Neuropathic Pain
Therapeutic Class Review (TCR)

June 9, 2022

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Post-herpetic Neuralgia (PHN)	Diabetic Peripheral Neuropathy (DPN)	Neuropathic Pain	Fibromyalgia	Other Indications
capsaicin OTC[1]	generic	--	--	X*	--	Treatment of mild to moderate pain
duloxetine (Cymbalta®)[2]	generic†, Eli Lilly	--	X (in adults)	--	X (≥ 13 years of age)	Major depressive disorder; generalized anxiety disorder; chronic musculoskeletal pain
duloxetine‡ (Drizalma Sprinkle™)[3]	Sun	--	X (in adults)	--	X (in adults)	Major depressive disorder; generalized anxiety disorder; chronic musculoskeletal pain
gabapentin (Neurontin®)[4]	generic, Pfizer/Viatris	X (in adults)	--	--	--	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 aged 3 to 12 years
gabapentin (Gralise®)[5]	Almatica	X (in adults)	--	--	--	--
gabapentin enacarbil (Horizant®)[6]	Xenoport/Arbor	X (in adults)	--	--	--	Treatment of moderate-to-severe primary restless legs syndrome in adults
lidocaine 5% (Lidoderm®)[7]	generic, Endo	X (in adults)	--	--	--	--
lidocaine 1.8%§ (Ztlido®)[8]	Scilex	X (in adults)	--	--	--	--
milnacipran (Savella®)[9]	Allergan	--	--	--	X (in adults)	--

* Not an FDA-approved indication; data supports this use.

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

‡ Drizalma Sprinkle (duloxetine delayed-release) was FDA-approved via the 505(b)(2) pathway, in which approval relied, at least in part, on data not developed by the applicant.[10]

§ 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.[11,12]

FDA-Approved Indications (continued)

Drug	Manufacturer	Post-herpetic Neuralgia (PHN)	Diabetic Peripheral Neuropathy (DPN)	Neuropathic Pain	Fibromyalgia	Other Indications
pregabalin (Lyrica®)[13]	generic, Pfizer/Viatris	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¶ (Lyrica CR®)[14]	generic, Pfizer	X	X	--	--	--
tapentadol ER‖ (Nucynta ER®)[15]	Collegium	--	X (in adults)	--	--	--

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

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

‖ Immediate-release tapentadol (Nucynta®) 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 Averitas, is indicated for the treatment of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy of the feet.[16] Administration by a healthcare professional in a well-ventilated area is required. Qutenza will not be discussed in detail in this Therapeutic Class Review.

Tapentadol ER (Nucynta ER) is a Schedule II controlled substance. Pregabalin (Lyrica, Lyrica CR) is a Schedule V controlled substance.

The use of duloxetine (Cymbalta, Drizalma Sprinkles) for the treatment of major depressive disorder, general anxiety disorder, and chronic musculoskeletal pain as well as the use of gabapentin (Neurontin) and pregabalin (Lyrica) for the treatment of partial seizures or restless leg syndrome (Horizant only) are not addressed in this therapeutic class review.

Products that are available as kits are not included in this Therapeutic Class Review. This includes convenience kits that are prescription products co-packaged with over-the-counter (OTC) products and/or medical supplies.

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 been defined as the pain that evolves as a result of direct injury or disease to the nervous system, specifically the somatosensory system.[17]

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 (AAN) 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.[18] 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.[19,20,21,22,23]

Diagnosis of DPNP is based on the presence of symptoms, findings on physical exam, and the exclusion of other etiologies of painful sensory neuropathy. 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 reflexes are commonly performed tests used to screen, diagnose, and assess DPNP.[24] General treatment measures include glycemic control, foot care, and the treatment of pain.

Both duloxetine (Cymbalta, Drizalma Sprinkle) 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.[25]

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, Drizalma Sprinkle). [26] 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. 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 review was published.

