Therapeutic Class Overview
Neuropathic Pain Agents

Therapeutic Class

Overview/Summary: The agents approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain include duloxetine (Cymbalta®), gabapentin (Neurontin®), gabapentin extended-release (Gralise®), gabapentin enacarbil (Horizant®), lidocaine patches (Lidoderm®) and pregabalin (Lyrica®).[1-6] These agents and their respective FDA-approved indications are listed in Table 1. The exact mechanisms by which these agents exert their analgesic effects are unknown. Neuropathic pain arises as a consequence of a lesion or disease that affects the nervous system. Symptoms often include a burning, tingling, sharp or stabling pain and may occur at any time of day. Despite the available medications for symptomatic relief and analgesia, their effectiveness is unpredictable, dosing can be complicated, onset of action is delayed and adverse events are common.[7]

The analgesic properties of duloxetine are believed to result from potent inhibition of neuronal serotonin and norepinephrine reuptake and a less potent inhibition of dopamine reuptake. Duloxetine is typically dosed once daily for the treatment of diabetic neuropathy.[1] Gabapentin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake or degradation.[2] Gabapentin is administered three times daily, while the extended-release formulation is administered once daily. Gabapentin enacarbil, a prodrug of gabapentin, is rapidly hydrolyzed to gabapentin in the gastrointestinal tract and is dosed twice daily for the management of postherpetic neuralgia. Gabapentin enacarbil does not demonstrate saturable absorption, resulting in a higher bioavailability and less variability in serum levels compared to gabapentin. Due to pharmacokinetic differences, the three gabapentin products are not interchangeable with one another.[2-4] Lidocaine is an amide-type local anesthetic that stabilizes neuronal membranes by inhibiting the ionic fluxes required for conduction of impulses. Topical application of the lidocaine patch is sufficient to produce analgesia, but results in minimal absorption.[5] The lidocaine topical patch should be applied to the painful area for 12 hours and then removed for the following 12 hours.[5] Pregabalin may produce anti-nociceptive effects through its high affinity binding to the α2Δ subunit of voltage-gated sodium channels. As with gabapentin, pregabalin is structurally similar to GABA but does not directly bind to or augment the response of GABA.[6] Only gabapentin immediate-release is currently available generically.

Table 1. Current Medications Available in the Class[1-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Duloxetine (Cymbalta®)	Management of chronic musculoskeletal pain, management of fibromyalgia, management of neuropathic pain associated with diabetic peripheral neuropathy, treatment of generalized anxiety disorder and treatment of major depressive disorder	Delayed-release capsule: 20 mg 30 mg 60 mg	-
Gabapentin (Neurontin®)	Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients >12 years of age with epilepsy, adjunctive therapy in the treatment of partial seizures in patients 3 to 12 years of age and management of postherpetic neuralgia	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/ 5 mL Tablet: 600 mg 800 mg	✔
Gabapentin extended-	Management of postherpetic neuralgia	Extended-release tablet:	-

release (Gralise®)		300 mg 600 mg	
Gabapentin enacarbil (Horizant®)	Management of postherpetic neuralgia and moderate-to-severe primary restless legs syndrome	Extended-release tablet: 300 mg 600 mg	-
Lidocaine patch (Lidoderm®)	Relief of pain associated with postherpetic neuralgia	Topical patch: 5%	-
Pregabalin (Lyrica®)	Adjunctive therapy for adult patients with partial onset seizures, management of fibromyalgia, management of neuropathic pain associated with diabetic peripheral neuropathy and management of postherpetic neuralgia:	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg	-

Evidence-based Medicine

- All of the agents Food and Drug Administration (FDA)-approve for the treatment of neuropathic pain have demonstrated safety and efficacy in clinical studies when compared to placebo.[8-31]
- Patients with postherpetic neuralgia who were transitioned from gabapentin to pregabalin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. In a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed.[32]
- In a 52-week, open-label study comparing duloxetine to routine care (gabapentin, amitriptyline or venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant treatment-group differences observed in Euro Quality of Life assessment questionnaire scores; however, results differed with regard to short form (SF)-36 subscale scores. In one study, there were no significant treatment-group differences in SF-36 subscale scores, but other subscale scores for physical functioning, bodily pain, mental health and vitality favored duloxetine.[33,34]
- A second head-to-head study demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.[35]
- Several large meta-analyses and systematic reviews have been conducted that further support the safety and efficacy of these agents in their FDA-approved indications.[36-43]
- In a meta-analysis by Quilici et al, limited available clinical study data suitable for indirect comparison, demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain.[43]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - First-line treatments for postherpetic neuralgia include a tricyclic antidepressant, gabapentin, pregabalin or topical lidocaine patches.[44,45]
    - Topical lidocaine may be considered first-line in the elderly, especially if there are concerns of adverse events with oral medications.[45]
    - For the treatment of diabetic neuropathy, the American Association of Clinical Endocrinology and American Academy of Neurology (AAN) recommend tricyclic antidepressants, anticonvulsants and topical capsaicin to provide symptomatic relief. Moreover, the AAN states that the use of duloxetine or venlafaxine should be considered. There is insufficient evidence to recommend one agent over another. [46,47]

- Other Key Facts:
    - Immediate-release gabapentin (Neurontin®) is the only agent within the class that is available generically.
    - Pregabalin (Lyrica®) is the only neuropathic pain agent that is classified as a controlled substance (Schedule V).
    - In May 2012 Watson Laboratories settled a patent litigation lawsuit with Endo Pharmaceuticals, allowing Watson to launch its generic 5% lidocaine topical patch (Lidoderm®) as early as September 2013.

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4. Horizant® [package insert]. Research Triangle Park (NC): GlaxoSmithKline; 2012 Jun.
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6. Lyrica® [package insert]. New York (NY): Pfizer Inc.; 2011 Jun.
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Therapeutic Class Review
Neuropathic Pain Agents

Overview/Summary

The agents approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain include duloxetine (Cymbalta®), gabapentin (Neurontin®), gabapentin extended-release (Gralise®), gabapentin enacarbil (Horizant®), lidocaine patches (Lidoderm®) and pregabalin (Lyrica®). All of these agents are FDA-approved for the treatment of postherpetic neuralgia with the exception of duloxetine, which is indicated for neuropathic pain associated with diabetic neuropathy.[1-8] The exact mechanisms by which these agents exert their analgesic effects are unknown. Neuropathic pain arises as a consequence of a lesion or disease that affects the nervous system. The most common types of neuropathic pain include diabetic peripheral neuropathy, postherpetic neuralgia, trigeminal neuralgia and central post-stroke pain.[9] Symptoms often include a burning, tingling, sharp or stabling pain and may occur at any time of day. The treatment of neuropathic pain is complex, and patients may need multiple agents to experience relief. Despite the available medications for symptomatic relief and analgesia, their effectiveness is unpredictable, dosing can be complicated, onset of action is delayed and adverse events are common.

The analgesic properties of duloxetine are believed to result from potent inhibition of neuronal serotonin and norepinephrine reuptake and a less potent inhibition of dopamine reuptake. Duloxetine is typically dosed once daily for the treatment of diabetic neuropathy. It also is indicated for the management of chronic musculoskeletal pain, fibromyalgia, generalized anxiety disorder and major depressive disorder. The most common adverse events associated with duloxetine include nausea, somnolence and dizziness. Duloxetine is not available generically.[1]

Gabapentin is structurally related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake or degradation. Gabapentin is typically administered three times daily, while the extended-release formulation is administered once daily. Immediate-release gabapentin is also approved as an adjunctive treatment of partial seizures with and without secondary generalization. Gabapentin enacarbil, a prodrug of gabapentin, is rapidly hydrolyzed to gabapentin in the gastrointestinal tract and is dosed twice daily for the management of postherpetic neuralgia. Gabapentin enacarbil does not demonstrate saturable absorption which results in a higher bioavailability and less variability in serum levels compared to gabapentin. Due to these pharmacokinetic differences, the three gabapentin products are not interchangeable with one another. Gabapentin immediate-release is the only agent contained within this review that is available generically.[2-4]

Lidocaine is an amide-type local anesthetic that is believed to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The absorption of lidocaine following application a topical patch is sufficient to produce analgesia, but less than the amount necessary to produce a complete sensory block. The lidocaine topical patch should be applied to the painful area for 12 hours and then removed for the following 12 hours.[5] Lidocaine patches are not available generically; however, generic products are available for other lidocaine formulations. The most frequently reported adverse events are dermatologic in nature and include burning sensation at application site, dermatitis, pruritus and erythema.

Pregabalin may produce anti-nociceptive effects through its high affinity binding to the α2Δ subunit of voltage-gated sodium channels. Similar to gabapentin, pregabalin is structurally similar to GABA but does not directly bind to or augment the response of GABA. In addition to postherpetic neuralgia, pregabalin is approved for the treatment of neuropathic pain associated with diabetic neuropathy, fibromyalgia and adjunctive therapy for patients with partial onset seizures.[6] Pregabalin is the only neuropathic pain agent that is classified as a controlled substance (Schedule V).

According to current clinical guidelines for postherpetic neuralgia, tricyclic antidepressants, gabapentin, pregabalin and topical lidocaine patches are all effective and should be considered for treatment.[10] In addition, topical lidocaine patches may be considered first-line treatment in elderly patients.[11] For the treatment of painful diabetic neuropathy, the American Academy of Neurology and American Association of Clinical Endocrinologists state that consideration should be given to amitriptyline, duloxetine and venlafaxine, as well as gabapentin and pregabalin. Other treatment algorithms recommend a step-wise approach with tricyclic antidepressants as initial therapy followed by anticonvulsants and opioids.[12,13]

There are limited head-to-head studies available that directly compare the neuropathic pain agents to one another. In one study of patients with postherpetic neuralgia who were transitioned from gabapentin to pregabalin, no significant difference was reported between treatments with regard to pain, based on a visual analog scale. Some patients required an increase in pregabalin dosage to improve the analgesic effect after transitioning from gabapentin.[14] In a 52-week, open-label study comparing duloxetine to gabapentin, amitriptyline or venlafaxine for the treatment of diabetic peripheral neuropathic pain, no significant differences were observed between treatments with regard to quality of life questionnaire scores; however, results differed with regard to short-form-36 subscale scores. In another study, there were no significant treatment-group differences in SF-36 subscale scores, and in the other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine.[15,16] In a head-to-head study by Tanenberg et al, duloxetine was noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.[17]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Duloxetine (Cymbalta®)	Selective serotonin- and norepinephrine-reuptake Inhibitors	-
Gabapentin (Neurontin®)	Anticonvulsants, miscellaneous	✔
Gabapentin extended-release (Gralise®)	Anticonvulsants, miscellaneous	-
Gabapentin enacarbil (Horizant®)	Anticonvulsants, miscellaneous	-
Lidocaine patch (Lidoderm®)	Topical anesthetics	-
Pregabalin (Lyrica®)	Anticonvulsants, miscellaneous	-

Indications

Table 2. Food and Drug Administration Approved Indications[1-8]

Indication	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Adjunctive therapy for adult patients with partial onset seizures	-	-	-	-	-	✔
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients >12 years of age with epilepsy	-	✔ †	-	-	-	-
Management of chronic musculoskeletal pain	✔ *	-	-	-	-	-
Management of fibromyalgia	✔	-	-	-	-	✔
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔	-	-	-	-	✔
Management of postherpetic neuralgia	-	✔	✔	✔	✔	-
Relief of pain associated with postherpetic neuralgia	-	-	-	-	-	✔
Moderate-to-severe primary restless legs syndrome	-	-	-	✔ ‡	-	-
Treatment of generalized anxiety disorder	✔	-	-	-	-	-
Treatment of major depressive disorder	✔	-	-	-	-	-

*This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
† Adjunctive therapy in the treatment of partial seizures in patients 3 to 12 years of age
‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.

In addition to their respective Food and Drug Administration-approved indications, the neuropathic pain agents have been used off-label in various other conditions. Duloxetine has been evaluated for use in the management of urinary incontinence, while gabapentin has been used in the treatment of diabetic peripheral neuropathy, migraine prophylaxis, hot sweats and hemodialysis associated pruritus. Lidoderm patches have been used for the treatment of diabetic peripheral neuropathy, while pregabalin has been studied in patients with generalized anxiety disorder.[7,8]

Pharmacokinetics

Table 3. Pharmacokinetics[1-8]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Duloxetine	30 to 80	~70	Not reported	8 to 17
Gabapentin	27 to 60*	76 to 81	None	5 to 7
Gabapentin extended-release	Not reported	Not reported	None	8
Gabapentin enacarbil	75	94	Gabapentin	5.1 to 6.0
Lidocaine patch	<3	70	Monoethylglycine -xylidide, glycinexylidide	1.5 to 2
Pregabalin	≥90	90 to 99	None	5.0 to 6.5

*Gabapentin bioavailability is not dose proportional. The bioavailability is reduced as the dosage increases.

Clinical Trials

Clinical studies demonstrating the efficacy of the neuropathic pain agents in their Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[14-54]

In patients with postherpetic neuralgia, treatment with lidocaine patches results in significant pain relief compared to placebo.[25-27] In addition, treatment with lidocaine patches has been associated with higher rates of patient preference, less use of rescue medication and decreases in allodynia and neuropathic symptoms compared to placebo.[26,27] A noncomparative, open-label study evaluating lidocaine patches for the management of postherpetic neuralgia supports the findings of placebo-controlled studies[19].

Duloxetine demonstrates consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36) and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported adverse events in patients receiving duloxetine include nausea, somnolence anorexia, and dysuria.[22-24]

Gabapentin has also demonstrated superiority over placebo in alleviating pain, improving functional outcomes and improving quality of life in patients with postherpetic neuralgia. Treatment with gabapentin significantly improves average daily pain and sleep, Short form-McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores compared to placebo. Commonly reported adverse events in patients receiving gabapentin include somnolence, drowsiness, dizziness, ataxia, peripheral edema and infection.[28,29] In studies comparing placebo, gabapentin and morphine sustained-release as monotherapy to combination therapy with gabapentin and morphine sustained-release in patients with postherpetic neuralgia, results demonstrate that combination therapy achieves greater analgesia at lower doses of each agent, compared to monotherapy with either agent alone. Combination therapy was most commonly associated with constipation, sedation and dry mouth.[30] Within these studies, doses of gabapentin of up to 3,600 mg/day were evaluated.[28-30]

An extended-release formulation of gabapentin has also demonstrated efficacy in the treatment of postherpetic neuralgia. In two placebo-controlled studies, gabapentin extended-release achieved significant improvements in average daily pain and sleep interference scores.[31,32] In one study, a larger proportion of patients receiving gabapentin extended-release reported ≥50% baseline reduction in average daily pain scores compared to placebo.[31] In general, treatment with gabapentin extended-release

was well tolerated; dizziness, headache, somnolence and peripheral edema were the most commonly reported adverse events.[31,32] In another placebo-controlled study, it was concluded that gabapentin extended-release may be particularly effective in patients with postherpetic neuralgia presenting with sharp, dull, sensitive or itchy pain.[33] Within these studies, gabapentin extended-release at doses of up to 1,800 mg/day were evaluated.[31-33]

Clinical study data for the basis of FDA approval of gabapentin enacarbil for the treatment of postherpetic neuralgia are not published. According to the package insert, the efficacy of gabapentin enacarbil (1,200, 2,400 and 3,600 mg/day) was established in a randomized, placebo-controlled, 12-week study in adult patients with postherpetic neuralgia for at least three months (N=371). Patients had significant pain as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥4 on the 11-point numerical scale. Treatment with gabapentin enacarbil significantly improved the mean pain score and increased the proportion of patients with ≥50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all three doses of gabapentin enacarbil as early as week one and maintained to study end. An additional benefit of using doses of gabapentin enacarbil >1,200 mg/day was not demonstrated.[4] Results of a second, published, placebo-controlled study confirms these findings. Gabapentin enacarbil 1,200 mg/day was superior to placebo in providing postherpetic neuralgia pain relief, as well as in improving sleep, POMS, Patient Global Impression of Change and SF-MPQ scores. Reported adverse events were similar to what has been reported with gabapentin and gabapentin extended-release, and included dizziness, headache and nausea.[34]

Pregabalin demonstrates consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and postherpetic neuralgia-related pain. Similar outcomes to what have been described for the other neuropathic pain agents have been observed with pregabalin compared to placebo; significant improvements in pain relief, functional outcomes and quality of life. Commonly reported adverse events in patients receiving duloxetine include dizziness, somnolence, infection, headache, dry mouth, weight gain and peripheral edema.[35-46] Two, noncomparative, open-label studies evaluating pregabalin for the management of postherpetic neuralgia supports the findings of placebo-controlled studies [20-21] In one of these noncomparative studies, long-term treatment of postherpetic neuralgia with pregabalin (52 weeks) was found to be safe and effective.[20]

Patients with postherpetic neuralgia who were transitioned from gabapentin to pregabalin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. In a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed.[14]

Head-to-head studies among the neuropathic pain agents are rare. In a 52-week, open-label study comparing duloxetine to routine care (gabapentin, amitriptyline or venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant treatment-group differences observed in EQ-5D questionnaire scores; however, results differed with regard to SF-36 subscale scores. In one study, there were no significant treatment-group differences in SF-36 subscale scores between treatments, but the other subscale scores for physical functioning, bodily pain, mental health and vitality favored duloxetine.[15,16] A second head-to-head study demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.[17]

