1 to 1,800 mg gabapentin or placebo once daily as a 2-week titration following by 8 weeks of stable dosing and then 1 week of dose tapering (n=452). Notably, patients were excluded if they had not responded previously to gabapentin  $\geq$  1,200 mg/day or pregabalin  $\geq$  300 mg/day or had dose-limiting adverse effects to gabapentin in the past. The primary endpoint was the change in average daily pain intensity score from baseline to week 10 using baseline observation carried forward (BOCF) and the 11-point numerical rating scale (NRS) (range, 0 [no pain] to 10 [most severe pain]). At the final week, the least squares mean change in pain was -2.12 with gabapentin compared to -1.63 with placebo (p=0.013; difference, 0.49; 95% confidence interval [CI], -0.88 to -0.11). Adverse effects occurred in 53.4% of patients taking gabapentin compared to 39.8% of patients taking placebo. The most common adverse effects reported with gabapentin were dizziness, somnolence, headache, and nausea.

Another 10-week, multinational, double-blind, randomized, placebo-controlled, phase 3 trial also assessed the safety and efficacy of extended-release gabapentin.<sup>136</sup> Adult patients with PHN were randomized 1:1:1 to 1,800 mg gabapentin once daily or divided into 2 daily doses or placebo as a 2-week titration following by 8 weeks of stable dosing and then 1 week of dose tapering (n=407). Again, patients were excluded if they had not responded previously to gabapentin  $\geq$  1,200 mg/day or pregabalin  $\geq$  300 mg/day or had dose-limiting adverse effects to gabapentin in the past. The primary endpoint was the change in average daily pain intensity score (range, 0 to 10) from baseline to week 10 using BOCF. At the final week, the least squares mean change in pain intensity score was -1.85 with gabapentin once daily and -1.72 with gabapentin twice daily compared to -1.42 with placebo (p= not significant for either versus placebo). Adverse effects occurred in 57% to 58% of patients taking gabapentin compared to 48% of patients taking placebo. The most common adverse effects reported with gabapentin were dizziness, headache, somnolence, and peripheral edema.

### ***gabapentin enacarbil (Horizant) versus placebo***

A double-blind, randomized study was conducted where 115 patients with PHN completed a 7-day baseline period and 11-day gabapentin run-in period.<sup>137</sup> Eligible patients (n=101) were randomized and received a total of 1,200 mg gabapentin enacarbil (n=47) or placebo (n=54) administered twice daily for 14 days. The remaining patients discontinued from the study before randomization for the following reasons: adverse events, not eligible, not adhering to the protocol, and patient request. Improvement in mean weekly pain scores from baseline to the end of treatment (primary endpoint) was significantly greater for gabapentin enacarbil (-2.1) versus placebo (-1.2; p=0.0321). Significant improvements from gabapentin enacarbil versus placebo were also seen in sleep, mood, and patient

global assessment ( $p < 0.05$ ). Lastly, gabapentin enacarbil provided a significant increase in average steady state gabapentin concentrations versus gabapentin capsules in the same patients ( $n = 42$ ;  $p = 0.005$ ).

### ***lidocaine 5% patch (Lidoderm) versus placebo or no treatment***

In a double-blind, crossover trial with 35 patients with postherpetic neuralgia, lidocaine 5% patch was compared to no treatment for a single dose.<sup>138</sup> Lidocaine performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours. A 2-week trial of lidocaine patch versus vehicle patch was performed in a double-blind manner in 32 patients with constant pain who had been considered responders in an open-label lead-in. Lidocaine patch was statistically significantly better than vehicle in terms of time to exit from trial, daily average pain relief, and patient's preference of treatment. Half of the patients also took oral medication commonly used in the treatment of postherpetic neuralgia, but use was similar between groups.

### ***lidocaine 1.8% patch (Ztlido) versus placebo***

A 2-week, multidose, double-blind, crossover trial compared lidocaine 1.8% patch to vehicle patch in 32 patients who were previously considered responders in an open-label trial of the lidocaine patch.<sup>139</sup> Approximately half of the patients were also treated with oral medication commonly used to treat postherpetic neuralgia. Statistically significant differences favoring lidocaine patch were reported regarding time to exit from the trial (14 versus 3.8 days at  $p < 0.001$ ), daily average pain relief, and patient's preference of treatment.