According to the 2021 AAN guidelines for the management of painful diabetic neuropathy, treatments include gabapentinoids (gabapentin and pregabalin); TCAs; serotonin norepinephrine reuptake inhibitors (SNRIs), such as duloxetine; and/or sodium channel blockers (valproic acid; off label) (all Level B recommendations).[27] Gabapentin was deemed to be probably more effective than placebo and pregabalin was rated possibly effective. Duloxetine was rated as probably effective while amitriptyline was deemed to be possibly effective. Tapentadol was found to be possibly effective, however the guidelines recommend *against* the use of opioid medications in the treatment of DPN (Level B). Overall,

individual agents in each class were found to have similar efficacy, thus assessment of patient comorbidities, side effect profiles, cost, as well as patient preference should be considered (Level B). Topical (e.g., capsaicin), nontraditional (e.g., Ginkgo biloba), and non-pharmacologic treatments (e.g., Tai Chi) may be offered for patients preferring these products (Level C). If treatment with a specific drug does not result in meaningful improvement or leads to significant side effects, a trial of a different drug class is recommended (Level B). If partial improvement is achieved with an initial drug class, a trial of a drug from a different effective class or combination therapy with an agent from a different effective class should be offered (Level B). 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. The guidelines state that patients should be counseled that a reasonable goal of therapy is to reduce, and not necessarily eliminate, pain.

The American Diabetes Association's (ADA) 2022 Standards of Medical Care in Diabetes recommends either pregabalin, duloxetine, or gabapentin (off-label) as initial pharmacologic treatments for neuropathic pain in diabetes (Level A evidence).[28] Off-label use of topical capsaicin, TCAs, venlafaxine, and carbamazepine may also be effective. Tapentadol is not recommended as a first- or second-line agent due to safety concerns, high risk for addiction, and modest pain reduction. Additionally, use of any opioids for chronic neuropathic pain should be avoided due to potential for addiction.

Fibromyalgia

Fibromyalgia is a chronic disorder characterized by pain, fatigue, and sleep disturbances.[29,30,31] It predominantly affects women and is difficult to treat. A multidisciplinary approach should be utilized.

The American College of Rheumatology (ACR) combined the 2010 diagnostic criteria for fibromyalgia and the 2011 modified criteria into a single set of criteria (2016 modified criteria).[32,33] 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 (SSS), which includes somatic symptoms, waking unrefreshed, cognition, and fatigue, is employed. Fibromyalgia may be diagnosed in adults when all of the following criteria are met: presence of generalized pain, defined as pain in ≥ 4 of 5 regions; symptoms have been present at a similar level for ≥ 3 months; WPI ≥ 7 and SSS score ≥ 5 OR WPI of 4 to 6 and SSS score ≥ 9; and a diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses. According to the 2010 criteria set, 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.

The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the United States (US) Food and Drug Administration (FDA) and the American Pain Society (APS) initiated the ACTTION-APS Pain Taxonomy (AAPT) to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders.[34] The 2019 AAPT diagnostic criteria for fibromyalgia include core symptoms (dimension 1) as well as other associated signs and symptoms (dimension 2). It uses multisite pain (MSP) with a minimum number of required sites regardless of their anatomical distribution as a primary diagnostic criteria. The core diagnostic criteria (dimension 1) include: MSP defined as ≥ 6 or more pain sites from a total of 9 possible sites; moderate to severe sleep problems or fatigue; and presence of MSP plus fatigue or sleep problems for ≥ 3 months. Other non-pain symptoms (dimension 2), such as tenderness, dyscognition, musculoskeletal stiffness, and environmental sensitivity or hypervigilance (bright lights, loud noises,

smells, cold temperature) are also considered. Fibromyalgia is associated with many comorbidities that may be categorized as other somatic pain disorders, psychiatric conditions, sleep disorders, rheumatic diseases, and other conditions. Fibromyalgia often persists; however, many patients may identify strategies over time that can moderate symptoms.

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.[35,36] 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.[37] 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.[38] 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, Drizalma Sprinkle), 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[39,40,41,42,43,44,45,46,47,48,49,50,51,52,53]

Drug	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, Drizalma Sprinkle)	Potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS)
gabapentin (Gralise, Neurontin)	Binds to the presynaptic α2-delta subunit of voltage sensitive calcium channels which may modulate the release of excitatory neurotransmitters that participate in nociception
gabapentin enacarbil (Horizant)	Prodrug of gabapentin; gabapentin binds to the presynaptic α2-delta subunit of voltage sensitive calcium channels which may modulate the release of excitatory neurotransmitters that participate in nociception
lidocaine (Lidoderm, Ztlido)	Stabilizes neuronal membranes by inhibiting the ionic fluxes required for initiation and conduction of impulses
milnacipran (Savella)	Potentiation of serotonergic and noradrenergic activity in the CNS; exact mechanism in fibromyalgia is unknown
pregabalin (Lyrica, Lyrica CR)	Pregabalin binds to presynaptic α2-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[54,55,56,57,58,59,60,61,62,63,64,65]

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% (± 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 metabolites which are renally excreted.