Several large meta-analyses and systematic reviews have been conducted that further support the safety and efficacy of these agents in their FDA-approved indications.[47-54] In a meta-analysis by Quilici et al, limited available clinical study data suitable for indirect comparison, demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain.[54]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Devers et al[18] Lidocaine 5% transdermal patch applied for 12 hours daily (up to 3 patches could be applied at once)	OL Patients 23 to 85 years of age diagnosed with peripheral neuropathic pain	N=16 12 weeks	Primary: Degree of pain relief using a verbal five-point scale Secondary: Not reported	Primary: Thirteen patients (81%) reported either “moderate relief”, “a lot of relief”, or “complete relief” from the lidocaine patch. Of these 13 patients, all noted a reduction in brush-evoked mechanical allodynia. All patients who responded to medication continued to experience relief throughout the duration of the study. Secondary: Not reported
Katz et al[19] Lidocaine 5% transdermal patch applied for 12 hours daily (up to 3 patches could be applied at once)	OL Patients 20 to 99 years of age diagnosed with PHN	N=332 28 days	Primary: Changes in pain intensity, pain interference in quality of life, pain relief, patient and physician global assessments Secondary: Not reported	Primary: Mean scores for all measures of pain intensity were significantly lower than baseline scores at all evaluations (*P*=0.0001). At the end of the study 40% of patients experienced ≥50% reduction in average daily pain intensity. Mean pain interference with quality of life scores were significantly lower compared to baseline at all evaluations (*P*=0.0001). The majority of patients responded to lidocaine treatment within the first week. There was a significant improvement from baseline in pain relief at all evaluations (*P*=0.0001). Overall, 58% of patients reported moderate to complete pain relief at day 28. The results of the physician global assessments and patient global assessments were similar. Approximately 60% of patients were judged to have complete improvement or moderate (“a lot of”) improvement at day 28, slight improvement was reported in approximately 15% of patients, and no change was reported in 20% of patients. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Ifuku et al[14] Pregabalin Without changing the frequency of dosing, gabapentin was substituted with pregabalin at one-sixth dosage of gabapentin. After 2 weeks, the dosage was increased in patients who requested a dosage increase and if VAS pain score was ≥25 mm after substitution.	PRO Study Grade: Not applicable Patients with PHN who were being administered gabapentin, and whose pain had continued for 3 months or more after being infected with herpes zoster	N=32 Duration not specified	Primary: VAS pain score Secondary: Not reported	Primary: During evaluation after two weeks, the VAS pain score was 46.9±22.5 mm; thus, no significant difference was observed in the score before and after the substitution (*P*>0.05). However, the score varied greatly among patients. Regarding changes in individual VAS pain scores, the score in the patients with most pain relief was -18 mm and in the patients with maximum pain exacerbation was 30 mm. Twenty-two patients had increased dosage to improve the analgesic effect after the substitution. Although no significant difference was observed in VAS pain scores after substitution of gabapentin with pregabalin in the titration group (scores increased from 51.5±23.0 to 52.1±20.3 mm; *P*>0.05), regarding the judgment of the effect of action after the dosage increase, VAS pain scores significantly decreased from 52.1±20.3 to 35.5±21.2 mm (*P*<0.05). Secondary: Not reported Safety: Although no significant difference was observed in the number of patients with somnolence and dizziness before and after the substitution, the number of patients with peripheral edema increased significantly in the group where gabapentin was substituted with pregabalin (*P*<0.05). Serious adverse events interfering with daily life were not observed before and after the substitution. Limitations: Not applicable Conclusion: Results suggest that the analgesic action of pregabalin in PHN was six times that of gabapentin in terms of effectiveness in dosage conversion. With regards to adverse events, although the incidence of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				peripheral edema was higher with pregabalin compared to gabapentin, the finding was not conclusive because the present trial was conducted in a small number of patients. Although pain reduction can be expected to increase with pregabalin dosage, it is necessary to increase the dosage gradually and carefully because of exacerbation of adverse events.
Ogawa et al[20] (abstract) Pregabalin 150 to 600 mg/day	OL Study Grade: Not applicable Patients with PHN	N=126 52 weeks	Primary: SF-MPQ Secondary: Not reported	Primary: SF-MPQ showed a decrease over time with treatment. The changes of VAS and present pain intensity at trial end were -28.3 mm and -1.1 score, respectively. Secondary: Not reported Safety: The commonly reported adverse events were dizziness, somnolence, peripheral edema, and weight gain, and most of them were mild to moderate in intensity. No new adverse events were observed during long-term administration compared to short-term administration (13 weeks). Limitations: Not applicable Conclusion: Pregabalin is safe and effective for long-term treatment of PHN.
Xochilcal-Morales et al[21] Pregabalin 150 to 600 mg/day	MC, OL, PRO Study Grade: Not applicable Patients ≥18 years of age diagnosed with neuropathic pain	N=121 12 weeks	Primary: Change from baseline to end of treatment/last observation carried forward in weekly main pain score on daily pain rating	Primary: Pregabalin significantly reduced the weekly mean pain score on daily pain rating scale scores from baseline to end of treatment/last observation carried forward (-3.8; 95% CI, -4.2 to -3.3; *P*<0.0001). Secondary: Reductions from baseline to end of treatment/least observation carried forward were observed for all secondary efficacy outcomes (*P*<0.0001). Pain and sleep interference were significantly improved compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	associated with diabetic peripheral neuropathy, PHN, chemotherapy-induced peripheral neuropathic pain, or HIV-related peripheral neuropathic pain; with a score ≥40 mm on a VAS and a daily pain rating score ≥4 throughout screening		scale Secondary: Pain, anxiety, sleep interference, treatment satisfaction, Patient Global Impression of Change, Clinician Global Impression of Change	baseline across all weeks of the trial, as early as one week after initiation of pregabalin (*P*<0.0001). Safety: The most commonly reported adverse events were somnolence, dizziness, weight gain, and peripheral oedema. Nine patients (7.4%) discontinued the trial because of the adverse events and 25 patients (20.7%) temporarily stopped or reduced their pregabalin dose because of adverse events. Limitations: None Conclusion: Flexible-dose pregabalin significantly reduced pain and anxiety and improved sleep and was generally well tolerated in Latin American patients with neuropathic pain.
Yan et al[22] Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT Study Grade: Good Adult Chinese patients with diabetic peripheral neuropathic pain and Brief Pain Inventory 24-hour average pain severity rating ≥4	N=215 12 weeks	Primary: Change from baseline to endpoint in Brief Pain Inventory average pain score Secondary: Brief Pain Inventory-severity and -interference, Patient Global Impression of	Primary: Mean change from baseline to endpoint in Brief Pain Inventory average pain score was not significantly different between treatments (-2.31±0.18 vs -2.69±0.19; *P*=0.124). Duloxetine-treated patients showed significantly greater pain reduction compared to placebo-treated patients at weeks one, two, and four (*P*=0.004, *P*=0.009, and *P*=0.006), but not at week eight (*P*=0.125) and 12 (*P*=0.107). Secondary: Duloxetine-treated patients experienced significant improvement in PGII (2.32±0.11 vs 2.64±0.10; *P*=0.028), CGIS (-1.24±0.11 vs -0.99±0.11; *P*=0.036), AUC for pain relief, Brief Pain Inventory-severity pain right now (-2.72±0.26 vs -1.99±0.25; *P*=0.012), and Brief Pain Inventory-interference walking ability (-2.45±0.24 vs -1.82±0.23; *P*=0.016).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Improvement, Clinical Global Impressions of Severity, EQ-5D, Athens Insomnia Scale	Patients receiving duloxetine had numerically higher 30 and 50% response rates on Brief Pain Inventory average pain compared to placebo-treated patients. A higher proportion of patients receiving duloxetine (62.5%) met the criteria for sustained response compared to patients receiving placebo (50.5%). All other secondary efficacy measures, including health outcomes measures, were numerically but not significantly improved in patients receiving duloxetine compared to patients receiving placebo. Safety: Duloxetine-treated patients reported nausea, somnolence, anorexia, and dysuria significantly more compared to placebo. Limitations: Treatment duration was only 12 weeks and could not assess whether patients would benefit from a long-term treatment. Pain was assessed using patients' self-reporting scales and some level of bias cannot be excluded. Conclusion: Although the primary study endpoint was not achieved, the overall observed response pattern suggests the efficacy of duloxetine in the treatment of Chinese patients with diabetic peripheral neuropathic pain. The safety profile for duloxetine is similar to that reported in other global trials.
Armstrong et al[23] Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	3 DB, MC, PC, RCT Study Grade: Not applicable Patients with diabetic	N=1,139 12 weeks	Primary: Patient-reported functional outcomes (SF-36, Brief Pain Inventory, EQ-5D)	Primary: Diabetic peripheral neuropathic pain patients treated with duloxetine 60 mg QD or BID had greater improvement, compared to placebo, in all SF-36 domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Within treatment group changes among the domain scores ranged from 0.9 to 23.5 points. Duloxetine 60 mg BID showed some advantage over duloxetine 60 mg QD on general health (*P*=0.02) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	peripheral neuropathic pain		Secondary: Not reported	mental health (*P*=0.04) status. Consistent results were seen in the ITT population with the exception that the above indicated advantages of duloxetine 60 mg BID over 60 mg QD in the domains of general and mental health were not significant. Duloxetine 60 mg QD and 60 mg BID were significantly superior to placebo at reducing scores in all Brief Pain Inventory interference items thereby indicating improvements in all seven items, with similar results demonstrated for the ITT population. In the analysis of the EQ-5D, patients on duloxetine 60 mg QD (*P*=0.004) and 60 mg BID (*P*<0.001) were both significantly better compared to placebo for the trial completers. Results for the ITT analysis were consistent, thus demonstrating the superiority of duloxetine 60 mg QD and BID compared to placebo with regard to changes in all included function and quality of life measures. Secondary: Not reported Safety: Not reported Limitations: Not applicable Conclusion: Acute treatment with duloxetine was associated with significant improvement in functional outcomes in persons with diabetic peripheral neuropathic pain.
Kajdasz et al[24] Duloxetine 20 or 60 mg QD, or 60 mg BID	Post-hoc analysis of 3 DB, MC, PC, RCT Study Grade:	N=1,139 12 weeks	Primary: Response rate (defined as ≥30 and ≥50% reductions from	Primary: NNTs based on 50% reduction for patients receiving duloxetine 60 mg QD and 60 mg BID were 5.2 (95% CI, 3.8 to 8.3) and 4.9 (95% CI, 3.6 to 7.6), respectively, based on last observation carried forward. Similarly, NNTs of 5.3 (95% CI, 3.8 to 8.3) for 60 mg QD and 5.7 (95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	Not applicable Patients with diabetic peripheral neuropathic pain		baseline in weekly mean of the 24-hour average pain severity scores) Secondary: NNH (based on rates of dis-continuation due to adverse events)	CI, 4.1 to 9.7) for 60 mg BID observed based on baseline observation carried forward. Secondary: The NNHs based on discontinuation due to adverse events were 17.5 (95% CI, 10.2 to 58.8) with duloxetine 60 mg QD and 8.8 (95% CI, 6.3 to 14.7) with duloxetine 60 mg BID. Safety: Not reported Limitations: Not applicable Conclusion: These post hoc results suggest that duloxetine was effective and well tolerated for the management of diabetic peripheral neuropathic pain and further support the importance of duloxetine as a treatment option for clinicians and patients to assist in the management of diabetic peripheral neuropathic pain.
Galer et al[25] Lidocaine 5% transdermal patch vs placebo patch	DB, PC, PG, RCT Adults with PHN involving the torso area for ≥1 month and in whom allodynia was observed on physical examination	N=150 3 weeks	Primary: Change from baseline to week three in neuropathic pain scale and four sub-items of this scale (composite score, total descriptor score, nonallodynic score, and 4 Score [sum of the scores of the four descriptors	Primary: The reduction in pain scores for all four composite endpoints was consistently larger in the lidocaine patch group compared to the placebo group (*P*=0.043, *P*=0.042, *P*=0.022, and *P*=0.013 respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			"sharp," "hot," "dull," and "deep"]) Secondary: Not reported	
Galer et al[26] Lidocaine 5% transdermal patch for 12 hours daily (up to 4 patches could be applied at once) vs placebo	PC, RCT, XO Patients 62 to 96 years of age with PHN already enrolled in the OL protocol and using lidocaine patches on a regular basis for ≥1 month	N=33 28 days	Primary: Time to exit the study (patients exited the study when their verbal pain relief rating decreased by ≥2 categories for any two consecutive days when compared to pre-study OL pain report) Secondary: Not reported	Primary: The median time to exit was >14 days in the lidocaine group compared to 3.8 days in the placebo group (*P*<0.001). Significantly more patients (78.1%) preferred treatment with lidocaine compared to 9.4% of patients who preferred treatment with placebo (*P*<0.001). The number of subjects reporting moderate or greater pain relief was 29 in the lidocaine group compared to 13 in the placebo group (*P* values not reported). A total of seven subjects used rescue pain relief medications throughout the study (three in the lidocaine group and four in the placebo group; *P* value not reported). Secondary: Not reported
Meir et al[27] Lidocaine 5% transdermal patch applied for 12 hours daily (up to 4 patches could be applied at once) vs placebo	DB, PC, PRO, RCT, XO Patients ≥21 years of age suffering from chronic painful peripheral focal neuropathic syndromes that were superficial	N=58 28 days	Primary: Ongoing pain intensity (during the first eight hours, every two hours after patch application on day one, and one hour after daily removal of the patch)	Primary: At all time points, ongoing pain intensity decreased compared to pretreatment values in both the lidocaine and placebo groups (*P*<0.001 and *P*<0.05). The differences between groups were significant at two hours (*P*=0.003), four hours (*P*=0.004), four days (*P*=0.03), five days (*P*=0.02), and seven days (*P*=0.002). The AUC values show that lidocaine was more effective during the first eight hours and over the course of the treatment week compared to placebo (*P*=0.017 and *P*=0.018 respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and localized to a limited skin zone		allodynia, quality of neuropathic symptoms, quality of sleep Secondary: Not reported	At all time points, allodynia decreased compared to pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.005), four hours (P=0.009) and six hours (P=0.017) after the first patch application and at day five (P=0.035). Adjusted AUC values show better allodynia relief compared to placebo during the first eight hours (P=0.023) and for the remainder of the treatment period (P=0.03). There was a significant reduction in neuropathic symptoms in the lidocaine group compared to baseline (P=0.032), but no significant differences were observed between the lidocaine and placebo groups at any time. No significant differences were observed between the lidocaine and placebo groups in quality of sleep. Secondary: Not reported
Rowbotham et al[28] Gabapentin 3,600 mg/day vs placebo	DB, MC, PC, RCT Study Grade: Good Patients ≥18 years of age with pain present for >3 months after healing of a herpes zoster skin rash; pain intensity score ≥40 mm (on the	N=229 8 weeks	Primary: Change in the average daily pain score Secondary: Average daily sleep scores, SF-MPQ, Patient Global Impression of Change, Clinician Global Impression of Change, SF-36,	Primary: The average daily pain score was significantly reduced at trial end with gabapentin (33.3% reduction) compared to placebo (7.7% reduction). At the end of eight weeks, gabapentin showed an average daily pain score of 4.2 (decrease of 2.1) compared to 6.0 with placebo (decrease of 0.5; P<0.001). This reduction was established at week two, with a further reduction at week four. At week eight, pain reduction was maintained at the week four level. Secondary: Gabapentin significantly improved average sleep rating scores compared to placebo (P<0.001). SF-MPQ scores were significantly improved for total pain (P<0.001), as well as sensory pain (P<0.001) and affective pain (P<0.001) with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	100 mm VAS of the SF-MPQ) at screening and randomization; average daily diary pain score ≥4 (0 to 10 scale) during baseline; and discontinuance of muscle relaxants, anticonvulsants, mexiletine, topical analgesics, and antiviral agents ≥2 weeks prior to screening		POMS	gabapentin compared to placebo. SF-MPQ ratings were significantly improved with gabapentin compared to placebo (*P*<0.01). This included a rating of 'no pain' at the final week in 16.0 and 8.8% of patients receiving gabapentin and placebo. The Patient Global Impression of Change questionnaire indicated that gabapentin provided valuable pain reduction for many patients. At trial end, 43.2 and 12.1% of patients receiving gabapentin and placebo reported their pain as 'much' or 'moderately' improved. The majority of patients receiving placebo reported no change in pain level (59.5%) compared to gabapentin (22.9%). The Clinician Global Impression of Change showed similar results. On the SF-36, measures relating to physical functioning, role-physical, bodily pain, vitality, and mental health all showed gabapentin to be superior compared to placebo (*P*≤0.01 for all). Patients receiving gabapentin showed significantly greater improvement compared to patients receiving placebo in the POMS assessments of depression-dejection, anger-hostility, fatigue-inertia, and confusion-bewilderment, and total mood disturbance (*P*≤0.01 for all). Safety: Minor adverse events deemed to be treatment-related were reported in 54.9 and 27.6% of patients receiving gabapentin and placebo. No serious adverse events were reported. One death occurred with placebo and was not considered to be treatment-related. Overall, the most frequently reported adverse events with gabapentin were somnolence (27.4 vs 5.2%), dizziness (23.9 vs 5.2%), ataxia (7.1 vs 0%), peripheral edema (9.7 vs 3.4%), and infection (8.0 vs 2.6%). A total of 13.3 and 9.5% of patients receiving gabapentin and placebo withdrew from the trial due to an adverse event. Limitations: None

