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 Therapeutic 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. 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.	Capsule: 100 mg 300 mg 400 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Adjunctive therapy in the treatment of partial seizures in patients 3 to 12 years of age. Management of postherpetic neuralgia.	Solution: 250 mg/5 mL Tablet: 600 mg 800 mg	
Gabapentin extended-release (Gralise®)	Management of postherpetic neuralgia.	Extended-release tablet: 300 mg 600 mg	-
Gabapentin enacarbil (Horizant®)	Management of postherpetic neuralgia. Moderate-to-severe primary restless legs syndrome.	Extended-release tablet: 300 mg 600 mg	-
Lidocaine patch (Lidoderm®)	Management of 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. Management of neuropathic pain associated with spinal cord injury. Management of postherpetic neuralgia.	Capsule: 25 mg 50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Oral solution: 20 mg/mL	-

*Generic available in one dosage form or strength.

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 non-inferior 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®), duloxetine, and topical lidocaine patches are the agents within the class that are available generically.
    - Pregabalin (Lyrica®) is the only neuropathic pain agent that is classified as a controlled substance (Schedule V).

References

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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.[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. 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 or spinal cord injury, 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, American Association of Clinical Endocrinologists, and the American Diabetes Association 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.[12-15]

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.[16] 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.[17,18] In a head-to-head study by Tanenberg et al, duloxetine was non-inferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.[19] Tesfaye et al evaluated the combination of duloxetine and pregabalin compared to high dose monotherapy with either agent alone in patients with diabetic peripheral neuropathy who were non-responders to traditional dosages of either medication and found there to be no statistically significant difference between using a high dose monotherapy regimen or a combination regimen.[20]

Medications

Table 1. Medications Included Within Class Review[1-8]

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	-

*Available generically in one dosage form or strength.

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 neuropathic pain associated with spinal cord injury	-	-	-	-	-	✔
Management of postherpetic neuralgia	-	✔	✔	✔	✔	✔
Moderate-to-severe primary restless legs syndrome in adults	-	-	-	✔ ‡	-	-
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.
† Also indicated as adjunctive therapy in the treatment of partial seizures in patients three 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 respective Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[16-63]

In patients with postherpetic neuralgia, treatment with lidocaine patches provide significant pain relief compared to placebo.[29-31] 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.[30,31] A noncomparative, open-label study evaluating lidocaine patches for the management of postherpetic neuralgia supports the findings of placebo-controlled studies.[22]

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.[25,26,28]

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.[32,33] 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.[34] Within these studies, doses of gabapentin of up to 3,600 mg/day were evaluated.[32-34]

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.[35,36] In one study, a larger proportion of patients receiving gabapentin extended-release reported ≥50% baseline reduction in average daily pain scores compared to placebo.[35] In general, treatment with gabapentin extended-release was well tolerated; dizziness, headache, somnolence and peripheral edema were the most commonly reported adverse events.[35,36] 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.[37] Within these studies, gabapentin extended-release at doses of up to 1,800 mg/day were evaluated.[35-37]

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 two additional published placebo-controlled studies 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. Adverse events were similar to gabapentin and gabapentin extended-release.[38,39]

Pregabalin demonstrates consistent "superiority" over placebo in alleviating diabetic peripheral neuropathic pain, spinal cord-related 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.[40-54] Two, noncomparative, open-label studies evaluating pregabalin for the management of postherpetic neuralgia supports the findings of placebo-controlled studies [23-24] In one of these noncomparative studies, long-term treatment of postherpetic neuralgia with pregabalin (52 weeks) was found to be safe and effective.[23]

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.[16]

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.[17,18] A second head-to-head study demonstrated duloxetine to be non-inferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had experienced an inadequate pain response to gabapentin.[19] Tesfaye et al evaluated the combination of duloxetine and pregabalin compared to high dose monotherapy with either agent alone in patients with diabetic peripheral neuropathy who were non-responders to traditional dosages of either medication and found there to be no statistically significant difference between using a high dose monotherapy regimen or a combination regimen.[20]