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

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.[66] Naphthol is also known to cause ocular toxicity which may be of concern in diabetics.[67]

Drug	Bioavailability (%)	Tmax (hrs)	Half-life (hrs)	Active Metabolites	Excretion (%)
duloxetine (Cymbalta)	N/A	6	12	None	Urine: 70 Feces: 20
duloxetine (Drizalma Sprinkle)	N/A	5	12.4	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[68,69,70,71,72,73,74,75,76,77,78,79]

Capsaicin (OTC) has no contraindications. Capsaicin should not be used near eyes, mucus membranes, or skin with abrasions, irritation, infection, or inflammation. If irritation does occur, flush the affected area with water. Inhalation of airborne capsaicin following removal of clothing covering capsaicin cream can cause coughing or sneezing. 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. Contact with eyes should be avoided.

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 patches (Ztlido) in patients allergic to para-aminobenzoic acid (PABA) derivatives. There is risk of methemoglobinemia with use of local anesthetics; patients with high-risk comorbidities should be monitored closely for signs and symptoms including cyanotic skin discoloration, headache, lightheadedness, or shortness of breath.

Duloxetine (Cymbalta, Drizalma Sprinkle) and milnacipran (Savella) 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. Duloxetine is not indicated to treat diabetic peripheral neuropathy in pediatric patients but duloxetine (Cymbalta) is indicated to treat fibromyalgia in patients ≥ 13 years of age.

Treatment with SNRIs, including duloxetine and milnacipran, has been associated with increases in blood pressure and heart rate compared to placebo. Blood pressure and heart rate 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 cytochrome P-450 (CYP) 1A2 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. Milnacipran has been associated with increases in heart rate ≥ 20 beats per minute over baseline. For patients who experience a sustained increase in heart rate while receiving milnacipran, dose reduction or discontinuation of milnacipran may be clinically warranted.

Use of SNRIs may cause symptoms of sexual dysfunction including decreased libido. Males have reported ejaculatory issues and erectile dysfunction. Females may experience delayed or absent orgasm.

The development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome-like reaction has been reported with SNRI (duloxetine, milnacipran) 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 monoamine oxidase inhibitors (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). Due to the potential for serotonin syndrome, concurrent use of duloxetine or milnacipran with linezolid, intravenous (IV) methylene blue, or within 14 days of an MAOI is contraindicated. Additionally, initiating treatment with an MAOI within 5 days of stopping duloxetine or milnacipran is contraindicated. SNRIs, including duloxetine and milnacipran, may increase the risk of bleeding events. Concurrent use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may increase the 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. SNRIs may trigger an angle closure attack in a patient with anatomically narrow angles without a patent iridectomy.

A gradual reduction in the dose of serotonergic agents rather than abrupt cessation is recommended whenever possible. Abrupt discontinuation of SNRIs has been associated with dizziness, headache, irritability, paresthesias, insomnia, and seizures.

SNRIs may cause hyponatremia resulting from development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk is highest in elderly patients, those requiring diuretic treatment, or in those with volume depletion.

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 duloxetine and milnacipran.

Severe skin reactions, including erythema multiforme and Stevens-Johnson syndrome (SJS), have been reported with duloxetine. Duloxetine should be discontinued at the first sign of hypersensitivity.

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.[80] 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.

Various hypersensitivity reactions including anaphylaxis and angioedema have been reported with gabapentin. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a multi-organ hypersensitivity reaction, has also occurred with gabapentin, including gabapentin enacarbil. Some cases have been fatal or life threatening. Manifestations of DRESS typically include fever, rash, facial swelling, 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.

In December 2019, the FDA issued a drug safety communication regarding serious breathing difficulties in patients using gabapentin (Neurontin, Gralise, Horizant) or pregabalin (Lyrica, Lyrica CR) who also have other respiratory risk factors such as (e.g., opioid pain medications, other CNS depressant drugs, COPD, advanced age).[81] Labeling for these products have been updated to advise that at risk patients should be started on gabapentinoid therapy at the lowest dose and monitored for symptoms of respiratory depression and sedation.