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Conclusion: Gabapentin is effective in the treatment of pain and sleep interference associated with PHN. Mood and quality of life also improve with gabapentin.
Rice et al[29] Gabapentin 1,800 or 2,400 mg/day vs placebo	DB, MC, PC, RCT Study Grade: Good Patients ≥18 years of age with pain present for >3 months after healing of an acute herpes zoster skin rash, and an average pain score ≥4 (11-point scale)	N=334 7 weeks	Primary: Change in average daily pain diary score Secondary: Mean weekly sleep interference score, SF-MPQ, Clinician Global Impression of Change, Patient Global Impression of Change, SF-36	Primary: Change in average daily pain diary score showed significant improvements with gabapentin compared to placebo. The average score with placebo was 6.4 vs 5.3 (reduction of 15.7%), for gabapentin 1,800 mg/day was 6.5 vs 4.3 (reduction of 34.5%), and for gabapentin 2,400 mg/day was 6.5 vs 4.2 (reduction of 34.4%). The difference between placebo and gabapentin 1,800 mg/day was 18.8% (95% CI, 10.9 to 26.8; *P*<0.01). The difference between placebo and gabapentin 2,400 mg/day was 18.7% (95% CI, 10.7 to 26.7; *P*<0.01). Differences between gabapentin and placebo were significant from week one (1,200 mg/day) onward. The proportion of patients showing a ≥50% reduction in mean pain score from baseline was significantly higher (*P*=0.001) with gabapentin 1,800 (32%) and 2,400 mg/day (34%) compared to placebo (14%). Secondary: Sleep interference diaries showed a similar pattern of improvement to the pain diary, with gabapentin showing greater improvement compared to placebo from week one onward. For the last week of treatment, the difference between placebo and gabapentin 1,800 mg/day was 0.9 (95% CI, 0.4 to 1.4; *P*<0.01). The difference between placebo and gabapentin 2,400 mg/day was 1.1 (95% CI, 0.7 to 1.6; *P*<0.01). SF-MPQ showed improvements in all parameters during treatment, with greater improvements with gabapentin. The difference between gabapentin and placebo was significant (*P*<0.05) for the sensory score, total score, and VAS of pain during the previous week (2,400 mg/day only).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At trial end, 44 (*P*=0.002 vs placebo), 44 (*P*=0.001 vs placebo), and 19% of clinicians rated patients' conditions as 'very much improved' or 'much improved. At trial end, 41 (*P*=0.003 vs placebo), 43 (*P*=0.005 vs placebo), and 23% of patients reported their condition as 'very much improved' or 'much improved.' Patients receiving gabapentin experienced significantly greater improvements in mean score for the vitality scale of the SF-36 (P<0.05) compared to patients receiving placebo. Patients receiving gabapentin 1,800 mg/day showed significantly greater improvements in mean score for scales of bodily pain (*P*<0.01) and mental health (*P*<0.05) compared to patients receiving placebo. Safety: Withdrawals due to adverse events were more common with both doses of gabapentin compared to placebo, and 38% of gabapentin withdrawals occurred within the first week, and 76% within the first three weeks. Dizziness (seven percent) and drowsiness (five to six percent) were the most common adverse events necessitating withdrawal among patients receiving gabapentin. There were five serious adverse events; one, three, and one with placebo, gabapentin 1,800 mg/day, and gabapentin 2,400 mg/day. All were considered not to be treatment-related. Limitations: None Conclusion: Results confirm the role of gabapentin as an efficacious and well tolerated treatment for PHN.
Gilron et al[30] Placebo (lorazepam 0.3	DB, PC (active), RCT, 4-way XO	N=57 (n=35 with diabetic	Primary: Mean daily pain intensity in	Primary: Daily pain at maximal tolerated doses of trial drugs were as follows: 5.72±0.23 at baseline, 4.49±0.34 with placebo, 4.15±0.33 with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg, with a target daily dose of 1.6 mg) for 5 weeks vs morphine sustained-release 30 mg, with a target daily dose of 120 mg for 5 weeks vs gabapentin 400 mg, with a target daily dose of 3,200 mg for 5 weeks vs gabapentin 300 mg plus morphine sustained-release 15 mg, with target daily doses of 2,400 and 60 mg for 5 weeks	Study Grade: Good Patient 18 to 89 years of age with painful diabetic neuropathy or PHN; patients with diabetic neuropathy had distal, symmetric, sensory diabetic polyneuropathy as determined on the basis of their medical history and either an unequivocal decrease in response to pinprick, temperature, or vibration in both feet or bilaterally decreased or absent ankle-jerk reflexes; patients with PHN had had an eruption of herpes zoster rash not more recently than 6 months prior to	neuro-pathy, n=22 with PNH) 20 weeks	patients receiving a maximum tolerated dose Secondary: Pain (SF-MPQ), maximal tolerated doses, mood, quality of life	gabapentin, 3.70±0.34 with morphine, and 3.06±0.33 with combination therapy (P<0.05 for combination vs placebo, gabapentin, and morphine). The analysis of the percent change in pain intensity indicated greater reduction of pain with the use of combination therapy compared to placebo (20.4% greater reduction; P=0.03), and other comparisons were not significant. The primary analysis showed no significant main effect of either sequence or treatment period, but the effects of drug treatment (P<0.001) and carryover (P=0.04) were significant. Secondary: Patients' total scores in response to SF-MPQ with combination therapy were lower compared to placebo (P<0.05), gabapentin (P<0.05), or morphine (P<0.05). The maximal tolerated dose of morphine was 45.3±3.9 mg as a single agent, as compared to 34.4±2.6 mg with combination therapy (P<0.05). The maximal tolerated dose of gabapentin was 2,207±89 mg as a single agent, compared to 1,705±83 mg with combination therapy (P<0.05). The maximal tolerated dose of lorazepam was 1.38±0.05 mg. Patients' scores for pain-related interference with mood with combination therapy were lower compared to placebo (P<0.001) and morphine (P=0.03), and scores for pain-related interference with general activity, normal work, sleep, and enjoyment of life were significant when patients were receiving any active treatment compared to placebo (P<0.05 for all). Based on SF-36 responses, combination therapy was associated with higher scores for vitality (P=0.007) and social functioning (P=0.004) compared to placebo, and higher scores compared to morphine for vitality (P=0.03) and social functioning (P=0.04). All active treatments were associated with significantly lower scores on the Beck Depression Inventory compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	enrollment			Safety: At maximal tolerated doses, combination therapy was associated with a higher frequency of constipation compared to gabapentin (*P*=0.006) but not morphine, and with a higher frequency of dry mouth compared to morphine (*P*=0.03) but not gabapentin. Limitations: Data from the blinding questionnaire indicate that one third of patients guessed they were receiving an active drug while they were receiving placebo. Such guesses may have led to higher expectations during treatment with the active placebo and may have resulted in lower self-assessments of pain intensity than might have been reported with the use of an inert placebo and consequently decreased the difference between treatment with gabapentin or placebo. Maximal tolerated doses were slightly lower than those reached in previous trials of gabapentin. Conclusion: Gabapentin and morphine combined achieved better analgesia at lower doses of each drug compared to either as a single agent, with constipation, sedation, and dry mouth as the most frequent adverse events.
Irving et al[31] (abstract) Gabapentin ER QD (1,800 mg administered in the evening) or BID (600 mg administered in the morning and 1,200 mg administered in the evening) vs placebo	DB, PC, RCT Study Grade: Not applicable Patients with pain for ≥3 months after healing of acute herpes zoster skin rash and who had baseline average	N=158 4 weeks	Primary: Changes from baseline to week four in average daily pain score and average daily sleep interference score Secondary: Not reported	Primary: Changes for average daily pain score were -1.93±0.28, -2.24±0.29, and -1.29±0.29 with gabapentin ER QD, gabapentin ER BID, and placebo, respectively (*P*=0.089 and *P*=0.014 vs placebo), with 25.85, 28.80, and 11.80% of patients reported ≥50% decrease from baseline average daily pain score. Changes in sleep interference scores were -1.94±0.30, -2.28±0.30, and -1.16±0.30, respectively (*P*=0.048 and *P*=0.006 vs placebo). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	daily pain score ≥4 on a 10 point Numerical Rating Scale			Safety: Common adverse events with all treatments were dizziness (22.2, 11.3, and 9.8%) and somnolence (9.3, 7.5, and 7.8%). Limitations: Not applicable Conclusions: BID gabapentin ER is effective and safe for the treatment of pain associated with PHN.
Wallace et al[32] (abstract) Gabapentin ER administered QD or in divided doses for a total daily dose of 1,800 mg vs placebo	DB, MC, PC, RCT Study Grade: Not applicable Patients with post-zoster pain for ≥3 months and a baseline average daily pain score ≥4 on a 10 point Numerical Rating Scale	N=407 10 weeks	Primary: Changes from baseline to week 10 in average daily pain score (baseline observation carried forward) Secondary: Changes from baseline to week 10 in average daily pain score (last observation carried forward), average daily sleep interference score	Primary: Between group differences in the least squares mean change in average daily pain score (baseline observation carried forward) did not reach significance (-1.85 [*P*=0.110 vs placebo], -1.72 [*P*=0.255 vs placebo], and -1.42). Secondary: The least squares mean average daily pain score (last observation carried forward) with gabapentin ER QD, but not with gabapentin ER administered in divided doses, significantly improved compared to placebo (-2.28; *P*=0.032 vs placebo). Daily sleep interference scores significantly improved with gabapentin ER QD compared to placebo (-2.49 vs -1.63; *P*<0.001). Safety: Most adverse events were mild to moderate in severity. Among patients receiving gabapentin ER, 12 and 11% withdrew due to adverse events, most commonly for dizziness (two and three percent), with gabapentin ER QD and in divided doses. Treatment-related adverse events occurred in 31% of all patients receiving gabapentin ER. The most common adverse events with gabapentin ER included dizziness (10 and 15%), headache (four and seven percent), somnolence (three and seven percent), and peripheral edema (five and five percent), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Limitations: Not applicable Conclusion: The primary efficacy endpoint of this trial for gabapentin ER was not met, most likely due to the unexpectedly large placebo response. Outcomes on secondary endpoints suggest the potential efficacy of gabapentin ER QD. Gabapentin ER was well tolerated in the trial.
Jensen et al[33] (abstract) Gabapentin ER 1,800 mg QD vs gabapentin ER 600 mg BID vs placebo	RCT Study Grade: Not applicable Patients with moderate to severe PHN	N=158 Duration not specified	Primary: Measure of different pain qualities Secondary: Not reported	Primary: Gabapentin ER, especially when administered BID, had the greatest effect on sharp, dull, sensitive, and itchy pain. Few between-condition effects were found for global ratings of intensity or unpleasantness, and for hot, cold, deep, or surface pain qualities. Secondary: Not reported Safety: Not reported Limitations: Not applicable Conclusion: Results provide further support for the importance of assessing specific pain qualities as outcomes in clinical trials. Results may also be used by clinicians for identifying patients for whom gabapentin ER may be particularly effective; patients with PHN presenting with pain described as sharp, dull, sensitive, or itchy
Backonja et al[34] Gabapentin enacarbil 1,200 mg BID	DB, PC, RCT Study Grade: Good	N=116 14 days	Primary: Change in mean weekly pain score from baseline to trial	Primary: After randomization, patients receiving gabapentin enacarbil had a significantly greater decrease in weekly pain scores from baseline to trial end compared to placebo (-2.10±1.63 vs -1.20±1.69; *P*=0.0321).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo All patients entered a 7 day baseline period, followed by an 11 day gabapentin titration and maintenance (600 mg TID) phase prior to randomization.	Patients 18 to 89 years of age with pain at the site of their herpes zoster rash for >3 months after healing and who had a self-reported average pain scale ≥4 and <10 (scale of 1 to 10) in the week prior to screening, and an average pain score ≥4 during a 7 day baseline period		end Secondary: Change in mean weekly pain score from baseline to week one, proportion of patients showing either a ≥30 or ≥50% reduction in mean pain score between baseline and the end of treatment, sleep interference, POMS, Patient Global Impression of Change, SF-MPQ	Patients randomized to gabapentin enacarbil or placebo had the same change from baseline during the initial OL treatment with gabapentin (-1.70±1.47 vs placebo, -1.70±1.56; *P*=0.9817). However, once patients were randomized to the trial drug, a significant improvement in the pain was seen with gabapentin enacarbil, with an additional decrease in weekly pain score from the gabapentin treatment period to trial end of -0.40±1.35, compared to worsening of pain scores with placebo (0.40±1.46; *P*=0.0012). Secondary: Patients receiving gabapentin enacarbil had a significantly greater decreased in weekly pain scores compared to baseline to week one compared to placebo (-1.70±1.40 vs -1.00±1.49; *P*=0.0299). A significantly greater proportion of patients receiving gabapentin enacarbil achieved a ≥30% improvement in weekly pain score from baseline to trial end compared to placebo (55.3 vs 27.8%; *P*=0.0073). The corresponding values for ≥50% were 27.7 and 18.5% (*P*=0.2582). Gabapentin enacarbil was associated with significantly greater improvements in weekly sleep interference scores from baseline to trial end compared to placebo (-2.20±1.76 vs -0.90±1.75; *P*=0.0010). Gabapentin enacarbil was associated with significantly greater improvements in four of seven POMS domains from baseline to trial end compared to placebo (total mood disturbance; *P*=0.0231, depression-dejection; *P*=0.0265, anger-hostility; *P*=0.0145, and vigor-activity; *P*=0.0257). Gabapentin enacarbil was associated with significantly greater improvements in components of the SF-MPQ from baseline to trial end compared to placebo (total score; *P*=0.0209, sensory score; *P*=0.0073, 0 to 100 VAS pain scale; *P*=0.0121, and present pain intensity score; *P*=0.0257).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Safety: A total of 49.5% of patients reported at least one treatment-emergent adverse event. The most commonly reported events with gabapentin enacarbil were dizziness, nausea, and headache and most were reported as generally mild or moderate in severity. Severe adverse events occurred in five patients; one and four receiving gabapentin enacarbil and placebo. No patient receiving gabapentin enacarbil withdrew treatment due to an adverse event. Limitations: Use of sequential gabapentin and gabapentin enacarbil treatments; clinical outcome comparisons between these two drugs must be interpreted cautiously. Conclusion: Gabapentin enacarbil was effective in providing PHN pain relief, improving gabapentin exposure compared to gabapentin capsules and was generally safe and well tolerated in patients with PHN.
Rosenstock et al[35] Pregabalin 100 mg TID vs placebo TID	DB, MC, PC, PG, RCT Patients with 1- to 5-year history of diabetic peripheral neuropathy and average daily pain score ≥4 on an 11-point numeric pain-rating scale	N=146 8 weeks	Primary: Pain score Secondary: SF-MPQ scores, sleep interference scores, Patient Global Impression of Change and Clinician Global Impression of Change scores, SF-36 Health Survey scores, POMS scores,	Primary: Mean pain score was significantly improved with pregabalin compared to placebo (3.99 vs 5.46; *P*=0.0001). Secondary: Compared to placebo, pregabalin treatment resulted in significant improvements in mean sleep interference score, SF-MPQ total score, VAS score, present pain intensity score, Patient Global Impression of Change, Clinician Global Impression of Change, bodily pain scores of the SF-36 health survey, and tension/anxiety and total mood disturbance of the POMS evaluation (*P*≤0.05 for all). No significant differences were observed between treatment groups in mental health and vitality scores of the SF-36 health survey and anger/hostility, vigor/activity, and fatigue/inertia scores of the POMS evaluation (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adverse events	The most commonly reported adverse events were dizziness (35.5 vs 11.4%), somnolence (19.7 vs 2.9%), infection (14.5 vs 5.7%), and peripheral edema (10.5 vs 1.4%).
Sabatowski et al[36] Pregabalin 150 or 300 mg/day vs placebo	DB, MC, PC, RCT Patients with PHN who did not respond to treatment with gabapentin ≥1,200 mg/day	N=238 8 weeks	Primary: Pain score Secondary: Sleep interference, HRQoL as assessed by SF-36 Health Survey, adverse events	Primary: Pregabalin 150 (*P*=0.0002) and 300 mg/day (*P*=0.0001) significantly improved mean pain scores compared to placebo. Percentage of patients who had ≥50% decrease in mean pain scores was significantly higher in the pregabalin 150 and 300 mg/day groups compared to the placebo group (26 vs 28 vs 10%, respectively; *P*<0.05 for all). Secondary: Pregabalin, at both doses, also significantly improved mean sleep interference scores, Patient Global Impression of Change scores, and HRQoL compared to placebo (*P*<0.05 for all). Adverse events that occurred in ≥10% of pregabalin-treated patients include dizziness, somnolence, peripheral edema, headache, and dry mouth. The adverse events appeared to be dose-related.
Guan et al[37] Pregabalin 150 to 600 mg/day vs placebo	DB, MC, PG, RCT Study Grade: Good Chinese patients 18 to 75 years of age with a primary diagnosis of painful diabetic peripheral neuropathy or PHN; patients	N=347 8 weeks	Primary: Mean pain score (daily pain rating scale) Secondary: Daily Sleep Interference Scale, SF-MPQ scale, Patient Global Impression of Change or Clinician Global Impression of	Primary: Treatment with pregabalin resulted in significant improvement from 6.30±1.58 to 3.70±0.14 compared to treatment with placebo (6.40±1.53 to 4.30±0.19), with a least squares mean score difference of -0.6 (*P*=0.005). The duration-adjusted average change score was significantly better with pregabalin (*P*=0.001). A repeated measures analysis of daily pain rating scale scores during the eight weeks found significant efficacy for pregabalin beginning at two weeks (*P*<0.02) and continuing through week eight (with the exception of week four). A response rate, defined as the proportion of patients with ≥30% reduction in daily pain rating scale, was significantly larger with pregabalin compared to placebo (64.0 vs 52.0%; *P*=0.041). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	with diabetic peripheral neuropathy had type 1 or 2 diabetes with HbA_{1c} ≤11% and painful, distal, symmetrical, sensorimotor polyneuropathy between 1 to 5 years; patients with PHN had pain ≥3 months after recovery from herpes zoster skin rash, moderate to severe neuropathic pain over 4 consecutive days		Change	Treatment with pregabalin resulted in significant improvements in all secondary outcomes compared to treatment with placebo (Sleep interference score: least squares mean difference, -0.5; 95% CI, -0.93 to -0.07; *P*=0.023, SF-MPQ VAS score [0 to 100], -6.56; 95% CI, -11.65 to -1.47; *P*=0.012; SF-MPG present pain intensity score, -0.35; 95% CI, -0.58 to -0.12; *P*=0.003; Patient Global Impression of Change score (0 to 7), -0.33; 95% CI, -0.55 to -0.11; *P*=0.004; and Clinician Global Impression of Change score (0 to 7), -0.39; 95% CI, -0.63 to -0.16; *P*=0.001). Safety: A total of 103 patients reported at least one adverse events with pregabalin compared to 41 patients receiving placebo (*P*=0.105), with the most common event being dizziness, occurring with an incidence of 11.2% among pregabalin-treated patients. Other adverse events were lethargy, somnolence, peripheral edema, and increased weight, which were common with both treatments and there were no differences between them. Most adverse events were mild in severity. No deaths occurred during the trial. Five serious adverse events occurred; two of which (chest pain and ischemic stroke) resulted in discontinuations. Limitations: The trial did not distinguish between PHN and diabetic peripheral neuropathy; therefore, the actual effects of pregabalin on efficacy and tolerability for each of these pain sates are unknown. The inclusion/exclusion criteria of the trial limit the ability to extrapolate beyond the small, selected population. Conclusion: Results suggest that relative to placebo, pregabalin 150 to 600 mg/day was effective and well tolerated in Chinese patients diagnosed with moderate to severe diabetic peripheral neuropathy or PHN, indicated through improved pain scores and Patient Global Impression of Change scores.
Moon et al[38]	DB, MC, PC,	N=241	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pregabalin 150 to 600 mg/day vs placebo	RCT Study Grade: Good Outpatients ≥18 year of age with a diagnosis of peripheral neuropathic pain syndrome from diabetic peripheral neuropathy, PHN, or post-traumatic neuropathic pain (including postsurgical); patients diagnosed with diabetic peripheral neuropathy had painful distal, symmetrical, or sensorimotor polyneuropathy due to diabetes (type 1 or 2); HbA_{1c} ≤11%; and documented symptoms of diabetic peripheral	10 weeks	End point (week eight) mean daily pain rating scale score (average of the last seven available scores) Secondary: Weekly mean daily pain rating scale score, the Duration Adjusted Average Change of adjust mean daily pain rating scale, the proportion of responders whose daily pain rating scale scores at end point were reduced ≥30 or ≥50% compared to baseline scores, Daily Sleep Interference Scale, EQ-5D, Medical Outcome Study, HADS, Patient Global Impression of	Daily pain rating scale scores at end point was significantly lower with pregabalin compared to placebo (least squares mean difference, -0.50; 95% CI, -1.00 to 0.00; *P*=0.049). A numeric reduction in mean daily pain rating scale scores at end point was also reported for the evaluable pregabalin population compared to placebo; however, the comparison did not reach significant (least squares mean difference, -0.48; 95% CI, -1.00 to 0.05; *P* value not significant). Secondary: Using repeated-measures analysis of the weekly mean daily pain rating scale scores, the least squares mean daily pain rating scale scores for pregabalin were lower compared to placebo during weeks one to eight, with difference ranging from -0.45 to -0.29. Significance was reached only for comparisons at week four (-0.43; 95% CI, -0.85 to -0.01; *P*=0.044) and week eight (-0.45; 95% CI, -0.88 to -0.02; *P*=0.039). The difference in least squares mean daily pain rating scale scores over the eight week DB period with pregabalin compared to placebo was -0.38 (95% CI, -0.75 to -0.01; *P*=0.042). Mean change in Duration Adjusted Average Change scores from baseline to end point was -1.24±1.32 and -0.87±1.49 with pregabalin and placebo, a significant difference in favor of pregabalin (least squares mean difference, -0.37; 95% CI, -0.74 to -0.01; *P*=0.044). A ≥50% reduction in daily pain rating scale score from baseline was reported by more patient receiving pregabalin compared to patients receiving placebo (26.1 vs 14.3%; *P*=0.041). In total, 42.2 and 35.1% of patients receiving pregabalin and placebo reported ≥30% reduction in daily pain rating scale scores from baseline to end point, a difference that did not reach significance (*P* value not reported). Analyses resulting in a significant treatment difference between baseline and end point that favored pregabalin were the end point mean Medical Outcome Study sleep interference score (least squares mean difference, -0.65; *P*=0.018), Medical Outcome Study sleep