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.[55-64] 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.[62]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ifuku et al[16] 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 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
Raskin et al[17] Duloxetine 60 mg BID vs routine care (gabapentin, amitriptyline, and venlafaxine)	ES, OL, RCT Adult patients who presented with pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes	N=237 52 weeks	Primary: Not reported Secondary: SF-36, EQ-5D	Primary: Not reported Secondary: No significant treatment-group differences were observed in the SF-36 subscales or in the EQ-5D questionnaire.
Wernicke et al[18] Duloxetine 60 mg BID vs	ES, OL, RCT Adult patients who presented with pain due to bilateral	N=293 52 weeks	Primary: Not reported Secondary: Health outcomes	Primary: Not reported Secondary: There were significant treatment-group differences observed in favor of duloxetine in the SF-36 physical component summary score, and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
routine care (gabapentin, amitriptyline, and venlafaxine)	peripheral neuropathy caused by type 1 or 2 diabetes			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. 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. There were no significant treatment-group differences observed in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 SBP, 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).
Tanenberg et al[19] Duloxetine vs pregabalin vs	MC, NI, OL, RCT Adult patients with type 1 or 2 with HbA_{1c} ≤12%, and diabetic peripheral neuropathic pain who had been	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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
duloxetine plus pregabalin	treated with gabapentin (900 mg/day) and had an inadequate response		night pain ratings, Clinician Global Impression of Severity, Brief Pain Inventory severity and interference, Beck Depression Inventory II, Patient Global Impression of Improvement, Sheehan Disability Scale, response rate	The NI comparison between duloxetine and combination therapy on the 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.
Tesfaye et al[20] (COMBO-DN) Duloxetine 120 mg QD or pregabalin 600 mg QD vs duloxetine 60 mg and pregabalin 300 mg QD Each patient received either 60 mg or 300 mg of pregabalin for 8 weeks	DB, MC, PG, RCT Patients ≥ 18 years of age, with diabetic peripheral neuropathic pain caused by type 1 or 2 diabetes mellitus who did not respond to eight weeks of initial therapy with 60 mg of duloxetine or 300 mg of pregabalin after 8 weeks	N=339 (N=804) 8 weeks (16 weeks)	Primary: BPI-MSF Secondary: Response rates, BPI-MSF severity items, and in BPI-MSF average pain	Primary: At the end of the combination/high-dose therapy period, no statistically significant difference between combination and high dose monotherapy in the primary variable of the mean change in BPI-MSF 24-hour average pain was seen (-2.35; vs -2.16; mean difference, -0.19; 95% CI, -0.61 to 0.23; P=0.370). Secondary: A numerically but non-significantly larger proportion of patients in the combination group (N=86 [52.1%]) compared to the high-dose monotherapy group (N=64 [39.3%]) achieved ≥50% reduction in BPI-MSF 24-hour average pain at the end of combination/high dose therapy (P=0.068). At the end of the combination/high-dose therapy period, between-therapy differences for other secondary efficacy measures consistently favored combination therapy; however, differences were not statistically significant, with the exception of the Hospital Anxiety and Depression Scale (mean difference, -0.62 [0.31]; 95% CI, -1.228 to -0.002;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
before starting high dose/combination therapy.				P=0.049).
Devers et al[21] 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[22] 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Ogawa et al (abstract)[23] Pregabalin 150 to 600 mg/day	OL 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
Xochilcal-Morales et al[24] Pregabalin 150 to 600 mg/day	MC, OL, PRO Patients ≥18 years of age diagnosed with neuropathic pain 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	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 scale Secondary: Pain, anxiety, sleep interference, treatment satisfaction, Patient Global Impression of Change, Clinician Global Impression of Change	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 baseline across all weeks of the trial, as early as one week after initiation of pregabalin (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Yan et al[25] Duloxetine 60 to 120 mg daily vs placebo	DB, PC, RCT 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 Improvement, Clinical Global Impressions of Severity, EQ-5D, Athens Insomnia Scale	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 Patient Global Impression of Improvement (2.32±0.11 vs 2.64±0.10; *P*=0.028), Clinical Global Impressions of Severity (-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). 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.
Armstrong et al[26] Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Patient-reported functional outcomes (SF-36, Brief Pain Inventory, EQ-5D) Secondary:	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 mental health (*P*=0.04) status. Consistent results were seen in the ITT