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.

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.

Peripheral edema and weight gain are a concern with pregabalin products. Peripheral edema was not associated with cardiovascular complications or deterioration of hepatic or renal function in clinical trials. There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin, including reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). 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.

Visual changes, creatine kinase elevations, decreased platelet count, and PR interval prolongation have also been reported with pregabalin.

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

Tapentadol ER has a boxed warning regarding abuse potential, life-threatening respiratory depression, accidental exposure, interaction with alcohol, neonatal withdrawal syndrome, 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. Patients and caregivers should be counseled on recognizing respiratory depression and getting emergency medical care immediately for known or suspected overdoses, even if naloxone is administered. Additionally, the availability of naloxone for emergency treatment of opioid overdose should be discussed with the patient/caregiver when tapentadol ER is started or when the prescriptions are renewed. Prescribing naloxone should be based on the patient's risk factors for overdose (e.g., concurrent CNS depressants [benzodiazepines, skeletal muscle relaxants], history of opioid use disorder, prior opioid overdose). Consideration should also be given for prescribing naloxone if the potential exists for household members (e.g., children, close contacts) to accidentally ingest the opioid leading to overdose.

Tapentadol ER should be used cautiously in patients with a history of seizures. Serotonin syndrome could result from concomitant use of other medications that exhibit serotonergic activity. Concomitant use of tapentadol ER with opioids may increase the risk of central sleep apnea. Because of the potential for reduced respiratory drive with tapentadol ER, and the resultant retention of carbon dioxide, patients with evidence of increased intracranial pressure or brain tumor must be monitored closely. Adrenal insufficiency and severe hypotension could also occur with tapentadol ER treatment. Avoid abrupt discontinuation of tapentadol ER in patients who are dependent on opioids; doses should be gradually tapered to prevent withdrawal.

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.[82] 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[83,84,85,86,87,88,89,90,91,92,93,94]

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. Coadministration with other drugs associated with methemoglobinemia (e.g., nitrates, antibiotics, anticonvulsants) may increase the risk of developing the condition.

Concurrent use of duloxetine and an antiplatelet or anticoagulant drug may potentiate the risk of bleeding; monitor patients on an NSAID, warfarin, or aspirin closely when starting or stopping duloxetine therapy. Duloxetine (Cymbalta, Drizalma Sprinkle) should not be used within 2 weeks of stopping an MAOI. Additionally, when converting from duloxetine to an MAOI, there must be a washout period of at least 5 days. 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. 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. 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 SNRI (e.g., duloxetine, milnacipran therapy; SNRIs 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. If a patient already treated with an SNRI needs to initiate therapy with linezolid or methylene blue due to no alternative agents, the SNRI should be discontinued, and the patient should be monitored for symptoms of serotonin syndrome for 5 days or for 24 hours after the last dose, whichever comes first; the SNRI may be resumed 24 hours following the last linezolid or methylene blue dose.

Duloxetine is a moderate inhibitor of CYP2D6 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. Duloxetine exposure is affected by inhibitors of CYP2D6 and CYP1A2 resulting in increased duloxetine levels. 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. There is a risk of respiratory depression and sedation that may lead to death with concomitant treatment of gabapentin (Neurontin) with opioids (e.g., morphine, hydrocodone, oxycodone, buprenorphine). Alcohol accelerates the release of gabapentin enacarbil (Horizant) from the extended-release tablet, increasing the risk for adverse events; alcohol should not be consumed during gabapentin enacarbil treatment. Milnacipran inhibits the reuptake of norepinephrine; therefore, concomitant use 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 IV 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 skeletal muscle relaxants or 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. Concurrent use with serotonergic agents may lead to serotonin syndrome.

ADVERSE EFFECTS[95,96,97,98,99,100,101,102,103,104,105,106]

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 data are obtained from package inserts and are not meant to be comparative or all inclusive.