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	neuropathy for 1 to 5 years; patients with PHN had a diagnosis ≥3 months after healing from an acute herpes zoster skin rash; and patients with post-traumatic neuropathic pain had a diagnosis of chronic pain for ≥3 months		Change, Clinician Global Impression of Change	disturbance (-5.62; *P*=0.034), Medical Outcome Study sleep quantity (-0.44; *P*=0.018), and the HADS-A score (-0.85; *P*=0.038). Medical Outcome Study somnolence favored placebo (4.71; *P*=0.046). No significant differences were found between treatments for Medical Outcome Study snoring score (favored placebo), Medical Outcome Study awakening short of breath or with a headache, Medical Outcome Study optimal sleep, Medical Outcome Study sleep adequacy, Medical Outcome Study overall sleep problems index, EQ-5D utility score or VAS, or HADS-D. On the Patient Global Impression of Change scale at week eight, 74.7% of patients receiving pregabalin and 72.0% of patients receiving placebo reported their condition improved (*P* value not significant). On the Clinician Global Impression of Change scale at week eight, 73.1 and 66.2% considered themselves improved (*P*=0.046). Safety: The proportions of early discontinuations due to adverse events were 4.9% with pregabalin and 7.7% with placebo. Half of the patients receiving pregabalin (50.0%) and 35.9% of patients receiving placebo reported adverse events. Treatment-related adverse events were reported by 43.8 and 29.5% of patients receiving pregabalin and placebo. In patients receiving pregabalin, dizziness, somnolence, face edema, peripheral edema, and weight gain were the most frequently reported adverse events. Limitations: None Conclusion: Flexible-dose pregabalin (150 to 600 mg/day) was associated with significant, although modest, reduction in mean daily pain rating score; an improvement in anxiety and subjective sleep; and generally good tolerability compared to placebo in Korean patients with neuropathic pain due to diabetic peripheral neuropathy, PHN, or post-traumatic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				neuropathic pain.
Richter et al[39] (abstract) Pregabalin 150 or 600 mg/day vs placebo	DB, MC, PC, RCT Patients with painful diabetic peripheral neuropathy	N=246 6 weeks	Primary: Pain score Secondary: Sleep interference, pain intensity, sensory and affective pain scores, Clinician Global Impression of Change, Patient Global Impression of Change, adverse events	Primary: Pregabalin significantly reduced pain score from baseline compared to placebo (4.3 vs 5.6; *P*=0.0002) and increased the percentage of patients with ≥50% decrease from baseline pain (39 vs 15% for placebo; *P*=0.002). Secondary: Pregabalin significantly improved sleep interference score, pain intensity, sensory and affective pain scores, and Clinician Global Impression of Change and Patient Global Impression of Change scores compared to placebo. Dizziness was the most common adverse reaction.
Dworkin et al[40] Pregabalin 600 (if CrCl >60 mL/minute) or 300 mg/day (if CrCl 30 to 60 mL/minute) vs placebo	DB, MC, PC, PG, RCT Patients with PHN	N=173 8 weeks	Primary: Pain scores Secondary: Sleep interference, SF-MPQ, SF-36 Health Survey, POMS, Patient Global Impression of Change, Clinician Global Impression of Change, adverse events	Primary: Pregabalin-treated patients had greater decreases in pain compared to placebo-treated patients (pain score, 3.60 vs 5.29; *P*=0.0001). Greater percentage of patients in the pregabalin than placebo groups experienced ≥50% decrease in pain (50 vs 20%, respectively; *P*<0.05). Secondary: Sleep, SF-MPQ scores, bodily pain and general health perception of the SF-36 Health Survey, POMS depression/dejection scale, Patient Global Impression of Change, and Clinician Global Impression of Change were significantly improved with pregabalin when compared to placebo (*P*<0.05 for all). No significant differences were observed between treatment arms in physical functioning, physical role limitations, social functioning, mental health, emotional role limitations, and vitality of the SF-36 Health

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Survey or other POMS scales. Dizziness (28.1 vs 11.9%), somnolence (24.7 vs 7.1%), peripheral edema (19.1 vs 2.4%), amblyopia (11.2 vs 1.2%), and dry mouth (11.2 vs 2.4%) were the most frequently occurring adverse events compared to placebo.
Lesser et al[41] Pregabalin 75, 300, and 600 mg/day administered in divided doses (TID) vs placebo	DB, MC, PC, RCT Patients with 1- to 5-year history of diabetic peripheral neuropathy and average weekly pain score ≥4 on an 11-point numeric pain-rating scale	N=338 5 weeks	Primary: Pain score Secondary: Sleep interference score, global impression of change, SF-MPQ, SF-36 Health Survey, Patient Global Impression of Change, Clinician Global Impression of Change, adverse events	Primary: Compared to placebo, mean pain score was significantly improved with pregabalin 300 (*P*=0.0001) and 600 mg/day (*P*=0.001), but not with pregabalin 75 mg/day (*P*=0.6267). Secondary: Compared to placebo, percentages of reduction in pain, mean sleep interference scores, SF-MPQ total scores, Patient Global Impression of Change and Clinician Global Impression of Change scores, VAS scores, and present pain intensity scores were significantly improved with pregabalin 300 mg/day and 600 mg/day, but not with pregabalin 75 mg/day (*P*≤0.05 for all). Most common reported adverse events were dizziness (7.8 to 39.0 vs 5.2%), somnolence (3.9 to 26.8 vs 4.1%), and peripheral edema (3.9 to 13.4 vs 2.1%).
Freynhagen et al[42] Pregabalin flexible-dose regimen of 150, 300, 450, and 600 mg/day with weekly dose escalation based on responses and tolerability vs	DB, MC, PC, PG, RCT Patients with chronic PHN or painful diabetic peripheral neuropathy	N=338 12 weeks	Primary: Pain score Secondary: Pain-related sleep interference, Patient Global Impression of Change, adverse events	Primary: Compared to placebo, both regimens of pregabalin improved pain symptoms (*P*<0.002 for both). Secondary: Both regimens of pregabalin significantly improved sleep interference (*P*<0.001 for both) and Patient Global Impression of Change (*P*<0.01) compared to placebo. Treatment-related adverse events occurred in 66.3% of the patients. The most common treatment-related adverse events were dizziness

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
pregabalin fixed-dose regimen of 300 mg/day for 1 week, followed by 600 mg/day for 11 weeks vs placebo				(4.8 vs 1.5%), peripheral edema (1.5 vs 0%), weight gain (0.7 vs 0%), and somnolence (1.8 vs 0%). Rate of adverse events was higher in the fixed-dose group than the flexible-dose group (74.2 vs 68.8%; *P* value not reported) and more patients withdrew from treatment due to adverse events in the fixed-dose group (25 vs 17 vs 7.7% of placebo group; *P* values not reported).
Skvarc et al[43] Pregabalin 75 to 150 mg BID vs placebo	DB, PC, PRO, RCT Study Grade: Good Outpatients 30 to 80 years of age who, despite naproxen use, had herpes zoster pain assessed ≥4 on a 0 to 10 point scale during the period between day 7 and 14 of acute disease	N=29 3 weeks	Primary: Assessment of pain severity using the 11-point Likert scale Secondary: Patients' ratings of the severity of allodynia, hyperalgesia, and burning, prickling and tingling sensations, and their rating of quality of sleep and physical activity	Primary: The main pain score decreased from seven at the initial visit to two at the concluding visit with pregabalin; the decrease was similar (from seven to two) with placebo. Secondary: Allodynia scoring decreased from eight to 0.5 with pregabalin, and from five to zero with placebo. Pressure hyperalgesia scoring decreased from eight at the initial visit to zero at the concluding visit with pregabalin, and from six to zero with placebo. There were no significant differences between the two treatments with regard to allodynia or pressure hyperalgesia, nor with respect to other observations of pain quality: burning sensation, prickling sensation, electric shock sensation, heat hyperalgesia, and cold hyperalgesia. There were no significant differences between the two treatments with regard to sleep and physical activity assessments. Safety: The most common adverse events were dry mouth with an incidence of 65.5%; this was followed by tiredness (55.2%), dizziness (44.8%), somnolence (44.8%), vertigo (41.4%), constipation (20.7%), diplopia (17.2%), and flatulence (13.8%). Patients receiving pregabalin suffered more adverse events compared to patients receiving placebo (52 vs 36), but the only significant difference between the treatments was in relation to dizziness and somnolence.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Limitations: None Conclusion: Results did not prove any significant effect of pregabalin in pain relief in patients with acute zoster pain or in the onset of postherpetic neuralgia in comparison to placebo. The use of pregabalin was related to a significant increase in the appearance of adverse events.
Roth et al[44] Pregabalin vs placebo	Review (9 trials) Study Grade: Not applicable Patients with diabetic peripheral neuropathy or PHN	N=not reported Duration not specified	Primary: Pain, sleep Secondary: Not reported	Primary: In patients with painful diabetic peripheral neuropathy, five RCTs assessed efficacy of pregabalin administered TID or BID. Treatment with pregabalin 300 or 600 mg/day significantly decreased endpoint mean pain scores compared to placebo. Doses of 75 and 150 mg/day (and 300 mg/day BID) did not produce significant pain relief vs placebo. Patients with PHN experienced significant reductions in mean pain scores with both TID and BID regimens across all pregabalin dosages (150 to 600 mg/day). One trial included patients with either diabetic peripheral neuropathy or PHN, and both flexible- (150 to 600 mg/day) and fixed-dose (600 mg/day) pregabalin significantly improved the mean pain score compared to placebo. Pregabalin 300 and 600 mg/day significantly decreased endpoint mean sleep interferences scores compared to placebo in patients with painful diabetic peripheral neuropathy, while lower doses of pregabalin did not differ from placebo. Significant improvements in sleep interference scores were seen as early as week one1. In patients with PHN, compared to placebo, 150, 300, and 600 mg/day of pregabalin significantly improved endpoint mean sleep interference scores and these effects were seen as early as week one. Secondary: Not reported Safety: The occurrence of adverse events appeared to be dose-related, with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				more frequent adverse events at higher doses. In patients with painful diabetic peripheral neuropathy, pregabalin was generally well tolerated, with a low rate of discontinuation due to adverse events (five to eight percent). The most frequently reported adverse events were central nervous system-related and of mild to moderate severity. Dizziness, somnolence, and peripheral edema were the most common adverse events reported and were common causes of discontinuation. Limitations: Not applicable Conclusion: In addition to an analgesic benefit, pregabalin may decrease pain-related sleep interference in patients with painful diabetic peripheral neuropathy and PHN.
Sharma et al[45] Pregabalin 150, 300, or 600 mg/day vs placebo	RETRO (9 MC, PC, RCTs) Study Grade: Good Adult patients with PHN or diabetic peripheral neuropathy; patients with PHN were adults with neuropathic pain for ≥6 months after healing of the herpes zoster rash, average daily pain score	N=1,982 Duration not specified	Primary: Time to onset for individual treatment arms that statistically separated from placebo Secondary: Not reported	Primary: For diabetic peripheral neuropathy, five of the seven treatment arms successfully maintained efficacy at trial end point. In the PHN trials, six of seven treatment arms demonstrated efficacy at end point. Depending on the pregabalin treatment arm, the time to onset for significant pain relief vs placebo ranged from treatment day one to treatment day seven in diabetic peripheral neuropathy trials. The time to onset was treatment day one for four treatment arms and treatment day two for the remaining successful treatment arms in the PHN trials. Of the total 1,205 diabetic peripheral neuropathy or PHN patients treated with pregabalin, 760 (63%) experienced significant pain relief on day one or two. In the 11 treatment arms for which efficacy was maintained at trial end point, the daily dosage at time to onset was 300 mg for four of the five successful arms in diabetic peripheral neuropathy patients and 75 mg in the other successful arm. For two diabetic peripheral neuropathy trials in which the time to onset was on treatment days seven and four, the dose-escalation schedules were the most gradual, reaching 300 mg/day level on treatment day six or later. For the PHN treatment arms in which efficacy was seen on treatment days one or two, the dosage at time to onset was 75 mg in five arms and 150

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	≥4; patients with diabetic peripheral neuropathy were adults with type 1 or 2 diabetes, HbA_{1c} ≤11%, painful distal symmetric sensorimotor poly-neuoropathy, average daily pain score ≥4, and ≥40 mm score			mg in the remaining arm. In the individual effect analysis, only patients who were responders (those with a 30% or greater reduction from baseline in mean pain score at end point) were considered. A one point or greater improvement in mean pain score was seen significantly earlier for pregabalin responders compared to patients receiving placebo (*P*<0.0001). Across all diabetic peripheral neuropathy trials, at least 25% of patients achieved a one point or greater improvement in mean pain score by day one (pregabalin at 300 mg/day) or two (pregabalin at 600 mg/day) compared to day four for placebo (150 mg/day; *P*=0.0232, 300 an 600 mg/day; *P*<0.0001). Across all PHN trials, at least 25% of patients receiving pregabalin achieved a one point or greater improvement in mean pain score by treatment day two, whereas this criterion for placebo patients was not met until day 18 (*P*<0.001). Half of the pregabalin treated patients showed a one point or greater improvement with only three to five days of treatment depending on the dose and type of neuropathic pain experienced. Secondary: Not reported Safety: Not reported Limitations: The nine included trials were not identical and were not prospectively designed to evaluate time to onset. By definition, time to onset cannot be calculated in the treatment arms that did not maintain efficacy at trial end point. Conclusion: For patients who will respond to pregabalin, statistically significant and sustained reduction of pain associated with diabetic peripheral neuropathy and PHN occurs early, usually by the end of two days of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				pregabalin treatment.
Semel et al[46] Pregabalin 150, 300, or 600 mg/day vs placebo	Pooled analysis of 11 PC, RCTs Study Grade: Not applicable Adult patients with diabetic peripheral neuropathy or PHN; patients with diabetic peripheral neuropathy had a diagnosis of type 1 or 2 diabetes and a diagnosis of painful diabetic peripheral neuropathy for ≥3 months to ≥1 years; patients with PHN had pain present for ≥3 or >6 months after healing of herpes zoster rash	N=2,516 Duration not specified	Primary: Endpoint average pain score on daily pain rating scale, daily pain rating scale score responders (≥30 and ≥50% reduction), daily pain rating scale score ≤3 Secondary: Not reported	Primary: Comparable dose-related improvements in endpoint mean pain score were observed for pregabalin across age groups. Similar results were observed for improvements in endpoint mean sleep interference scores. Placebo-corrected least squares mean differences in pain with pregabalin between age groups were -0.155 (95% CI, -0.412 to 0.109; *P*=0.2497) for patients 18 to 64 years of age vs patients ≥75 years of age; -0.157 (95% CI, -0.419 to 0.105; *P*=0.2402) for patients 65 to 74 years of age vs patients ≥75 years of age; and 0.002 (95% CI, -0.215 to 0.218; *P*=0.9882) for patients 18 to 64 years of age vs patients 65 to 74 years. Overall, there were significant differences among age groups in placebo patients with respect to pain relief (*P*=0.005), indicating a trend for decreasing placebo response with older age. Patients treated with placebo 18 to 64 years of age showed the largest improvement in average pain score (-1.47) compared to patients receiving placebo 65 to 74 years of age (-1.05; *P*=0.0112) or patients receiving placebo ≥75 years of age (-0.86; *P*=0.0031). No significant differences in placebo pain response were observed between those 65 to 74 years of age and those ≥75 years (*P*=0.3318). Significant dose-dependent reductions in endpoint mean pain score on daily pain rating scale scores were observed for pregabalin vs placebo for pooled age groups (*P*<0.0001). For patients ≥75 years of age, significant improvements in endpoint mean pain score were observed for pregabalin vs placebo at al dosages (pregabalin 150 mg/day-placebo difference, -0.90 [*P*=0.0005]; 300 mg/day-placebo difference, -1.37 [*P*<0.0001]; and 600 mg/day-placebo difference, -1.81 [*P*<0.0001]). Significant differences in placebo-corrected endpoint mean pain were also observed for all pregabalin dosages in patients 65 to 74 years (-0.77 [*P*=0.0009], -1.28 [*P*<0.0001], and -1.71 [*P*<0.0001]). In patients 18 to 65 years, pregabalin provided significant improvements with 300 (-0.67; *P*=0.0003) and 600 mg/day (-1.08;