### ***pregabalin ER (Lyrica CR) versus placebo***

A 19-week, randomized, withdrawal trial had 2 phases comparing pregabalin CR and placebo.<sup>140</sup> In the 6-week, single-blinded phase, 801 patients with pain after 3 months of healing herpes zoster skin rash and a baseline numeric rating pain scale of  $\geq 4$  were randomized to receive either pregabalin CR (82.5 mg to 660 mg per day) or placebo. A total of 413 patients experienced at least a 50% reduction in pain during the first phase and moved onto the 13-week, double blinded phase (pregabalin CR,  $n = 208$ ; placebo,  $n = 205$ ). The primary efficacy outcome was the time to loss of therapeutic response (LTR;  $< 30\%$  decrease in weekly mean pain score from single-blind baseline or discontinuation due to adverse event or lack of efficacy). While median time to LTR was not estimable, pregabalin CR significantly increased time to LTR compared to placebo with significantly fewer LTR events with pregabalin CR than with placebo (13.9% [29] versus 30.7%; [63];  $p < 0.0001$ ). Secondary endpoint pain scores were also measured weekly to assess clinical efficacy in both phases of the study. Pregabalin CR was shown to significantly improve pain scores when compared to placebo, least square mean difference of -1 (95% CI, -1.34, -0.65;  $p < 0.0001$ ) from double-blind baseline to end-point, respectively.

## **Diabetic Peripheral Neuropathic Pain (DPNP) and Neuropathic Pain (NP)**

### ***capsaicin versus amitriptyline***

An 8-week double-blind, multicenter, parallel study compared the safety and efficacy of capsaicin cream and oral amitriptyline in 235 patients with painful diabetic neuropathy involving the feet.<sup>141</sup> Two hundred thirty-five patients were randomized to treatment. A visual analogue scale of pain intensity and measurements of interference by pain with functional activities were recorded at onset and at 2-week intervals. Capsaicin and amitriptyline produced equal and statistically significant improvements in

pain over the course of the study. By the end of 8 weeks, 76% of patients in each group experienced less pain, with a mean reduction in intensity of more than 40%. By the end of the study, the interference with daily activities by pain had diminished significantly ( $p=0.001$ ) in both groups. No systemic side effects were observed in patients treated with capsaicin. Most patients receiving amitriptyline experienced at least 1 systemic side effect, ranging from somnolence to neuromuscular and cardiovascular adverse effects.

### ***duloxetine (Cymbalta) versus placebo***

In a 12-week, multicenter, double-blind study, 457 patients experiencing pain due to diabetic polyneuropathy were randomly assigned to treatment with duloxetine 20 mg once daily, 60 mg once daily, 60 mg twice daily, or placebo.<sup>142</sup> The 2 higher doses of duloxetine demonstrated statistically significant greater improvement than placebo in the 24-hour mean VAS for pain, the primary efficacy measure, beginning 1 week after randomization and continuing throughout the 12-week trial. Significantly more patients in all 3 active-treatment groups achieved a 50% reduction in the 24-hour mean VAS for pain compared with placebo. Duloxetine treatment was considered to be safe and well tolerated with less than 20% discontinuation due to adverse events. The FDA-approved dosage of duloxetine for DPNP is 60 mg/day.

In a similar study, patients with diabetic peripheral neuropathic pain (DPNP) were randomized to treatment with duloxetine 60 mg once or twice daily or placebo for 12 weeks.<sup>143</sup> Both doses of duloxetine were superior to placebo in reducing the 24-hour average pain severity score. Treatment with duloxetine also resulted in greater improvement in the secondary endpoints of Clinical Global Impression of Severity (CGI-S) and Patient's Global Impression of Improvement (PGI-I). The study was performed by the manufacturer of duloxetine. The FDA-approved dosage of duloxetine for DPNP is 60 mg/day.

### ***pregabalin (Lyrica) versus nonsteroidal anti-inflammatory drugs (NSAIDs)***

A randomized, double-blind, 14-week, 2-period, crossover study evaluated pregabalin versus placebo in patients with DPN using an NSAID for non-DPN-related pain.<sup>144</sup> During period-1, patients ( $n=301$ ) received pregabalin 150 mg to 300 mg per day or placebo. During period-2 patients were switched to the opposite therapy. A 14-day washout separated the 2 treatment periods. The primary efficacy measure of mean weekly DPN pain at treatment end was not significantly different between pregabalin and placebo. However, a sensitivity analysis (mixed-model repeated measures) found greater pain score reductions with pregabalin than placebo at weeks 2 to 4 and overall (all  $p<0.05$ ). A secondary endpoint analysis of the mean treatment difference in DPN-related sleep interference, favored pregabalin over placebo ( $p=0.0009$ ).