Drug	Weight Change	Nausea	Diarrhea	Somnolence	Dizziness	Dry Mouth	Constipation	Edema	Tremor
duloxetine (Cymbalta)	reported	23	9	11	9	11	10	nr	2
duloxetine (Drizalma Sprinkle)	reported	23	9	11	9	11	10	nr	2
gabapentin (Neurontin)	reported	4	6	21	28	5	4	8	reported
gabapentin (Gralise)	reported	nr	3.3	4.5	10.9	2.8	1.4	3.9	nr
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	4–35.7	8–45	2–15	0–10	0-16	0-3
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
tapentadol ER (Nucynta ER)	reported	27	7	14	18	7	13	nr	3

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.
nr = not reported.

Gabapentin has an 8% 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 and with the diagnosis of heart failure as an exacerbation can occur. In clinical trials, pregabalin (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, Drizalma Sprinkle) and milnacipran (Savella).

In clinical trials, the most common adverse effects reported (versus placebo) with duloxetine delayed-release capsules (Cymbalta) in adolescents with fibromyalgia were nausea (25% versus 15%), decreased appetite (15% versus 3%), vomiting (15% versus 5%), decreased weight (15% versus 5%), headache (14% versus 11%), nasopharyngitis (9% versus 2%), and somnolence (9% versus 3%).

SPECIAL POPULATIONS[107,108,109,110,111,112,113,114,115,116,117,118]

Pediatrics

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

The use of pregabalin ER (Lyrica CR), milnacipran (Savella), and tapentadol ER (Nucynta ER) have not been adequately studied in children for indications discussed in this therapeutic class review.

Gabapentin (Neurontin) is indicated for treatment of partial seizures in children ≥ 12 years of age 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 < 18 years of age have not been studied.

Pregabalin (Lyrica) is indicated for the adjunctive treatment of partial-onset seizures in children ≥ 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 < 18 years of age have not been studied.

Duloxetine (Cymbalta) is indicated for the treatment of fibromyalgia in pediatric patients ≥ 13 years of age; however, duloxetine (Drizalma Sprinkle) does not have this indication in pediatric patients. The safety and effectiveness of duloxetine (Cymbalta, Drizalma Sprinkle) in the management of diabetic peripheral neuropathy in patients < 18 years of age have not been studied.

Pregnancy

Capsaicin is negligibly systemically absorbed and is not expected to result in fetal exposure. Lidocaine 5% patch (Lidoderm) is 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.

Milnacipran (Savella) and gabapentin (Gralise) are Pregnancy Category C. Previously Pregnancy Category C, labeling for duloxetine (Cymbalta, Drizalma Sprinkle), gabapentin (Horizant, Neurontin), and pregabalin (Lyrica, Lyrica CR) have been updated to comply with the PLLR. There are no adequate and well-controlled studies of milnacipran, gabapentin, or pregabalin use in pregnant women; however, developmental toxicity, have been reported in animal studies at higher than recommended human dose equivalents for duloxetine, gabapentin enacarbil, and pregabalin and at lower than or equal to recommended human dose equivalents for gabapentin and milnacipran. Observational studies have not demonstrated a drug-associated risk for major birth defects or adverse outcomes with duloxetine use during pregnancy; however, there are risks to the fetus/neonate due to exposure to SNRIs during pregnancy. An observational study demonstrated use of duloxetine in the month prior to delivery may potentially increase the likelihood for postpartum hemorrhage. Neonates exposed to SNRIs in the month before delivery have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Women who are pregnant or intend on becoming pregnant while being treated with milnacipran or duloxetine should consult their physician. Women who are exposed to duloxetine, gabapentin, milnacipran, or pregabalin during their pregnancy should enroll in the pregnancy exposure registry.

Although classified as Pregnancy Category C, gabapentin (Gralise) has not been evaluated for use during pregnancy. However, it is recommended for women exposed to Gralise during pregnancy to enroll in the pregnancy exposure registry.

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, Drizalma Sprinkle) 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. Dosing recommendations based on creatinine clearance are outlined in the prescribing information. Gabapentin has not been studied in pediatric patients with renal insufficiency.

Milnacipran (Savella) should not be used in patients with ESRD; dose adjustment is necessary in patients with severe renal impairment (estimated creatinine clearance < 30 mL/min).

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.

Use of duloxetine (Cymbalta, Drizalma Sprinkle) should be avoided in patients with chronic liver disease or cirrhosis.