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				P<0.0001), but not with 150 mg/day. Generally, higher response rates were observed for ≥30% pain relief, ≥50% pain relief, and pain score at endpoint ≤3 with increasing pregabalin dose in all age groups. Moderately important improvements in pain (≥30% reduction) were observed in one-third to more than one-half of patients and substantial improvements in pain (≥50% reduction) in one-fifth to nearly one-half of patients who received 150 to 600 mg/day pregabalin across age groups regardless of the method of imputation. One-quarter to nearly one-half of patients had pain scores ≤3 at endpoint reflecting mild pain following treatment with 150 to 600 mg/day pregabalin. Secondary: Not reported Safety: The most common adverse events were dizziness, somnolence, peripheral edema, asthenia, dry mouth, weight gain, and infections. The RRs for these adverse events increased with pregabalin dose, but did not appear related to older age (≥65 years of age) or type of neuropathic pain. Limitations: Not applicable Conclusion: Pregabalin significantly reduced pain in older patients (≥65 years of age) with neuropathic pain and improvements in pain were comparable to those observed in younger patients.
Wernicke et al[16] Duloxetine 60 mg BID vs	ES, OL, RCT Study Grade: Not applicable	N=293 52 weeks	Primary: Not reported Secondary: Health outcomes	Primary: Not reported Secondary: There were significant treatment-group differences observed in favor of

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routine care (gabapentin, amitriptyline, and venlafaxine)	Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes			duloxetine in the SF-36 physical component summary score, and subscale scores of physical functioning, bodily pain, mental health, and vitality. A significant treatment-by-investigator interaction was seen for general health perceptions (*P*=0.073), mental health (*P*=0.092), and social functions (*P*=0.003) subscales. There were no significant treatment-group differences observed on the EQ-5D questionnaire. Safety: During the trial, four deaths occurred. Deaths were considered to be unrelated to the study drug or protocol procedures. During the trial, 22 (11.2%) duloxetine vs 16 (16.7%) routine care-treated patients experienced at least one serious adverse event. The most frequently reported serious adverse events for both treatments together were cerebrovascular accident and diabetes, and these events were not considered to be drug-related. Fourteen (4.8%) patients discontinued due to any adverse event; which included 11 and three duloxetine- and routine care-treated patients (*P*=0.560). A total of 157 (53.6%) patients reported at least one treatment-emergent adverse event, and there were no treatment-group differences in the overall incidence of these events. There was a significant increase in mean uric acid levels in routine care-treated patients compared to duloxetine-treated patients with regard to chemistry/urinalysis. Both treatments experienced a slight increase in HbA_{1c}, with duloxetine-treated patients experiencing a larger increase in the mean change from baseline to endpoint (*P*<0.001). No significant treatment-group differences were observed in low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglyceride levels. There were no significant treatment-group differences observed in the mean change in the Michigan Neuropathy Screening Instrument score from baseline to endpoint.

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				There were no significant treatment-group differences observed in either subset of patients in the ulnar F-wave, ulnar distal sensory latency, and peroneal compound muscle action potential from baseline to endpoint for all patients. There was a significant increase observed in the peroneal F-wave measure for routine care-treated patients (*P*=0.05). There were no significant treatment-group differences observed for any of the ophthalmologic exam measures. There was a significant treatment-group difference observed in the mean change in microalbumin/creatinine ratio from baseline to endpoint (*P*=0.031), with duloxetine-treated patients experiencing a bigger mean decrease compared to routine care-treated patients. There was no significant treatment-group difference observed in the mean change from baseline to endpoint vital signs and weight. One duloxetine-treated patient and one routine care-treated patient met the definition for sustained elevation in systolic blood pressure, and there were no significant differences between treatments. There were no ECG parameters that were significantly different between treatments. Significantly more routine-care patients had potentially clinically significant Fridericia-corrected QT interval increases (*P*=0.034). Limitations: Not applicable Conclusion: Results provide support for the use of duloxetine in the long-term management of diabetic peripheral neuropathic pain.
Raskin et al[15]	ES, OL, RCT	N=237	Primary: Not reported	Primary: Not reported

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Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	Study Grade: Not applicable Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	52 weeks	Secondary: SF-36, EQ-5D	Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire. Safety: A higher proportion of routine care-treated patients experienced one or more serious adverse events. No significant treatment-group difference was observed in the overall incidence of treatment-emergent adverse events. The treatment-emergent adverse events reported by at least 10% of patients receiving duloxetine 60 mg BID were nausea, and by the patients receiving routine care were peripheral edema, pain in the extremity, somnolence, and dizziness. Duloxetine did not appear to adversely affect glycemic control, lipid profiles, nerve function, or the course of diabetic peripheral neuropathic pain. Limitations: Not applicable Conclusion: Results demonstrate that duloxetine was safe and well tolerated compared to routine care in the long-term management of patients with diabetic peripheral neuropathic pain.
Tanenberg et al[17] Duloxetine vs pregabalin vs duloxetine plus pregabalin	MC, NI, OL, RCT Study Grade: Good Adult patients with type 1 or 2 with HbA_{1c} ≤12%, and diabetic peripheral neuropathic pain	N=407 12 weeks	Primary: Reduction from baseline in the weekly mean of the daily 24-hour pain diary ratings at week 12 Secondary: Worst pain and night pain ratings, Clinician	Primary: The estimated mean change in the daily pain severity score at 12 weeks was -2.6 for duloxetine and -2.1 for pregabalin, representing an observed 0.49 advantage of duloxetine; therefore, NI was established. Significant superiority vs pregabalin in the mean daily pain diary ratings was observed at weeks, two, three, and five through 11 with duloxetine and with duloxetine plus gabapentin at weeks two and eight, but between-treatment differences at the 12 week end point met NI criteria, not statistical superiority. The NI comparison between duloxetine and combination therapy on the

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	who had been treated with gabapentin (900 mg/day) and had an inadequate response		Global Impression of Severity, Brief Pain Inventory severity and interference, Beck Depression Inventory II, Patient Global Impression of Improvement, Sheehan Disability Scale, response rate	differences between end point mean changes in daily pain diary ratings in the ITT patient population was also met. Secondary: Reduction from baseline in Brief Pain Inventory average pain and Brief Pain Inventory worst pain severity ratings was significantly greater with duloxetine vs pregabalin, but differences between treatments were not significant for the other Brief Pain Inventory pain measures, Clinical Global Impression of Severity, depressive symptoms, or the Sheehan Disability Scale global measure. Also, no significant between-treatment differences were found among the various response outcomes. Safety: Significantly more discontinuations occurred as a result of adverse events with duloxetine (19.6%; *P*=0.04) compared to pregabalin (10.4%), but no vs combination therapy (13.3%; *P*=0.19). Peripheral edema associated with pregabalin (3.7%) was the only adverse event reported as a reason for discontinuation with significantly greater frequency compared to other treatments (duloxetine, 0%; *P*=0.3; combination therapy, 0%; *P*=0.03). Rates of discontinuation for other reasons did not differ among the treatments. The treatment-related adverse events of nausea, insomnia, hyperhidrosis, and decreased appetite occurred significantly more frequently with duloxetine compared to pregabalin. The frequency of insomnia was also significantly greater with duloxetine compared to combination therapy. The occurrence of peripheral edema was significantly greater with pregabalin compared to the other two treatments. Combination treatment was associated with significantly greater occurrences of nausea, hyperhidrosis, decreased appetite, and vomiting compared to pregabalin monotherapy. Limitations: OL conduct of the current trial may have influenced the evaluation of efficacy and adverse events by both patients and investigators. The relatively small number of patients with comorbid MDD or generalized

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				anxiety disorder (3.7%) included does not adequately represent the population of patients with diabetes because depression is twice as prevalent in those with vs without diabetes. The lack of a gabapentin monotherapy control group in the trial limits the conclusions drawn from any difference observed between duloxetine and combination therapy and must be viewed with caution. The minimum gabapentin dose allowed for inclusion into the trial was less than the recommended efficacious dose (1,800 mg/day). Conclusion: Duloxetine was NI to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin.
Wernicke J et al[47] Duloxetine vs placebo	MA (42 RCTs) Patients diagnosed with either an MDD, diabetic peripheral neuropathy, fibromyalgia, generalized anxiety disorder, or lower urinary tract infection	N=8,504 4 to 12 weeks	Primary: Vital signs, ECG findings, cardio-vascular side effects of the study drug Secondary: Not reported	Primary: Patients receiving duloxetine were noted to have statistically significant changes from baseline in ECG findings (PR, RR, QRS, QT intervals) compared to placebo (*P*<0.001). However, the differences in ECG findings of patients taking duloxetine were not judged to be of clinical significance. Demographic subgroup analysis suggests that there is no difference in risk of ECG abnormality or vital sign changes between patients ≥65 years of age and a younger population (*P* value not reported). Although patients receiving duloxetine experienced statistically significant pulse and blood pressure elevations compared to placebo (*P*<0.001), those changes were transient returning to baseline values with sustained therapy. There was no statistically significant difference between placebo and duloxetine groups in sustained blood pressure (*P*=0.631), SBP (*P*=0.740), or DBP (*P*=1.00) measured during three consecutive visits. Patients randomized to duloxetine therapy experienced higher incidences of palpitations (*P*=0.004), tachycardia (*P*=0.007), orthostatic

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				hypotension (*P*=0.004), increased blood pressure (*P*<0.001), blood total cholesterol (*P*=0.031), and peripheral coldness (*P*=0.044) compared to patients randomized to placebo. Secondary: Not reported
Lunn et al[48] Duloxetine vs placebo or control Only outcomes for painful peripheral neuropathy are reported.	SR (6 RCTs) Study Grade: Good Patients with painful peripheral neuropathy or chronic pain conditions	N=2,200 ≥8 weeks	Primary: Short term (≤12 weeks) improvement in pain Secondary: Long term (>12 weeks) improvement in pain, improvement in short and long term pain ≥30%, improvement in any validated quality of life score ≥30%	Primary: Three trials in painful diabetic neuropathy reported data on the primary outcome measure of 50% improvement of pain compared to baseline at <12 weeks. Patients were treated with duloxetine 20, 60, or 120 mg/day. Combining data from all doses from the three trials together, the RR of 50% improvement with any dose was 1.63 (95% CI, 1.35 to 1.97) greater than placebo. The RR of improvement was significantly greater compared to placebo for the 60 and 120 mg/day doses, but not 20 mg/day, for which it was 1.43 (95% CI, 0.98 to 2.09). The RR of improvement with 120 mg/day (1.66; 95% CI, 1.35 to 2.04) was not significantly greater compared to 60 mg/day (1.65; 95% CI, 1.34 to 2.03). The mean improvement in pain at <12 weeks on an 11-point Likert scale was significantly greater compared to placebo with 60 (-1.04; 95% CI, -1.37 to -0.71) and 120 mg/day (-1.16; 95% CI, -1.49 to -0.83) of duloxetine. Secondary: None of the included trials of painful diabetic neuropathy included outcomes >12 weeks. Two trials included data on >30% improvement of pain at ≤12 weeks. The results were similar to those for ≥50% improvement. Relative rates of improvement were significantly greater compared to placebo with duloxetine for the 60 mg/day (1.53; 95% CI, 1.27 to 1.83), 120 mg/day (1.55; 95% CI, 1.30 to 1.86), and for both doses combined (1.54; 95% CI, 1.30 to 1.82). Trials that included quality of life information used the SF-36. In painful diabetic neuropathy, the effect of duloxetine 20 mg was not significant

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				on any of the selected SF-36 subscores at up to 12 weeks (relevant physical, mental, and bodily pain subsections). The WMD of improvement on the physical summary component was significantly greater with 60 mg/day (2.51; 95% CI, 1.00 to 4.01) and 120 mg/day (2.80; 95% CI, 1.04 to 4.55). The weighted mean difference on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The weighted mean difference on the bodily pain subscale showed significantly more improvement compared to placebo with 60 mg/day (5.58; 95% CI, 1.74 to 9.42) and with 120 mg/day (8.19; 95% CI, 4.33 to 12.05). Three trials reported the Patient Global Impression of Change and pain at rest, and two reported the bodily pain index. The weighted mean difference for each outcome was significant and similar in magnitude for 60 and 120 mg/day. However, a clinically meaningful differences in the Patient Global Impression of Change is suggested as one point and hence the change associated with 60 mg/day (-0.59; 95% CI, -0.78 to -0.41) may not be clinically significant. The RR for the bodily pain index is significantly reduced by -0.97 (95% CI, -1.38 to -0.57) but again this borders on a change considered clinically significant. Safety: Not reported Limitations: All trials, except one, had dropout rates >20%. Conclusion: There is moderately strong evidence that duloxetine 60 and 120 mg/day are efficacious for treating pain in diabetic peripheral neuropathy and fibromyalgia but 20 mg/day is not. Minor adverse events are common at therapeutic doses but serious adverse events are rare.
Wiffen et al[49] Gabapentin	MA (15 RCTs) Patients with	N=1,468 Duration not	Primary: Evaluate analgesic	Primary: The study in acute post-operative pain (n=70) showed no benefit for gabapentin compared to placebo for pain at rest.

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vs placebo	acute and chronic pain; trials included patients with acute post-operative pain (1 trial), diabetic peripheral neuropathy (7 trials), PHN (2 trials), cancer-related neuropathic pain (1 trial), phantom limb pain (1 trial), Guillain Barre syndrome (1 trial), spinal cord injury pain (1 trial), and various neuropathic pains (1 trial)	specified	effectiveness and adverse effects of gabapentin for acute and chronic pain Secondary: Not reported	In chronic pain, the NNT with gabapentin for improvement in all trials with evaluable data was 4.3 (95% CI, 3.5 to 5.7), with 42% of participants improving on gabapentin compared to 19% of participants on placebo. The NNH for adverse events leading to withdrawal from a trial was not significant with 14% of patients withdrawing from active arms compared to 10% of patients in the placebo arms. The NNH for minor harm was 3.7 (95% CI, 2.4 to 5.4) (*P* values not reported). The NNT with gabapentin for effective pain relief in diabetic peripheral neuropathy was 2.9 (95% CI, 2.2 to 4.3) and for PHN 3.9 (95% CI, 3.0 to 5.7) (*P* values not reported). Secondary: Not reported
Moore et al[50] Gabapentin 1,200 mg/day vs placebo, no treatment, or any other active comparator Only results for PHN are reported (5 trials), when	SR (29 RCTs) Study Grade: Good Adult patients with 1 of 12 chronic pain conditions; 78% of patients had PHN, painful diabetic	N=3,571 ≥2 weeks	Primary: Patient reported pain intensity reduction of ≥30 and ≥50%, Patient Global Impression of Change Secondary: Any pain-related outcome	Primary: Pooled data from three trials (n=892) demonstrate that 33 and 20% of patients receiving gabapentin and placebo achieved ≥50% reduction in pain (risk ratio, 1.7; 95% CI, 1.3 to 2.2; NNT, 7.5; 95% CI, 5.2 to 14.0). In an AC comparing gabapentin to nortriptyline for nine weeks, 34 and 37% of patients achieved ≥50% reduction in pain. Pooled data from two trials (n=563) demonstrate that 15 and 6% of patients receiving gabapentin and placebo reported a Patient Global Impression of Change of very much improved (risk ratio, 2.7; 95% CI, 1.5 to 4.8; NNT, 11; 95% CI, 7.0 to 22.0).