### ***pregabalin ER (Lyrica CR)***

Support for effectiveness of pregabalin ER for the management of diabetic peripheral neuropathy was based on the efficacy of pregabalin (Lyrica) studies.<sup>145</sup>

### ***tapentadol ER (Nucynta ER) versus placebo***

A phase 3, randomized-withdrawal, placebo-controlled trial evaluated the safety and efficacy of tapentadol ER versus placebo.<sup>146</sup> The primary outcome was the change in pain intensity from randomization measured by the NRS taken twice daily. DPN patients ( $n=588$ ) who were dissatisfied



with their opioid and/or non-opioid analgesic treatment and scored at least 5 on the NRS (0=no pain, 10=pain as bad as you can imagine) were titrated to an optimal dose of tapentadol ER (100-250 mg twice daily) during a 3-week open-label phase. Those patients (n=395) who sustained a 1-point reduction in their NRS score were randomized to receive placebo or tapentadol ER for a 12-week double-blind phase. The least-squares mean difference between groups in the change in average pain intensity from the start of double-blind treatment to week 12 was -1.3 (95% CI, -1.7 to -0.92;  $p < 0.001$ , tapentadol ER versus placebo). A total of 60.5% of patients reported at least a 30% improvement in pain intensity from the start to the end of the open-label titration phase; of the patients who were randomized to tapentadol ER, 53.6% reported at least a 30% improvement from pre-titration to week 12 of the double-blind phase. The most common treatment-emergent adverse events that occurred during double-blind treatment with tapentadol ER included nausea, anxiety, diarrhea, and dizziness. Potential limitations of this study are related to the enriched enrollment randomized-withdrawal trial design, which may result in a more homogeneous patient population during double-blind treatment and may present a risk of unblinding because of changes in side effects from the open-label to the double-blind phase. Compared with placebo, tapentadol ER 100 to 250 mg twice daily provided a statistically significant difference in pain and was well-tolerated by patients with painful DPN.

## **Fibromyalgia**

### ***duloxetine (Cymbalta) versus placebo***

A 12-week, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of duloxetine in 354 female patients with fibromyalgia, with or without current major depressive disorder.<sup>147</sup> Patients received duloxetine 60 mg once daily or twice daily or placebo. The primary outcome was the Brief Pain Inventory (BPI) average pain severity score (defined as  $\geq 30\%$  reduction in this score). Compared with placebo, both duloxetine groups improved significantly more ( $p < 0.001$ ) on the BPI average pain severity score (60 mg daily [55%;  $p < 0.001$ ]; 60 mg twice daily [54%;  $p = 0.002$ ]; placebo [33%]). The treatment effect of duloxetine on pain reduction was independent of the effect on mood and the presence of major depressive disorder. Patients treated with duloxetine 60 mg once daily or twice daily had significantly greater improvement in remaining BPI pain severity and interference scores, Fibromyalgia Impact Questionnaire, Clinical Global Impression of Severity, Patient Global Impressions of Improvement (PGI-I), and several quality-of-life measures. Both doses of duloxetine were well tolerated. Duloxetine doses over 60 mg daily are not FDA-approved for treatment of fibromyalgia. In a similarly designed trial using only duloxetine 120 mg daily, similar results were found.<sup>148</sup>

Efficacy and safety of duloxetine in reducing pain severity in 520 fibromyalgia patients, with or without current major depressive disorder, were evaluated in a 6-month, multicenter, randomized, double-blind, placebo-controlled study.<sup>149</sup> Patients were randomly assigned to duloxetine (20 mg, 60 mg, or 120 mg) or placebo, administered once daily. After 3 months, the duloxetine 20 mg group titrated to 60 mg daily. The co-primary outcome measures were the BPI average pain severity score and PGI-I score. Patients treated with duloxetine 120 mg daily improved significantly more on the co-primary outcome measures at 3 months (change in BPI score [-2.31 versus -1.39;  $p < 0.001$ ] and PGI-I [2.89 versus 3.39;  $p = 0.004$ ]) and at 6 months (change in BPI [-2.26 versus -1.43;  $p = 0.003$ ] and PGI-I [2.93 versus 3.37;  $p = 0.012$ ]) compared to placebo. Duloxetine 60 mg per day also significantly improved the co-primary measures at 3 months, but improved only BPI at 6 months. Duloxetine was efficacious in patients both with and without major depressive disorder. There were no clinically significant



differences among treatment groups in adverse events. Duloxetine doses over 60 mg daily are not FDA-approved for treatment of fibromyalgia.