Milnacipran (Savella) should not be administered to patients with severe hepatic insufficiency as due to an increased risk of elevated 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[119,120,121,122,123,124,125,126,127,128,129,130]

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
duloxetine (Cymbalta)	**DPN:** 60 mg once daily **Fibromyalgia:** 30 mg once daily (adult and pediatric dose)	60 mg once daily (adult and pediatric dose)	20 mg, 30 mg, 60 mg delayed-release capsules
duloxetine (Drizalma Sprinkle)	**DPN:** 60 mg once daily **Fibromyalgia:** 30 mg once daily	60 mg once daily	20 mg, 30 mg, 40 mg, 60 mg delayed-release capsules
gabapentin* (Neurontin)	300 mg on day 1, 300 mg twice daily on day 2, then 300 mg three times a day	3,600 mg/day (in 3 divided doses)	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
gabapentin enacarbil (Horizant)	600 mg/day for 3 days	600 mg twice daily	300 mg, 600 mg extended-release tablets
lidocaine† (Lidoderm, 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) 5% patch (generic, Lidoderm)
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

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

*Available as 300 mg/6 mL oral solution for institutional use.

Dosages (continued)

Drug	Initial Dose	Maximum Dose	Availability
pregabalin (Lyrica)	**DPN:** 150 mg/day in 3 divided doses **PHN:** 150 mg/day in 2 to 3 divided doses **Fibromyalgia:** 150 mg/day in 2 divided doses **Neuropathic pain associated with spinal cord injury:** 150 mg/day in 2 divided doses	**DPN:** 300 mg/day **PHN:** 300 to 600 mg/day **Fibromyalgia:** 300 to 450 mg/day **Neuropathic Pain associated with spinal cord injury:** 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)	**DPN/PHN:** 165 mg once daily, after an evening meal Swallow tablet whole; do not split, crush, or chew	**DPN:** 330 mg once daily within 1 week, after an evening meal **PHN:** 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

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. Lidocaine patches may not stick when wet; avoid contact with water, such as bathing, swimming, or showering. Ztlido is safe to use in water (e.g., showering for 10 minutes, water immersion for 15 minutes). Patients should wash their hands after handling the patches. Avoid contact with eyes.

The Drizalma Sprinkles capsule can be opened; contents sprinkled over applesauce and consumed immediately. For administration via a nasogastric (NG) tube, contents can be added to an all plastic catheter tip syringe with 50 mL of water and administered through a 12 French or larger NG tube. Unlike Drizalma Sprinkle, the Cymbalta capsule should be swallowed whole; contents should not be sprinkled on food or mixed with liquid.

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.

Support for the effectiveness of duloxetine delayed-release (Drizalma Sprinkle) for its approved conditions was based on the efficacy of duloxetine delayed-release (Cymbalta) in clinical studies.[131] Likewise, support for effectiveness of pregabalin ER for the management of diabetic peripheral neuropathy was based on the efficacy of pregabalin (Lyrica) in clinical studies.[132]

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.[133] Patients with PHN for 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 categoric 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.[134] 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.[135] 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.[136] Adult patients with PHN were randomized 1:1 to receive 1,800 mg gabapentin or placebo once daily as a 2-week titration followed 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 ≥ 1,200 mg/day or pregabalin ≥ 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.[137] Adult patients with PHN were randomized 1:1:1 to receive 1,800 mg gabapentin once daily or divided into 2 daily doses or placebo as a 2-week titration followed 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 ≥ 1,200 mg/day or pregabalin ≥ 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 treatment regimen 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.[138] 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 with 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.[139] 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.[140] 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.[141] 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 ≥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.[142] 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.[143] 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.[144] 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.[145] 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 ($p=0.0009$).

tapentadol ER (Nucynta ER) versus placebo

A phase 3, randomized-withdrawal, placebo-controlled trial evaluated the safety and efficacy of tapentadol ER versus placebo.[146] 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 adult patients with fibromyalgia, with or without current major depressive disorder.[147] 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 ≥ 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.[148]

Efficacy and safety of duloxetine in reducing pain severity in 520 adult fibromyalgia patients, with or without current major depressive disorder, were evaluated in a 6-month, multicenter, randomized, double-blind, placebo-controlled study.[149] 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.