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possible.	neuropathy, or mixed neuropathic pain		indicating some improvement, withdrawals due to lack of efficacy, withdrawals due to adverse events	Pooled data from four trials (n=1,121) demonstrate that 38 and 20% of patients receiving gabapentin and placebo reported a Patient Global Impression of Change of much or very much improved (risk ratio, 1.9; 95% CI, 1.5 to 2.3; NNT, 5.5; 95% CI, 4.3 to 7.7). Secondary: Data on any pain-related outcome indicating some improvement and withdrawals due to lack of efficacy were not reported. Seventeen trials of 3,022 patients reported an adverse event withdrawal, which occurred in 12% of patients receiving gabapentin ≥1,200 mg/day, and eight percent of patients receiving placebo (risk ratio, 1.4; 95% CI, 1.1 to 1.7; NNH, 32; 95% CI, 19 to 100). Seventeen trials of 3,063 patients reported on withdrawals of any cause, which occurred in 20% of patients receiving gabapentin ≥1,200 mg/day compared to 19% of patients receiving placebo (risk ratio, 1.1; 95% CI, 0.9 to 1.2). Safety: Eleven trials of 2,356 patients reported on patients experiencing at least one adverse event, which occurred in 66 and 51% of patients receiving gabapentin ≥1,200 mg/day and placebo (risk ratio, 1.3; 95% CI, 1.2 to 1.4; NNH, 6.6; 95% CI, 5.3 to 9.0). Fourteen trials of 2,702 patients reported on patients experiencing serious adverse events, which occurred in 4.0 and 3.2% of patients receiving gabapentin ≥1,200 mg/day and placebo (risk ratio, 1.3; 95% CI, 0.9 to 2.0). Somnolence, drowsiness, or sedation was reported as an adverse event in 16 trials of 2,800 patients, and it occurred in 16 and 5% of patients receiving gabapentin ≥1,200 mg/day and placebo (risk ratio, 3.2; 95% CI, 2.5 to 4.2; NNH, 9.2; 95% CI, 7.7 to 12.0). Peripheral oedema was reported as an adverse event in nine trials of 2,042 patients, and it occurred in 8.2 and 2.9% of patients (risk ratio, 3.4; 95% CI, 2.1 to 5.3; NNH, 19; 95% CI, 14 to 29). Ataxia or gait disturbances were reported as an adverse event in five trials of 544 patients, and

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				occurred in 8.8 and 1.1% of patients (risk ratio, 4.5; 95% CI, 1.9 to 11.0; NNH, 13; 95% CI, 9 to 24). Deaths were rare in included trials. Four deaths occurred in PHN trials; two and one with placebo and gabapentin. Limitations: Included trials covered a large number of different painful conditions, and for some it is unclear whether antiepileptic drugs are effective in the condition. Main quality issues involve reporting of outcomes of interest, as well as a better reporting of adverse. There have been major changes in clinical trial reporting since the date of the earliest included trial (1998). Sources of bias could have affected the review. Conclusion: Gabapentin provides pain relief of a high level in about a third of patients who take it for painful neuropathic pain. Adverse events are frequent, but mostly tolerable. More conservative estimates of efficacy resulted from using better definitions of efficacy outcome at higher, clinically important, levels, combined with a considerable increase in the number of trials and participants available for analysis.
Chou et al[51] Gabapentin vs placebo (6 trials) and gabapentin vs tricyclic antidepressants (3	MA (18 RCTs) Patients with diabetic peripheral neuropathy or PHN	N=not reported (sample sizes n=12 to 334) 2 to 12 weeks	Primary: Proportion of patients reporting significant pain relief (≥50% improvement in pain score compared to baseline, or proportion reporting at least moderate or good improvement in	Primary: In three head-to-head trials (n=120), there was no difference between gabapentin and tricyclic antidepressants (amitriptyline or nortriptyline) for achieving pain relief for diabetic peripheral neuropathy and PHN (RR, 0.99; 95% CI, 0.76 to 1.29; *P* value not reported). There was no difference between gabapentin vs tricyclic antidepressants in rates of withdrawal due to adverse events (RR, 0.27; 95% CI, 0.03 to 2.34; *P* value not reported), but only three cases were reported in two trials. None of the trials reported serious adverse events. There was no significant difference between gabapentin and tricyclic antidepressants in risk of dizziness, dry mouth, or somnolence. In indirect analyses, gabapentin was worse than tricyclic antidepressants for achieving pain relief (RR, 0.41; 95% CI, 0.23 to 0.74; *P* value not reported).

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trials) and tricyclic antidepressants vs placebo (9 trials)			pain or global efficacy on a categorical scale), safety Secondary: Not reported	The discrepancy between direct and indirect analyses was statistically significant (*P*=0.008). Placebo-controlled tricyclic antidepressant trials were conducted earlier than the gabapentin trials, reported lower placebo response rates, had more methodological shortcomings, and were associated with funnel plot asymmetry. Secondary: Not reported
Moore et al[52] Pregabalin vs placebo	MA of (25 RCTs) Patients with acute and chronic pain; trials included patients with perioperative pain (6 trials), diabetic peripheral neuropathy (7 trials), PHN (5 trials), central neuropathic pain (2 trials), and fibromyalgia (5 trials)	N=7,652 24 hours acute pain, 4 to 26 weeks chronic pain	Primary: Analgesic effectiveness and adverse effects of pregabalin for acute and chronic pain Secondary: Not reported	Primary: There was no clear evidence of beneficial effects of pregabalin in established acute postoperative pain. No studies evaluated pregabalin in chronic nociceptive pain, like arthritis. Pregabalin at daily doses of 300, 450, and 600 mg was effective in patients with diabetic peripheral neuropathy, PHN, central neuropathic pain, and fibromyalgia. Pregabalin 150 mg daily was generally ineffective (*P* values not reported). Efficacy was demonstrated for dichotomous outcomes equating to moderate or substantial pain relief, alongside lower rates for lack of efficacy discontinuations with increasing dose. The best (lowest) NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for pregabalin 600 mg daily compared to placebo were 5.0 (95% CI, 4.0 to 6.6) for diabetic peripheral neuropathy, 3.9 (95% CI, 3.1 to 5.1) for PHN, 5.6 (95% CI, 3.5 to 14) for central neuropathic pain, and 11.0 (95% CI, 7.1 to 21.0) for fibromyalgia (*P* values not reported). Higher rates of substantial benefit were found in diabetic peripheral neuropathy and PHN than in central neuropathic pain and fibromyalgia. For moderate and substantial benefit on any outcome, NNTs for the former were generally six and below for 300 and 600 mg daily; for

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				fibromyalgia NNTs were much higher, and generally seven and above (*P* values not reported). With pregabalin 600 mg/day, somnolence typically occurred in 15 to 25% of patients, and dizziness occurred in 27 to 46% of patients. Treatment was discontinued due to adverse events in 18 to 28% of patients. The proportion of patients reporting at least one adverse event was not affected by dose, nor was the number with a serious adverse event, which was not more than with placebo (*P* values not reported.) Secondary: Not reported
Edelsberg et al[53] Pregabalin (3 trials), capsaicin (2 trials), gabapentin (2 trials), amitriptyline (1 trial), nortriptyline (1 trial), morphine (1 trial), tramadol (1 trial), and divalproex sodium (1 trial) vs placebo	MA and SR (12 RCTs) Study Grade: Good Patients with PHN	N=not specified 6 to 13 weeks	Primary: Percentage reduction in pain intensity Secondary: RR of withdrawal due to lack of efficacy, RR of withdrawal due to adverse events	Primary: The difference in the percentage reduction in pain intensity varied from 13.8 (tramadol) to 42.4% (amitriptyline). All differences were significant. Secondary: The RR of withdrawal due to lack of efficacy varied from 0.26 (gabapentin) to 1.17 (amitriptyline), among drugs for which this outcome was reported. However, none of these RRs were significant. RR of withdrawal due to adverse events ranged from 1.6 (divalproex sodium) to 8.4 (capsaicin); those for capsaicin (8.4), pregabalin (3.1), and gabapentin (1.9) were significant. RR of withdrawals due to adverse events was not reported for nortriptyline, morphine, or tramadol. Safety: Agents and adverse events with RRs significantly different from those of placebo were gabapentin: dizziness (RR, 3.76; 95% CI, 2.27 to 6.22) and somnolence (RR, 4.06; 95%; 2.29 to 7.31); pregabalin: dizziness (RR, 2.49; 95% CI, 1.68 to 3.60), somnolence (RR, 3.18; 95% CI, 1.87 to 5.41), dry mouth (RR, 2.73; 95% CI, 1.12 to 6.63), and ataxia (RR, 11.70; 95% CI, 1.55 to 88.54); nortriptyline: dizziness (RR, 39.17; 95% CI, 2.49 to 616.66); and morphine: nausea (RR, 5.47; 95% CI, 2.03 to

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				14.76). RRs of individual adverse events were not reported for amitriptyline or divalproex sodium. Limitations: The assumption that all RCTs were sufficiently similar in design to permit meaningful comparison. In addition, the scarcity of published RCTs and the small number of patients within most trials. Combination therapy was not considered in this analysis. Conclusion: Available literature establishes the efficacy of eight agents in the treatment of PHN, but does not provide adequate guidance as to which agents are best to treat the condition, in part because of inadequate reporting of data on tolerability and safety.
Quilici et al[54] Duloxetine vs pregabalin and gabapentin Placebo was used a common comparator.	MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials) Study Grade: Good Patients with diabetic peripheral neuropathic pain	N=not specified ≥5 to 13 weeks	Primary: Reduction in 24-hour pain severity, response rate (≥50% pain reduction), overall health improvement (Patient Global Impression of Improvement and Patient Global Impression of Change) Secondary: Not reported	Primary: *Direct comparisons* All three agents were superior to placebo for all efficacy parameters. For 24-hour pain severity effect values were -1.13 (95% CI, -1.36 to -0.89), -0.90 (95% CI, -1.23 to -0.57), and -1.44 (95% CI, -2.21 to -0.66) with duloxetine, pregabalin, and gabapentin. Corresponding effect values for response rates were 0.86 (95% CI, 0.63 to 1.09; NNT, 5; 95% CI, 3 to 7) and 0.84 (95% CI, 0.52 to 1.16; NNT, 5; 95% CI, 4 to 8) with duloxetine and pregabalin, and for Patient Global Impression of Improvement/Patient Global Impression of Change were -0.76 (95% CI, -1.00 to -0.51) and -1.29 (95% CI, -1.72 to -0.86) with duloxetine and pregabalin. *Indirect comparisons* For the primary efficacy outcome of 24-hour reduction in pain severity, a difference of -0.248 (95% CI, -0.677 to 0.162) was observed in favor of duloxetine over pregabalin. Duloxetine was not inferior to pregabalin on this outcome. For response rates, the difference between duloxetine and pregabalin was close to zero and not significant. For Patient Global Impression of Improvement/Patient Global Impression of Change outcomes, pregabalin showed an improvement of 0.542 points over

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060). Secondary: Not reported Safety: Duloxetine produced a significantly lower incidence of dizziness compared to pregabalin. No differences between these two treatments were observed in the rates of premature discontinuation, diarrhea, headache, and somnolence. Limitations: Data on gabapentin was limited and did not provide information on treatment response. A small number of clinical trials met criterion for inclusion. And exclusion of amitriptyline from the MA warrants discussion as it has been used in painful diabetic neuropathy for approximately 30 years. The clinical evidence for use of amitriptyline stems from a series of small trials mainly conducted in the 1980s and 1990s, which were not designed to meet current regulatory requirements. Conclusion: From the few available trials suitable for indirect comparison, duloxetine shows comparable efficacy and tolerability to gabapentin and pregabalin in diabetic peripheral neuropathic pain. Duloxetine provides an important treatment option for this disabling condition.

Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, NI=noninferiority, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized-controlled trial, RETRO=retrospective, RR=relative risk, SR=systemic review, XO=cross-over
Other abbreviations: BID=twice-daily, CrCl=creatinine clearance, ECG=electrocardiogram, ER=extended-release, EQ-5D=Euro Quality of Life Assessment, HADS=Hospital Anxiety And Depression Scale, HbA_{1c}=glycosylated hemoglobin, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, MDD=major depressive disorder, PHN=postherpetic neuralgia, POMS=Profile of Mood States, QD=once-daily, SF-36=Short Form 36, SF-HPQ=Short Form-McGill Pain Questionnaire, TID=three times daily, VAS=visual analog scale

Special Populations

Table 5. Special Populations[1-8]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Duloxetine	No dose adjustment is recommended for elderly patients on the basis of age. Safety and efficacy in children have not been established.	Not recommended in patients with end-stage renal disease or severe renal impairment (CrCl <30 mL/min).	Not recommended in patients with any hepatic insufficiency.	C	Yes (0.14%)
Gabapentin	Dose adjustment may be required in the elderly depending on renal function. FDA-approved for use in children ≥3 years of age	Renal dose adjustment is required; for creatinine clearances of 30 to 59 mL/min, a dose of 200 to 700 mg and dosing frequency of twice-daily is recommended. For creatinine clearances of 15 to 29 mL/min, a dose of 200 to 700 mg and dosing frequency of once-daily is recommended. For creatinine clearances of <15 mL/min, a dose of 100 to 300 mg and dosing frequency of once-daily is recommended.	Not studied in hepatic dysfunction.	C	Yes (% not reported); use with caution.
Gabapentin extended-release	Dose adjustment may be required in the	Renal dose adjustment is required; for creatinine	Not studied in hepatic dysfunction.	C	Yes (% not reported); use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	elderly depending on renal function. Safety and efficacy in children have not been established.	clearances of 30 to 60 mL/min, a dose of 600 to 1800 mg and dosing frequency of once-daily is recommended. Gabapentin extended-release should not be administered to patients with a creatinine clearance of <30 mL/min or patients receiving hemodialysis.			
Gabapentin enacarbil	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment is required; for creatinine clearances of 30 to 59 mL/min, a dose of 300 mg and dosing frequency of twice-daily is recommended, increasing to 600 mg as needed. For creatinine clearances of 15 to 29 mL/min, a dose of 300 mg and dosing frequency of once-daily is recommended, increasing to twice-daily if needed. For creatinine	Not studied in hepatic dysfunction.	C	Unknown*

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		clearances of <15 mL/min, a dose of 300 mg and dosing frequency of every other day is recommended, increasing to once-daily if needed. For patients on hemodialysis with a creatinine clearance of <15 mL/min, a dose of 300 mg following dialysis may be administered and increased to 600 mg if needed.			
Lidocaine patch	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.	B	Unknown; use with caution[†]
Pregabalin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Renal dose adjustment is required; for creatinine clearances of 30 to 60 mL/min, a total daily dose of 75 to 300 mg and dosing	No dosage adjustment required.	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.	frequency of two or three times daily is recommended. For creatinine clearances of 15 to 30 mL/min, a total daily dose of 25 to 150 mg and dosing frequency of once- or twice-daily is recommended. For creatinine clearances of <15 mL/min, a dose of 25 to 75 mg and dosing frequency of once-daily is recommended.			

* It is not known whether gabapentin derived from gabapentin enacarbil is secreted in human milk; however, gabapentin is secreted into human milk following oral administration of gabapentin products.
† Lidocaine patch has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk: plasma ratio of lidocaine is 0.4. Caution should be used when administering lidocaine patch to nursing women.

Adverse Drug Events

Table 6. Adverse Drug Events[1-8]

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Cardiovascular						
Angina pectoris	-	✔	-	-	-	-
Atrial fibrillation	<1	✔	-	-	-	-
Blood pressure increase	-	-	✔	-	-	-
Bradycardia	-	✔	-	-	✔	-
Bundle branch block	<1	-	-	-	-	-
Cardiac arrest	-	-	-	-	✔	-
Cerebrovascular accident	-	✔	-	-	-	-
Chest pain	-	-	-	-	-	1 to 4
Congestive heart failure	<1	✔	-	-	-	-
Flushing	3	-	-	-	-	-
Heart block	-	✔	-	-	-	-
Heart failure	-	✔	-	-	-	✔
Hypertension	<1	✔	✔	-	-	-
Hypotension	-	✔	-	-	✔	✔
Myocardial infarct	<1	✔	-	-	-	-
Orthostatic hypotension	<1	-	-	-	-	-
Palpitation	<2	✔	-	-	-	-
Pericardial effusion	-	✔	-	-	-	-
Pericardial rub	-	✔	-	-	-	-
Pericarditis	-	✔	-	-	-	-
Peripheral vascular disorder	-	✔	-	-	-	-
Postural hypotension	-	-	-	-	-	✔
Premature atrial contraction	-	✔	-	-	-	-
Pulmonary embolus	-	✔	-	-	-	-
Retinal vascular disorder	-	-	-	-	-	✔
ST depressed	-	-	-	-	-	✔
Syncope	<1	✔	-	-	-	✔
Tachycardia	<1	✔	-	-	-	-
Thrombophlebitis	-	✔	-	-	-	✔
Vasodilation	-	1.1	-	-	-	-
Ventricular extrasystoles	-	✔	-	-	-	-

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Ventricular fibrillation	-	-	-	-	-	✔
Central Nervous System						
Abnormal coordination	-	1.1 to 1.5	-	-	-	1 to 6
Abnormal dreams	2	✔	-	-	-	✔
Agitation	<5	✔	-	-	-	✔
Amnesia	-	1.2 to 2.2	-	-	-	1 to 6
Anxiety	3	✔	-	-	-	2
Apathy	-	✔	-	-	-	✔
Aphasia	-	✔	-	-	-	✔
Apraxia	-	✔	-	-	-	-
Asthenia	-	5.7	-	-	-	2 to 7
Ataxia	<1	3.3 to 12.5	-	-	-	1 to 20
Blurred vision	4	-	-	-	-	1 to 12
Central nervous system neoplasm	-	✔	-	-	-	-
Cerebellar syndrome	-	✔	-	-	-	✔
Choreoathetosis	-	✔	-	-	-	-
Circumoral paresthesia	-	✔	-	-	-	✔
Cogwheel rigidity	-	-	-	-	-	✔
Coma	-	-	-	-	-	✔
Confusion	-	✔	✔	-	✔	1 to 7
Delirium	-	-	-	-	-	✔
Delusions	-	-	-	-	-	✔
Depersonalization	-	✔	-	-	-	✔
Depression	<1	1.8	-	<3	✔	2
Disorientation	<1	-	-	-	-	1 to 2
Disturbance in attention	-	-	-	-	-	4 to 6
Dizziness	1 to 14	2.5 to 28.0	10.9	13 to 22	✔	5 to 45
Double vision	-	1.2 to 5.9	-	-	✔	2 to 12
Dysarthria	<1	2.4	-	-	-	✔
Dysautonomia	-	-	-	-	-	✔
Dyskinesia	-	-	-	-	-	✔
Dystonia	-	✔	-	-	-	✔
Emotional liability	-	4.2	-	-	-	-
Encephalopathy	-	✔	-	-	-	✔
Euphoria	-	✔	-	-	✔	2 to 7