### ***milnacipran (Savella) versus placebo***

A multicenter, double-blind, placebo-controlled trial randomized 1,196 patients with fibromyalgia to receive milnacipran 100 mg daily, 200 mg daily, or placebo for 15 weeks.<sup>150</sup> The 2 primary endpoints were rates of fibromyalgia composite responders (based on pain diary scores, PGI-Change [PGI-C], and Short Form 36 [SF-36]) and fibromyalgia pain composite responders (based on pain diary scores and PGI-C). Compared with placebo, significantly greater proportions of milnacipran-treated patients were fibromyalgia composite responders (100 mg:  $p=0.01$ ; 200 mg:  $p=0.02$ ) and fibromyalgia pain composite responders (100 mg:  $p=0.03$ ; 200 mg:  $p=0.004$ ). Milnacipran was associated with significant improvements in pain after 1 week of treatment (100 mg:  $p=0.004$ ; 200 mg:  $p=0.04$ ), global status (PGI-C:  $p<0.001$  for both doses), physical function (SF-36: 100 mg:  $p<0.001$ ; 200 mg:  $p=0.02$ ), and fatigue (Multidimensional Fatigue Inventory: 100 mg:  $p=0.04$ ). The most common adverse events with milnacipran were nausea, headache, and constipation.

Similarly, a 27-week, randomized, double-blind, multicenter study compared milnacipran 100 mg and 200 mg daily with placebo in the treatment of 888 patients with fibromyalgia and used the same primary endpoints as the above study.<sup>151</sup> After 3 months of stable dose treatment, a significantly higher percentage of milnacipran-treated patients met criteria as fibromyalgia responders versus placebo (milnacipran 200 mg,  $p=0.017$ ; milnacipran 100 mg,  $p=0.028$ ). A significantly higher percentage of patients treated with milnacipran 200 mg also met criteria as fibromyalgia pain responders versus placebo ( $p=0.032$ ). Significant pain reductions were observed after week 1 with both milnacipran doses. At 15 weeks, milnacipran 200 mg led to significant improvements over placebo in pain ( $p<0.05$ ), PGI-C ( $p<0.001$ ), and multiple SF-36 domains. Nausea and headache were the most common adverse events reported by milnacipran users.

A double-blind, placebo-controlled trial was performed to assess 1,025 patients with fibromyalgia who were randomized to receive milnacipran 100 mg daily ( $n=516$ ) or placebo ( $n=509$ ).<sup>152</sup> Patients underwent 4 to 6 weeks of flexible dose escalation followed by 12 weeks of stable-dose treatment. Two composite responder definitions were used as primary endpoints: 1) achievement of  $\geq 30\%$  improvement from baseline in the pain score and a rating of very much improved or much improved on the PGI-C scale; 2) these 2 measurements plus improvement criteria for pain and global status, as well as improvement in physical function on the SF-36 physical component summary score. After 12 weeks of stable-dose treatment, a significantly greater proportion of milnacipran-treated patients compared with placebo-treated patients showed clinically meaningful improvements on the 2-measure composite responder criteria ( $p<0.001$ ) and 3-measure composite responder criteria ( $p<0.001$ ). Milnacipran was well tolerated by most patients, with nausea being the most commonly reported adverse event.

### ***pregabalin (Lyrica) versus placebo***

A multicenter, double-blind, 8-week, randomized clinical trial compared pregabalin 150 mg, 300 mg, and 450 mg daily with placebo in pain, sleep, fatigue, and health-related quality of life in 529 patients with fibromyalgia.<sup>153</sup> The primary outcome was the comparison of endpoint mean pain scores, derived from daily diary ratings of pain intensity. Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo ( $-0.93$  on a 0 to 10 scale,  $p\leq 0.001$ ), and

significantly more patients in this group had  $\geq 50\%$  improvement in pain at the endpoint (29% versus 13% in the placebo group;  $p=0.003$ ). Dizziness and somnolence were the most frequent adverse events.

### ***pregabalin (Lyrica) plus duloxetine versus pregabalin (Lyrica) versus duloxetine***

In a double-blind, 4-period crossover study, patients with fibromyalgia were randomized to maximally tolerated doses of pregabalin, duloxetine, pregabalin-duloxetine combination or placebo for 6 weeks.<sup>154</sup> A total of 39 patients completed at least 2 treatment cycles. The primary outcome was daily pain (scale, 0 to 10). Daily pain during placebo, pregabalin, duloxetine, and combination was 5.1, 5, 4.1, and 3.7, respectively ( $p<0.05$  for combination versus placebo and pregabalin only). In addition, 18%, 39%, 42%, and 68%, of patients, respectively ( $p<0.05$  for combination versus placebo, pregabalin, and duloxetine), reported at least moderate global pain relief. Significant improvements were also reported in Fibromyalgia Impact Questionnaire scores, SF-36 scores, and the Medical Outcomes Study Sleep Scale scores for the combination compared to placebo, pregabalin, and duloxetine regarding.