Use of duloxetine for the treatment of fibromyalgia in pediatrics was evaluated in a 13-week placebo-controlled trials in 184 patients 13 to 17 years of age with juvenile fibromyalgia syndrome.[150] Treatment was initiated at 30 mg once daily for 1 week, then titrated to 60 mg once daily for 12 weeks as tolerated. The mean dosage of duloxetine was 49 mg/day. An improvement in the primary endpoint was change from baseline in Brief Pain Inventory (BPI)-Modified Short Form: Adolescent Version 24-hour average pain severity rating was demonstrated with duloxetine compared to placebo ($p=0.052$).

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.[151] 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.[152] 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).[153] 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 ≥ 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.[154] 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≤0.001), and significantly more patients in this group had ≥ 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.[155] 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 and SF-36 scores for the combination compared to placebo,

pregabalin, and duloxetine. In addition, significant improvements were reported in Medical Outcomes Study Sleep Scale scores for combination compared to placebo and duloxetine only.

META-ANALYSES

The efficacy of various pharmacologic and non-pharmacologic treatments for neuropathic pain was assessed in a systematic review of 67 randomized controlled trials.[156] Trials included adults with chronic diabetic neuropathy, postherpetic neuralgia, or trigeminal neuralgia. Individual systematic reviews were performed on the following interventions: SNRIs (duloxetine, venlafaxine, desvenlafaxine), TCAs, topical rubefacients (capsaicin), opioids (tramadol, oxycodone, buprenorphine, tapentadol), anticonvulsant medications (gabapentin, pregabalin, oxcarbazepine, topiramate), and acupuncture. The Cochrane Collaboration's risk-of-bias tool was used to assess each trial for potential bias. In the 40 anticonvulsant medication trials deemed to be of moderate quality, 46% of patients receiving active drug attained a clinically meaningful response compared to 30% of patients taking placebo (risk ratio [RR]=1.54; 95% CI, 1.45 to 1.63; number needed to treat [NNT] = 7). A difference in efficacy between agents was not observed. Gabapentin had the fewest withdrawals due to adverse events. In the 8 SNRI trials deemed to be of moderate quality, 57% of patients receiving active drug attained a clinically meaningful response compared to 41% taking placebo (RR = 1.45; 95% CI 1.33 to 1.59; NNT = 7). There was no difference in efficacy among the SNRIs. Ten capsaicin trials deemed to be of low quality demonstrated efficacy of active drug in 49% of patients versus 34% of patients receiving control (RR = 1.4; 95% CI, 1.26 to 1.55; NNT = 7). In the 6 opioid trials deemed to be of low quality, 49% of patients receiving active drug attained a clinically meaningful response compared to 36% of patients taking placebo (RR = 1.37; 95% CI 1.19 to 1.57; NNT = 8). The quality of evidence for TCAs and acupuncture was considered very low.

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.[157] 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.[158] 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).[159] 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 ≥ 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 ≥ 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 treatment. Moreover, various professional guidelines suggest different first-line and second-line treatments based on the indication. These include tricyclic antidepressants (TCAs), gabapentin (Gralise, Horizant, Neurontin), pregabalin (Lyrica), pregabalin ER (Lyrica CR), lidocaine transdermal patches (Lidoderm, Ztlido), duloxetine (Cymbalta, Drizalma Sprinkle), and topical capsaicin. According to the 2021 American Academy of Neurology (AAN) guidelines for the management of painful diabetic neuropathy, treatments include gabapentinoids (gabapentin and pregabalin); tricyclic antidepressants; serotonin norepinephrine reuptake inhibitors (SNRIs), such as duloxetine; and/or sodium channel blockers (off label) (all Level B recommendations). If treatment with a specific drug does not result in meaningful improvement or leads to significant side effects, a trial of a different drug class is recommended (Level B).

Duloxetine (Cymbalta, Drizalma Sprinkle), milnacipran (Savella), and pregabalin (Lyrica) are Food and Drug Administration (FDA)-approved for the treatment of fibromyalgia. Gabapentin (Gralise, Horizant, Neurontin) and off-label use of 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, Drizalma Sprinkle) 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, Drizalma Sprinkle) 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 pharmacologic therapy in the treatment of neuropathic pain, there are several options; however, comparative data and efficacy data in general are lacking. Factors to consider in 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. According to the American Diabetes Association, tapentadol is not recommended for neuropathic pain in diabetes as a first- or second-line agent due to safety concerns, high risk for addiction, and modest pain reduction.

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