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Excitation	-	-	-	-	✔	-
Extrapyramidal symptoms	-	-	-	-	-	✔
Facial paralysis	-	✔	-	-	-	-
Fatigue	2 to 11	3.4 to 11.0	-	6 to 7	-	1 to 8
Gait disturbances	-	1.5	-	-	-	1 to 8
Guillain-Barre syndrome	-	-	-	-	-	✔
Hallucination	-	✔	-	-	-	✔
Headache	13 to 14	3.3	4.2	12 to 15	-	5 to 14
Hemiplegia	-	✔	-	-	-	-
Hostility	-	7.6	-	-	-	✔
Hypoalgesia	-	-	-	-	-	✔
Hyperalgesia	-	-	-	-	-	✔
Hyperesthesia	-	✔	-	-	-	✔
Hyperkinesia	-	✔	-	-	-	-
Hypertonia	-	-	-	-	-	✔
Hypoaesthesia	1	-	-	-	-	2 to 3
Hypokinesia	-	2.5	-	-	-	✔
Hypotonia	-	✔	-	-	-	✔
Hysteria	-	✔	-	-	-	-
Insomnia	8 to 11	✔	-	-	-	-
Intracranial hypertension	-	-	-	-	-	✔
Irritability	1	-	-	4	-	-
Lethargy	1	-	1.1	-	-	1 to 2
Light headedness	-	-	-	-	✔	-
Manic reaction	<1	✔	-	-	-	✔
Memory impairment	-	-	✔	-	-	1 to 4
Migraine	-	✔	-	-	-	-
Mood altered/swings	1	-	-	-	-	-
Movement disorder	-	✔	-	-	-	-
Myoclonus	-	✔	-	-	-	1 to 4
Nervousness	1	2.4	-	-	✔	1
Neuralgia	-	-	-	-	-	✔
Nightmares	1	-	-	-	-	-
Nystagmus	-	8.3	-	-	-	✔
Paranoid reaction	-	✔	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Paresthesia	-	✔	-	-	✔	✔
Peripheral neuritis	-	-	-	-	-	✔
Personality disorder	-	✔	-	-	-	✔
Psychosis	-	✔	-	-	-	-
Psychotic depression	-	-	-	-	-	✔
Reflexes decreased	-	✔	-	-	-	-
Reflexes increased	-	✔	-	-	-	-
Restlessness	1	-	-	-	-	-
Seizures	<1	-	-	-	✔	-
Sleep disorder	1	-	-	-	-	-
Somnolence	7 to 15	8.4 to 21.4	4.5	20 to 27	✔	3 to 28
Speech disorder	-	✔	-	-	-	1 to 7
Stupor	-	✔	-	-	-	✔
Suicide attempt/ideation	<1	-	-	-	-	-
Thinking abnormal	-	1.7 to 2.7	-	-	-	1 to 9
Torticollis	-	-	-	-	-	✔
Tremor	1 to 3	6.8	-	-	✔	1 to 11
Trismus	-	-	-	-	-	✔
Twitching	1	1.3	-	-	✔	1 to 5
Unconsciousness	-	-	-	-	✔	-
Vertigo	1	✔	1.4	1 to 3	-	1 to 4
Dermatologic						
Abnormal body odor	-	✔	-	-	-	-
Abscess	-	✔	-	-	-	✔
Acne	<1	✔	-	-	-	-
Alopecia	<1	✔	-	-	-	✔
Angioedema	-	-	-	-	✔	✔
Blistering	-	-	-	-	✔	-
Bruising	-	-	-	-	✔	-
Burning sensation	-	-	-	-	✔	-
Cold sensation	-	-	-	✔	-	-
Contact dermatitis	-	-	-	-	✔	-
Cyst	-	✔	-	-	-	-
Depigmentation	-	-	-	-	✔	-
Desquamation	-	✔	-	-	-	-

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Dry skin	-	✔	-	-	-	✔
Ecchymosis	<1	-	-	-	-	-
Eczema	<1	✔	-	-	-	✔
Erythema	<1	-	-	-	✔	-
Exfoliative dermatitis	-	-	-	-	✔	✔
Fungal dermatitis	-	✔	-	-	-	-
Furunculosis	-	✔	-	-	-	-
Herpes simplex	-	✔	-	-	-	-
Herpes zoster	-	✔	✔	-	-	-
Hirsutism	-	✔	-	-	-	✔
Hyperhidrosis	6	-	-	-	-	-
Lichenoid dermatitis	-	-	-	-	-	✔
Maculopapular rash	-	✔	-	-	-	-
Melanosis	-	✔	-	-	-	✔
Nail disorder	-	✔	-	-	-	✔
Night sweats	1	-	-	-	-	-
Petechial rash	-	-	-	-	-	✔
Pruritus	1	1.3	-	-	-	✔
Psoriasis	-	✔	-	-	-	-
Purpuric rash	-	-	-	-	-	✔
Pustular rash	-	-	-	-	-	✔
Rash	1	1.2	✔	-	-	-
Skin atrophy	-	-	-	-	-	✔
Skin carcinoma	-	✔	-	-	-	-
Skin discoloration	-	✔	-	-	✔	-
Skin irritation	-	-	-	-	✔	-
Skin papules	-	-	-	-	✔	-
Skin necrosis	-	✔	-	-	-	✔
Skin nodules	-	✔	-	-	-	✔
Skin ulcer	-	✔	-	-	-	✔
Skin vesicles	-	-	-	-	✔	-
Stevens-Johnson syndrome	1	-	-	-	-	✔
Subcutaneous nodule	-	-	-	-	-	✔
Sweating	6	✔	-	-	-	-
Toxic epidermal necrolysis	1	-	-	-	-	-

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Urticaria	1	✔	-	-	-	✔
Vesiculobullous rash	-	✔	-	-	-	✔
Warm sensation	-	-	-	-	✔	-
Endocrine system						
Cushingoid appearance	-	✔	-	-	-	-
Diabetes mellitus	-	✔	-	-	-	-
Goiter	-	✔	-	-	-	-
Hyperthyroidism	-	✔	-	-	-	-
Hypoestrogen	-	✔	-	-	-	-
Hypothyroidism	-	✔	-	-	-	-
Ovarian failure	-	✔	-	-	-	-
Gastrointestinal						
Abdominal distention	-	-	-	-	-	1 to 2
Abdominal pain	<5	2.7	-	-	-	✔
Abnormal stools	2 to 3	✔	-	-	-	-
Anorexia	-	✔	-	-	-	-
Aphthous stomatitis	<1	-	-	-	-	✔
Bloody stool	<1	-	-	-	-	-
Cholecystitis	-	✔	-	-	-	✔
Cholelithiasis	-	✔	-	-	-	✔
Cholestatic jaundice	<1	-	-	-	-	-
Colitis	<1	✔	-	-	-	✔
Constipation	5 to 11	1.5 to 3.9	1.4	-	-	2 to 7
Decreased appetite	7 to 9	-	-	-	-	-
Diarrhea	8 to 13	5.7	3.3	-	-	-
Diverticulitis	<1	-	-	-	-	-
Dyspepsia	2 to 4	2.2	1.4	-	-	-
Dysphagia	<1	✔	-	-	-	✔
Eructation	<1	✔	-	-	-	-
Esophageal stenosis	<1	-	-	-	-	-
Esophageal ulcer	-	-	-	-	-	✔
Esophagitis	-	✔	-	-	-	✔
Fecal incontinence	-	✔	-	-	-	-
Flatulence	-	2.1	-	2 to 3	-	1 to 3
Gastritis	1	✔	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Gastric irritation	<1	-	-	-	-	-
Gastroduodenal ulcer	<1	✔	-	-	-	-
Gastroenteritis	-	✔	-	-	-	✔
Gastrointestinal hemorrhage	-	-	-	-	-	✔
Gamma-glutamyl transpeptidase elevated	-	✔	-	-	-	-
Gingivitis	<1	✔	-	-	-	-
Glossitis	-	✔	-	-	-	-
Gum hemorrhage	-	✔	-	-	-	-
Hepatomegaly	-	✔	-	-	-	-
Impaired gastric emptying	<1	-	-	-	-	-
Increased appetite	3 to 8	1.1	-	2	-	1 to 7
Increased salivation	-	✔	-	-	-	-
Irritable bowel syndrome	<1	✔	-	-	-	-
Melena	<1	✔	-	-	-	✔
Nausea	4 to 24	3.9 to 8.4	✔	6 to 7	-	-
Pancreatitis	-	✔	-	-	-	✔
Rectal hemorrhage	-	✔	-	-	-	✔
Stomatitis	-	✔	-	-	-	-
Vomiting	1 to 6	3.3 to 8.4	-	-	✔	1 to 3
Genitourinary						
Abnormal ejaculation	-	✔	-	-	-	✔
Acute kidney failure	-	✔	-	-	-	✔
Albuminuria	-	-	-	-	-	✔
Amenorrhea	-	✔	-	-	-	✔
Anorgasmia	-	✔	-	-	-	✔
Balanitis	-	-	-	-	-	✔
Bladder neoplasm	-	-	-	-	-	✔
Breast pain	-	✔	-	-	-	-
Cervicitis	-	-	-	-	-	✔
Cystitis	-	✔	-	-	-	-
Decreased libido	3 to 6	✔	-	<2	-	✔
Dysmenorrhea	-	✔	-	-	-	✔
Dyspareunia	-	-	-	-	-	✔
Dysuria	1	✔	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Ejaculation delayed	<3	-	-	-	-	-
Ejaculation dysfunction	<3	-	-	-	-	-
Erectile dysfunction	1 to 4	-	-	-	-	-
Epididymitis	-	-	-	-	-	✔
Female lactation	-	-	-	-	-	✔
Glomerulitis	-	-	-	-	-	✔
Gynecomastia	-	✔	-	-	-	-
Hematuria	-	✔	-	-	-	✔
Impotence	-	1.5	-	-	-	✔
Kidney calculus	-	-	-	-	-	✔
Leukorrhea	-	✔	-	-	-	✔
Menorrhagia	-	✔	-	-	-	✔
Metrorrhagia	-	-	-	-	-	✔
Micturition urgency	<1	-	-	-	-	-
Nephritis	-	-	-	-	-	✔
Nocturia	<1	✔	-	-	-	-
Oliguria	-	-	-	-	-	✔
Ovarian disorder	-	-	-	-	-	✔
Pollakiuria	1 to 3	-	-	-	-	-
Polyuria	-	✔	-	-	-	-
Pyelonephritis	-	✔	-	-	-	✔
Renal stone	-	✔	-	-	-	-
Urinary abnormality	-	-	-	-	-	✔
Urinary frequency	-	✔	-	-	-	✔
Urinary incontinence	-	✔	-	-	-	1 to 2
Urinary retention	<1	✔	-	-	-	✔
Urinary symptoms	1	-	-	-	-	-
Urinary tract infection	-	✔	✔	-	-	-
Urinary urgency	-	✔	-	-	-	-
Vaginal hemorrhage	-	✔	-	-	-	-
Hematopoietic and lymphatic						
Anemia	<1	✔	-	-	-	✔
Ecchymosis	-	✔	-	-	-	✔
Eosinophilia	-	-	-	-	-	✔
Hypochromic anemia	-	-	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Leukocytosis	-	-	-	-	-	✔
Leukopenia	<1	1.1	-	-	-	✔
Lymphadenopathy	<1	✔	-	-	-	✔
Myelofibrosis	-	-	-	-	-	✔
Polycythemia	-	-	-	-	-	✔
Prothrombin decreased	-	✔	-	-	-	✔
Purpura	-	✔	-	-	-	✔
Thrombocythemia	-	-	-	-	-	✔
Thrombocytopenia	<1	✔	-	-	-	✔
Metabolic and Nutritional disorders						
Alkaline phosphate increase	1	✔	-	-	-	-
Alanine transaminase increase	1	-	-	-	-	-
Bilirubin increased	<1	-	-	-	-	-
Dehydration	<1	✔	-	-	-	-
Dyslipidemia	<1	-	-	-	-	-
Diabetic ketoacidosis	-	✔	-	-	-	-
Edema	-	✔	-	-	✔	1 to 6
Glucose tolerance decrease	-	-	-	-	-	✔
Gout	-	✔	-	-	-	-
Hepatic steatosis	<1	-	-	-	-	-
Hepatitis	<1	-	-	-	-	-
Hot flashes	2	-	-	-	-	-
Hypercholesterolemia	<1	-	-	-	-	-
Hyperglycemia	-	1.2	-	-	-	-
Hyperlipidemia	<1	-	-	-	-	-
Hypoglycemia	1	✔	-	-	-	1 to 3
Hyponatremia	<1	-	-	-	-	-
Lactic dehydrogenase increase	-	✔	-	-	-	-
Pain in extremity	-	-	1.9	-	-	-
Peripheral edema	<1	1.7 to 8.3	3.9	<3	-	2 to 16
Weight gain	<1	1.8 to 2.9	-	2 to 3	-	1 to 16
Weight loss	1 to 2	✔	-	-	-	-
Urate crystalluria	-	-	-	-	-	✔
Musculoskeletal						
Arthralgia	4	✔	-	-	-	2 to 6

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Arthritis	-	✔	-	-	-	-
Arthrosis	-	✔	-	-	-	✔
Back pain	3	1.8	1.7	-	-	1 to 4
Chondrodystrophy	-	-	-	-	-	✔
Fracture	-	1.1	-	-	-	-
Generalized spasm	-	-	-	-	-	✔
Joint swelling	-	-	✔	-	-	-
Leg cramps	-	✔	-	-	-	✔
Muscle cramp	4 to 5	-	-	-	-	-
Muscle spasms	3	-	-	-	-	2 to 4
Muscle tightness	1	-	-	-	-	-
Myalgia	1 to 3	2.0	-	-	-	✔
Myasthenia	-	✔	-	-	-	1
Neuropathy	-	-	-	-	-	2 to 9
Paraesthesia	2	-	-	-	-	-
Tendinous contracture	-	✔	-	-	-	-
Weakness	2 to 4	-	-	-	-	-
Respiratory						
Anaphylactic reaction	<1	-	-	-	-	-
Angioneurotic edema	<1	-	-	-	-	-
Apnea	-	✔	-	-	-	✔
Asthma	-	✔	-	-	-	-
Atelectasis	-	-	-	-	-	✔
Bronchiolitis	-	-	-	-	-	✔
Bronchitis	-	✔	-	-	-	1 to 3
Bronchospasm	-	✔	-	-	✔	-
Cough	3 to 6	1.8	-	-	-	-
Dyspnea	-	✔	-	-	✔	1
Epistaxis	-	✔	-	-	-	-
Hiccups	-	✔	-	-	-	✔
Hoarseness	-	✔	-	-	-	-
Hyperventilation	-	✔	-	-	-	-
Hypoxia	-	-	-	-	-	-
Laryngitis	-	✔	-	-	-	-
Laryngismus	-	-	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Lung edema	-	✔	-	-	-	✔
Lung fibrosis	-	-	-	-	-	✔
Mucositis	-	✔	-	-	-	-
Nasal obstruction	-	✔	-	-	-	-
Nasopharyngitis	4 to 9	-	2.5	-	-	-
Pharyngitis	-	1.2 to 2.8	-	-	-	-
Pharyngolaryngeal pain	1 to 3	-	-	-	-	1 to 3
Pneumonia	-	✔	✔	-	-	-
Respiratory depression	-	-	-	-	✔	-
Rhinitis	-	4.1	-	-	-	-
Sinusitis	-	✔	-	-	-	4 to 7
Snoring	-	✔	-	-	-	-
Upper respiratory infection	4	✔	✔	-	-	-
Voice alteration	-	✔	-	-	-	-
Yawn	<2	-	-	-	-	✔
Other						
Abnormal vision	-	✔	-	-	-	1 to 5
Abnormality of accommodation	-	✔	-	-	-	✔
Accidental injury	-	3.3	-	-	-	2 to 11
Addiction	-	-	-	-	-	✔
Allergic reaction	-	✔	-	-	-	✔
Amblyopia	-	2.7 to 4.2	-	-	-	-
Anaphylactic reaction	-	-	-	-	-	✔
Anisocoria	-	-	-	-	-	✔
Ascites	-	-	-	-	-	✔
Blepharitis	-	-	-	-	-	✔
Blindness	-	✔	-	-	-	✔
Bruxism	<1		-	-	-	-
Cellulites	-	✔	-	-	-	✔
Chills	-	✔	-	-	-	✔
Conjunctivitis	-	1.2	-	-	-	✔
Corneal ulcer	-	-	-	-	-	✔
Deafness	-	✔	-	-	-	-
Dry eyes	-	✔	-	-	-	✔
Dry mouth	5 to 15	1.7 to 4.8	2.8	3 to 4	-	1 to 15

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Ear infection	-	1.2	-	-	-	✔
Ear pain	-	✔	-	-	-	-
Exophthalmoses	-	-	-	-	-	✔
Extraocular palsy	-	-	-	-	-	✔
Eye disorder	-	-	-	-	-	1 to 2
Eye hemorrhage	-	✔	-	-	-	✔
Eye pain	-	✔	-	-	-	-
Facial edema	<1	✔	-	-	-	1 to 3
Feeling abnormal	-	✔	-	<3	-	1 to 3
Feeling drunk	-	✔	-	<3	-	1 to 2
Fever	1 to 2	10.1	-	-	-	✔
Flu-like syndrome	<1	-	-	-	-	1 to 2
Fluid retention	-	-	-	-	-	1 to 3
Glaucoma	<1	✔	-	-	-	-
Granuloma	-	-	-	-	-	✔
Hangover effect	-	✔	-	-	-	✔
Hepatitis	-	✔	-	-	-	-
Hernia	-	✔	-	-	-	-
Hyperacusis	-	-	-	-	-	✔
Hyperpyrexia	-	-	✔	-	-	-
Infection	-	5.1	-	-	-	3 to 14
Intentional injury	-	-	-	-	-	✔
Iritis	-	✔	-	-	-	✔
Keratitis	-	-	-	-	-	✔
Keratoconjunctivitis	<1	-	-	-	-	✔
Liver function tests abnormal	-	✔	-	-	-	-
Macular degeneration	<1	-	-	-	-	-
Maculopathy	<1	-	-	-	-	-
Malaise	<1	✔	-	-	-	✔
Miosis	-	-	-	-	-	✔
Mouth ulceration	-	-	-	-	-	✔
Mydriasis	-	-	-	-	-	✔
Neck pain	-	✔	-	-	-	-
Neck rigidity	-	-	-	-	-	✔
Nephropathy	<1	-	-	-	-	-

Adverse Event	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Night blindness	-	-	-	-	-	✔
Ophthalmoplegia	-	-	-	-	-	✔
Orgasm abnormality	2	-	-	-	-	-
Oropharyngeal edema	<1	-	-	-	-	-
Otic atrophy	-	-	-	-	-	✔
Overdose	-	-	-	-	-	✔
Pain	-	-	1.1	-	-	4 to 5
Papilledema	-	-	-	-	-	✔
Parosmia	-	-	-	-	-	✔
Pelvic pain	-	✔	-	-	-	✔
Periodontal abscess	-	-	-	-	-	✔
Phlebitis	<1	-	-	-	-	-
Photophobia	-	✔	-	-	-	✔
Photosensitivity reaction	<1	✔	-	-	-	✔
Ptosis	-	✔	-	-	-	✔
Retroperitoneal fibrosis	-	-	-	-	-	✔
Retinal edema	-	-	-	-	-	✔
Retinopathy	-	✔	-	-	-	-
Rigors	1	-	-	-	-	-
Seasonal allergy	-	-	✔	-	-	-
Sepsis	-	✔	-	-	-	-
Shock	-	-	-	-	-	✔
Taste loss	-	✔	-	-	-	✔
Taste perversion	-	✔	-	-	-	✔
Thirst	<1	✔	-	-	-	-
Tinnitus	-	✔	-	-	✔	✔
Toothache	-	✔	-	-	-	-
Tongue edema	-	-	-	-	-	✔
Uveitis	-	-	-	-	-	✔
Viral infection	-	10.9	✔	-	-	-
Visual field disturbance	<1	-	-	-	-	-
Withdrawal syndrome	<1	-	-	-	-	-

-Event not reported or incidence <1%.
✔ Percent not specified.