## **META-ANALYSES**

A pooled analysis of 18 randomized, double-blind, placebo-controlled trials assessed the benefit of pregabalin in patients with neuropathic pain who had previously received gabapentin compared to those who had not received gabapentin.<sup>155</sup> The authors found that there were no significant differences between the previously gabapentin-treated and non-gabapentin-treated cohorts in extent of pain relief and relief of pain-related sleep interference at any dose of pregabalin (150 to 600 mg/day) at 6, 8, or 12 weeks.

The efficacy of antidepressants in the treatment of fibromyalgia was determined by performing a meta-analysis of randomized, placebo-controlled trials with TCAs, SSRIs, SNRIs, and MAOIs.<sup>156</sup> Eighteen randomized controlled trials (median duration, 8 weeks; range, 4 to 28 weeks) involving 1,427 patients were included. Overall, there was strong evidence for an association of antidepressants with reduction in pain, fatigue, depressed mood, sleep disturbances, and improved health-related quality of life. Effect sizes for pain reduction were large for TCAs, medium for MAOIs, and small for SSRIs and SNRIs.

A Cochrane systematic review also assessed the efficacy of SNRIs compared to either placebo or comparator agents for the treatment of fibromyalgia ( $n=7,903$ ; 18 studies).<sup>157</sup> Included studies relevant to this class review evaluated duloxetine versus placebo (7 studies) and milnacipran versus placebo (9 studies). The authors determined that neither duloxetine nor milnacipran had clinically relevant benefit over placebo in pain relief, defined as  $\geq 50\%$  reduction in pain (31% with active treatment versus 21% with placebo; risk difference, 0.09 [95% CI, 0.07 to 0.11]; number needed to treat [NNT], 11 [95% CI, 9 to 14]). However, a clinically relevant difference was seen in  $\geq 30\%$  pain reduction (risk difference, 0.1 [95% CI, 0.08 to 0.12]; NNT, 10 [95% CI, 8 to 12]) and patients global impression of much or very much improved (RD 0.19 [95% CI, 0.12 to 0.26]; NNT, 5 [95% CI, 4 to 8]). No benefit was seen in reducing sleep problems, fatigue, or improvement in health-related quality of life. No difference was seen in serious adverse events with either agent compared to placebo, but an increased dropout rate was seen with active drug versus placebo (19% versus 10%, respectively).

## SUMMARY

Limited comparative head-to-head data exists on neuropathic pain. Moreover, various professional guidelines suggest different first-line and second-line treatments based on the indication. These include tricyclic antidepressants, gabapentin (Gralise, Horizant, Neurontin), pregabalin (Lyrica), opioids, lidocaine transdermal patches (Lidoderm), duloxetine (Cymbalta), and topical capsaicin. Pregabalin ER (Lyrica CR) and Ztlido lidocaine patches were not available at the time practice guideline was published.

Several gabapentin kits (Active-PAC with Gabapentin, SmartRx Gaba Kit, SmartRx Gaba-V Kit) are available. These kits incorporate gabapentin for oral use with various combinations of topical medications (e.g., menthol, lidocaine, methyl salicylate, capsaicin). Lidocaine transdermal patches are also found as a component of DermacinRx PHN Pak, Lidopure, LMR Plus, Neurcaine 5% Kit, and Zilacaine.

Duloxetine (Cymbalta), milnacipran (Savella), and pregabalin (Lyrica) are Food and Drug Administration (FDA)-approved for the treatment of fibromyalgia. Gabapentin (Gralise, Horizant, Neurontin) and tricyclic antidepressants have also been shown to be effective, while efficacy of pregabalin ER (Lyrica CR) for the management of fibromyalgia has not been proven.

Duloxetine (Cymbalta) should be avoided in severe renal impairment whereas gabapentin (Gralise, Horizant, Neurontin), milnacipran (Savella), and pregabalin (Lyrica) may be options that require dose adjustments. Pregabalin ER (Lyrica CR) should be avoided in those on hemodialysis. Lidocaine patches (Lidoderm, Ztlido) and the serotonin-norepinephrine reuptake inhibitors, duloxetine (Cymbalta) and milnacipran (Savella), should be avoided in hepatic impairment.

More evaluation is needed in the area of neuropathic pain to determine the most effective treatments. When prescribers choose to try pharmacologic therapy in the treatment of neuropathic pain, there are several options; however, comparative data and efficacy data in general are lacking. Factors for product selection should include approved indications, adverse event profiles of the products, ability to treat comorbidities, drug interactions, and contraindications.

Tapentadol ER (Nucynta ER) should only be initiated for diabetic peripheral neuropathy when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

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