Contraindications

Table 7. Contraindications[1-8]

Contraindication	Duloxetine	Gabapentin	Gabapentin extended-release	Gabap-entin enacarbil	Lidocaine patch	Pregabalin
Concomitant use with monoamine oxidase inhibitors	✔	-	-	-	-	-
History of sensitivity to amide-type anesthetics	-	-	-	-	✔	-
Hypersensitivity to the drug or its ingredients	✔	✔	✔	✔	✔	✔
Uncontrolled narrow-angle glaucoma	✔	-	-	-	-	-

Boxed Warnings

Boxed Warning for Cymbalta® (duloxetine)[1]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared with placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of duloxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared with placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Appropriately monitor patients of all ages who are started on antidepressant therapy and closely observe patients for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescribing health care provider. Duloxetine is not approved for use in children.

Warnings/Precautions

Table 8. Warnings and Precautions[1-8]

Warning/Precaution	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
Accidental exposure in children; small children or pets may suffer serious adverse effects from chewing or ingesting a new or used patches	-	-	-	-	✔	-
Activation of mania/hypomania; use with caution in patients with a history of mania	✔	-	-	-	-	-
Angioedema; has been reported during initial and maintenance treatment	-	-	-	-	-	✔
Carcinogenesis; a minor metabolite, 2, 6-xylidine, has been found to be carcinogenic in rats, although concentrations are negligible with use of topical lidocaine patches	-	-	-	-	✔	-
Clinical worsening and suicide risk; adult and pediatric patients with major depressive disorder may experience worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality)	✔	-	-	-	-	-
Controlled narrow-angle glaucoma; use with caution	✔	-	-	-	-	-
Creatine kinase elevations; has been reported	-	-	-	-	-	✔
Decreased platelet count; has been reported	-	-	-	-	-	✔
Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan Hypersensitivity; has been reported with anticonvulsants	-	✔	✔	✔	-	-
Elevated blood pressure; measure prior to initiating treatment and periodically measured throughout treatment	✔	-	-	-	-	-
Excessive dosing; application to larger areas or for a longer duration than recommended may result in increased lidocaine absorption leading to serious adverse events	-	-	-	-	✔	-
External heat sources; the placement of external	-	-	-	-	-	-

Warning/Precaution	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
heat over the application site is not recommended						
Eye exposure; contact with the eyes may cause severe irritation	-	-	-	-	-	-
Glycemic control may be worsened in some patients with diabetes	✔	-	-	-	-	-
Hazardous tasks; patients should not drive or operate machinery until they have gained sufficient experience with the drug as it may cause central nervous system depression	-	✔	-	✔	-	✔
Hepatotoxicity; has been reported	✔	-	-	-	-	-
Hyponatremia has been reported with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors	✔	-	-	-	-	-
Abnormal bleeding; the risk is higher with concomitant administration of aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants	✔	-	-	-	-	-
Neuropsychiatric effects; use in children 3 to 12 years of age is associated with central nervous system-related adverse events	-	✔	-	-	-	-
Non-intact skin; application to broken skin may result in higher drug concentrations in the blood	-	-	-	-	-	-
Not interchangeable with other gabapentin products due to differences in pharmacokinetics profiles	-	✔	✔	✔	-	-
Ophthalmological effects; have been reported, primarily blurred vision.	-	-	-	-	-	✔
Orthostatic hypotension and syncope have been reported most frequently in patients taking orthostatic-inducing medications, inhibitors of CYP1A2 or duloxetine doses of >60 mg daily	✔	-	-	-	-	-
Peripheral edema; caution should be used in patients with New York Heart Association Class III or IV heart failure	-	-	-	-	-	✔
Prolongation of PR interval; has been reported	-	-	-	-	-	✔
Seizures; this drug has not been evaluated in	✔	-	-	-	-	-

Warning/Precaution	Duloxetine	Gabapentin	Gabapentin extended-release	Gabapentin enacarbil	Lidocaine patch	Pregabalin
seizure disorder and caution should be used in patients with epilepsy						
Serotonin syndrome or neuroleptic malignant syndrome-like reactions are more likely to occur with concomitant administration of other serotonergic agents	✔	-	-	-	-	-
Severe skin reactions; erythema multiforme and Stevens-Johnson Syndrome have been reported	✔	-	-	-	-	-
Sudden and unexplained death in patients with epilepsy has been reported in premarketing studies of gabapentin	-	✔	-	-	-	-
Suicidal behavior and ideation; anticonvulsants increase the risk of suicidal thoughts or behavior in patients taking these drugs regardless of indication	-	✔	✔	✔	-	✔
Tumorigenic potential; a high incidence of tumor development occurred in mice	-	✔	✔	-	-	✔
Urinary hesitation and retention has been reported due to increased urethral resistance	✔	-	-	-	-	-
Weight Gain that is not associated with clinically important changes in blood pressure; however, the long-term cardiovascular effects of this weight gain are unknown	-	-	-	-	-	✔
Withdrawal precipitated seizure, status epilepticus; anticonvulsants should not be abruptly discontinued due to the possibility of increasing seizure frequency	-	✔	✔	✔*	-	✔

*Patients with restless legs syndrome who are taking the recommended dose of 600 mg once-daily may discontinue the drug without tapering. For patients with postherpetic neuralgia receiving twice-daily dosing, the dose should be tapered to 600 mg daily for one week prior to discontinuing the drug.

Drug Interactions

Table 9. Drug Interactions[1-8]

Generic Name	Interacting Medication or Disease	Potential Result
Neuropathic pain agents (gabapentin, gabapentin extended-release and pregabalin)	Ketorolac	Concurrent use of ketorolac and anticonvulsants may result in reduced anticonvulsant effectiveness.
Neuropathic pain agents (gabapentin, gabapentin extended-release and pregabalin)	Naproxen	Concurrent use of naproxen and anticonvulsants may result in reduced anticonvulsant effectiveness.
Neuropathic pain agents (gabapentin and gabapentin extended-release)	Morphine sulfate	Concurrent use of gabapentin and morphine may result in increase in gabapentin plasma concentrations.
Duloxetine	Inhibitors of CYP1A2 (e.g., cimetidine and ciprofloxacin)	Concurrent use of CYP1A2 inhibitors and duloxetine may result in increased duloxetine bioavailability and risk of adverse effects.
Duloxetine	Inhibitors of CYP2D6 (e.g., fluoxetine and quinidine)	Concurrent use of CYP2D6 inhibitors and duloxetine may result in increased duloxetine bioavailability and increase the risk of serotonin syndrome.
Duloxetine	Antiplatelet agents	Concurrent use of duloxetine and antiplatelet agents may result in an increased risk of bleeding.
Duloxetine	Serotonergic agents (e.g., selective 5-HT_1 receptor agonists, tramadol and linezolid)	Concurrent use of serotonergic agents and duloxetine may result in increased risk of serotonin syndrome. Symptoms may include agitation, overactive reflexes, ataxia, shivering, myoclonus, and altered consciousness, may occur in some patients, as a result of rapid accumulation of serotonin in the central nervous system. If coadministration of these agents is indicated, start with low dosages and closely monitor patients for adverse events. Be prepared to provide supportive care and stop the serotonergic agent.
Lidocaine patch	Antiarrhythmic drugs (e.g., mexiletine and tocainide)	Concurrent use of lidocaine patches and antiarrhythmic drugs may result in increased adverse events since the toxic effects are additive and potentially synergistic.
Lidocaine patch	Local anesthetics (e.g., benzocaine and tetracaine)	When concomitantly using lidocaine patches with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Dosage and Administration

Table 10. Dosing and Administration[1-8]

Generic Name	Adult Dose	Pediatric Dose	Availability
Duloxetine	Treatment of major depressive disorder: Capsule: initial, 40 to 60 mg/day divided BID or QD; maintenance, 60 mg QD; maximum, 60 mg QD Management of neuropathic pain associated with diabetic peripheral neuropathy: Capsule: 60 mg QD; lower initial doses may be considered in patients where tolerability is a concern and/or renal impairment is present Treatment of generalized anxiety disorder: Capsule: initial, 30 to 60 mg QD; maintenance, 60 mg to 120 mg QD; maximum, 120 mg QD; note: doses >60 mg QD have not been demonstrated to be more effective than 60 mg QD Management of fibromyalgia, management of chronic musculoskeletal pain: Capsule: initial, 30 mg QD; maintenance, 60 mg QD; maximum, 60 mg QD	Safety and efficacy in children have not been established.	Delayed-release capsule: 20 mg 30 mg 60 mg
Gabapentin	Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients >12 years of age with epilepsy: Capsule, solution, tablet: initial, 300 mg TID; maintenance, 900 to 1,800 mg/day in divided TID Management of postherpetic neuralgia: Capsule, solution, tablet: initial, 300 mg QD for one day, 300 mg BID for one	Adjunctive therapy in the treatment of partial seizures in pediatric patients 5 years of age and older: Capsule, solution, tablet: initial, 10 to 15 mg/kg/day divided TID for three days; maintenance, 25 to 35 mg/kg/day divided TID Adjunctive therapy in the treatment of partial seizures in pediatric patients 3 to 4 years of age:	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/ 5 mL Tablet: 600 mg 800 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	day, and 300 mg TID for one day; maintenance, 1,800 mg/day divided TID; note: additional benefit of using doses >1,800 mg daily was not demonstrated	Capsule, solution, tablet: initial, 10 to 15 mg/kg/day divided TID for three days; maintenance, 40 mg/kg/day divided TID Postherpetic neuralgia: Safety and efficacy in children have not been established.	
Gabapentin extended-release	Management of postherpetic neuralgia: Extended-release tablet: initial, 300 mg QD for one day, followed by 600 mg QD for one day, followed by 900 mg QD for four days, followed by 1,200 mg QD for four days, followed by 1,500 mg QD for four days, followed by 1,800 mg QD; maintenance, 1,800 mg QD	Safety and efficacy in children have not been established.	Extended-release tablet: 300 mg 600 mg
Gabapentin enacarbil	Management of postherpetic neuralgia: Extended-release tablet: initial, 600 mg QD in the morning for three days; maintenance, 600 mg BID; note: additional benefit of using doses >1,200 mg daily was not demonstrated Moderate-to-severe primary restless legs syndrome: Extended-release tablet: 600 mg QD at 5 pm; note: additional benefit of using 1,200 mg daily was not demonstrated; however, there was an increased incidence of dose-dependent adverse events	Safety and efficacy in children have not been established.	Extended-release tablet: 300 mg 600 mg
Lidocaine patch	Relief of pain associated with postherpetic neuralgia: Topical patch: apply up to three patches, only once for up to 12 hours within a 24-hour period.	Safety and efficacy in children have not been established.	Topical patch: 5%
Pregabalin	Adjunctive therapy for adult patients with partial onset seizures: Capsule: initial, 150 mg/day	Safety and efficacy in children have not been established.	Capsule: 25 mg 50 mg 75 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	divided BID or TID; maintenance, 150 to 600 mg/day divided BID or TID; maximum, 600 mg/day divided BID or TID Management of fibromyalgia: Capsule: initial, 150 mg/day divided BID; maintenance, 150 to 450 mg/day divided BID; maximum, 450 mg/day divided BID; note: additional benefit of using doses >450 mg daily was not demonstrated; however, there was an increased incidence of dose-dependent adverse events Management of neuropathic pain associated with diabetic peripheral neuropathy: Capsule: initial, 150 mg divided TID; maintenance, 150 to 300 mg/day divided BID or TID; maximum, 300 mg/day divided BID or TID; note: additional benefit of using doses >300 mg daily was not demonstrated; however, there was an increased incidence of dose-dependent adverse events Management of postherpetic neuralgia: Capsule: initial, 150 mg/day divided BID or TID; maintenance, 300 to 600 mg mg/day divided BID or TID; maximum, 600 mg/day divided BID or TID		100 mg 150 mg 200 mg 225 mg 300 mg

Drug regimen abbreviations: BID=twice daily, QD=once daily, TID=three times daily

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
European Federation of Neurological Societies:	Painful polyneuropathy • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy.

Clinical Guideline	Recommendations
Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)[11]	• Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. <u>Postherpetic neuralgia (PHN)</u> • Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies.
American Academy of Neurology/ American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[12]	<u>Anticonvulsants</u> • If clinically appropriate, pregabalin should be offered for treatment. • Gabapentin and sodium valproate should be considered for treatment. • There is insufficient evidence to support or refute the use of topiramate for treatment. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. <u>Antidepressants</u> • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. • Venlafaxine may be added to gabapentin for a better response. • There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. <u>Opioids</u> • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. <u>Other pharmacologic options</u> • Capsaicin and isosorbide dinitrate spray should be considered for treatment. • Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. • Lidocaine patch may be considered for treatment. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. <u>Nonpharmacologic options</u> • Percutaneous electrical nerve stimulation should be considered for

Clinical Guideline	Recommendations
	treatment. • Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. • Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[13]	Neuropathy • All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. • Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. • Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament. • Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes. • Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy. • When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized. • Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. • Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. • Maintain a referral network for podiatric and peripheral vascular studies and care.
American Diabetes Association: **Diabetic Neuropathies (2005)**[55]	Algorithm for the management of symptoms diabetic polyneuropathy • Exclude nondiabetic etiologies, followed by, • Stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, • Tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, • Anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, • Opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, • Consider pain clinical referral
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[10]	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit.

Clinical Guideline	Recommendations
	• The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.

Conclusions

The agents approved by the Food and Drug Administration (FDA) for the treatment of neuropathic pain include duloxetine (Cymbalta®), gabapentin (Neurontin®), gabapentin extended-release (Gralise®), gabapentin enacarbil (Horizant®), lidocaine patches (Lidoderm®) and pregabalin (Lyrica®). All of these agents are FDA-approved for the treatment of postherpetic neuralgia with the exception of duloxetine, which is indicated for neuropathic pain associated with diabetic neuropathy. Pregabalin is indicated for both postherpetic neuralgia and neuropathic pain associated with diabetic neuropathy. The exact mechanisms by which these agents exert their analgesic effects in various neuropathies have not been fully elucidated.

The neuropathic pain agents differ primarily in their dosing frequency and pharmacokinetic profiles. Duloxetine is dosed once daily for the treatment of diabetic peripheral neuropathic pain. Gabapentin is typically administered three times daily, while the extended-release formulation is administered once daily. Gabapentin enacarbil, the prodrug of gabapentin, is dosed twice daily for postherpetic neuralgia and once daily in patients with moderate-to-severe restless legs syndrome. Gabapentin enacarbil achieves more predictable serum concentrations and does not demonstrate saturable absorption, resulting in a higher bioavailability and less variability in serum levels compared to gabapentin. The lidocaine topical patch should be applied once daily to the painful area for 12 hours and then removed for the following 12 hours. Pregabalin is typically administered twice daily, but can be given up to three times daily. Of these agents, only gabapentin immediate-release is available generically in various formulations. Pregabalin is classified as a Schedule V controlled substance while none of the other agents are currently listed as controlled substances.

There are relatively few head-to-head studies comparing the neuropathic pain agents to one another. In patients with postherpetic neuralgia who were switched from gabapentin to pregabalin, there was no significant difference in pain, based on a visual analog scale, between the treatments.[14] In a 52-week, open-label study comparing duloxetine to gabapentin, amitriptyline or venlafaxine for the treatment of diabetic peripheral neuropathic pain, no significant treatment-group differences were observed in quality of life questionnaire scores; however, results differed with regard to short-form-36 subscale scores. In another study no significant treatment-group differences in SF-36 subscale scores were reported between duloxetine and other routinely used agents.[15,16] Duloxetine was noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin.[17] The results of a meta-analysis by Quilici et al showed that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain.[54]

The current clinical guidelines for the treatment neuropathic pain recommend that tricyclic antidepressants (amitriptyline, nortriptyline, desipramine), gabapentin, pregabalin, opioids and topical lidocaine patches are all effective and should be used in the treatment of postherpetic neuralgia, with no single agent being recommended over another.[10,11] For the treatment of painful diabetic neuropathy, the American Academy of Neurology states that tricyclic antidepressants, duloxetine, gabapentin, pregabalin, sodium valproate and venlafaxine be considered.[12]

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