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	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
Boyle et al (abstract)[27] Duloxetine 60 mg/day vs amitriptyline 50 mg/day vs pregabalin 300 mg/day	AC, DB, PG, RCT Patients ≥18 years of age with diabetes (type 1 or type 2) for ≥1 year and neuropathic pain of diabetic origin (≥1 of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or	N=83 4 weeks	Primary: Brief Pain Inventory Secondary: SF-36, sleep, mood and daytime sleepiness	Primary: All three treatments significantly reduced pain compared to placebo. No one treatment was “superior” to the others with regard to pain. Secondary: For sleep, pregabalin improved sleep continuity (*P*<0.001), whereas duloxetine increased wake and reduced total sleep time (*P*<0.01 and *P*<0.001). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there were a significantly higher number of adverse events in the pregabalin treatment group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	lancinating pains and hyperalgesia affecting both lower extremities at any level below the mid-thighs) and LANSS score >12			
Kajdasz et al[28] Duloxetine 20 or 60 mg QD, or 60 mg BID vs placebo	Post-hoc analysis of 3 DB, MC, PC, RCT Patients with diabetic peripheral neuropathic pain	N=1,139 12 weeks	Primary: Response rate (defined as ≥30 and ≥50% reductions from baseline in weekly mean of the 24-hour average pain severity scores) Secondary: NNH (based on rates of dis-continuation due to adverse events)	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% 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.
Galer et al[29] 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	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	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
	physical examination		descriptor score, nonallodynic score, and 4 Score [sum of the scores of the four descriptors "sharp," "hot," "dull," and "deep"]) Secondary: Not reported	
Galer et al[30] 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[31] Lidocaine 5% transdermal patch applied for 12 hours daily (up to 4 patches	DB, PC, PRO, RCT, XO Patients ≥21 years of age	N=58 28 days	Primary: Ongoing pain intensity (during the first eight hours, every two	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
could be applied at once) vs placebo	suffering from chronic painful peripheral focal neuropathic syndromes that were superficial and localized to a limited skin zone		hours after patch application on day one, and one hour after daily removal of the patch) allodynia, quality of neuropathic symptoms, quality of sleep Secondary: Not reported	(*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). 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[32] Gabapentin 3,600 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with pain present for >3 months after healing of a herpes zoster	N=229 8 weeks	Primary: Change in the average daily pain score Secondary: Average daily sleep scores, SF-MPQ, Patient	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	skin rash; pain intensity score ≥40 mm (on the 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		Global Impression of Change, Clinician Global Impression of Change, SF-36, POMS	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 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).
Rice et al[33] Gabapentin 1,800 or 2,400 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with pain present for >3 months after healing of an acute herpes	N=334 7 weeks	Primary: Change in average daily pain diary score Secondary: Mean weekly sleep interference	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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	zoster skin rash, and an average pain score ≥4 (11-point scale)		score, SF-MPQ, Clinician Global Impression of Change, Patient Global Impression of Change, SF-36	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). 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)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to patients receiving placebo.
Gilron et al[34] Placebo (lorazepam 0.3 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	DB, PC (active), RCT, 4-way XO 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	N=57 (n=35 with diabetic neuropathy, n=22 with PHN) 20 weeks	Primary: Mean daily pain intensity in patients receiving a maximum tolerated dose Secondary: Pain (SF-MPQ), maximal tolerated doses, mood, quality of life	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 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	months prior to enrollment			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.
Irving et al (abstract)[35] 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 Patients with pain for ≥3 months after healing of acute herpes zoster skin rash and who had baseline average daily pain score ≥4 on a 10 point Numerical Rating Scale	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
Wallace et al (abstract)[36] Gabapentin ER administered QD or in divided doses for a total daily dose of 1,800 mg vs placebo	DB, MC, PC, RCT 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			sleep interference score	
Jensen et al (abstract)[37] Gabapentin ER 1,800 mg QD vs gabapentin ER 600 mg BID vs placebo	RCT 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
Backonja et al[38] Gabapentin enacarbil 1,200 mg BID 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.	DB, PC, RCT 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	N=116 14 days	Primary: Change in mean weekly pain score from baseline to trial end Secondary: Change in mean weekly pain score from baseline to week one, proportion of patients showing either a ≥30 or ≥50% reduction in	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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	score ≥4 during a 7 day baseline period		mean pain score between baseline and the end of treatment, sleep interference, POMS, Patient Global Impression of Change, SF-MPQ	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).
Zhang et al[39] Gabapentin enacarbil 1,200 mg QD vs gabapentin enacarbil 2,400 mg QD vs gabapentin enacarbil	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of PHN with an 11-PI-NRS ≥4	N=371 14 weeks	Primary: Change from baseline of 24-hour average pain intensity score at the end of maintenance therapy Secondary: Change in 24-hour average pain intensity	Primary: Statistically significant improvements were observed in all gabapentin groups as compared to placebo. The adjusted mean standard error change from baseline reduction in 24-hour average pain intensity score from baseline to end of maintenance therapy was −1.66 (0.216) for the placebo treatment group as compared with least squares mean of −2.47 (0.204), −2.36 (0.237), and −2.72 (0.227) in the 1,200 mg, 2,400 mg, and 3,600 mg treatment groups, respectively. Unadjusted CIs for pairwise comparisons of active doses did not indicate a benefit of gabapentin enacarbil 3,600 mg over gabapentin enacarbil 2,400 mg (adjusted mean difference standard error=0.37 [0.329]; 95% CI, −0.28 to 1.01) or 1,200 mg (adjusted mean difference

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
3,600 mg QD vs placebo			scores, pain intensity scores, time to sustained improvement, sleep interference, nighttime awakenings due to pain, total nighttime awakenings, percent of days with use of sleep medications, increase in total sleep time	standard error=0.25 [0.306]; 95% CI, −0.35 to 0.86) nor 2,400 mg over 1,200 mg (adjusted mean difference standard error=−0.11 [0.314]; 95% CI, −0.73 to 0.51). However, the study was not powered for pairwise comparisons of active doses. Secondary: Most of the improvements in the 24-hour average pain intensity scores were achieved within the first four weeks across all treatment groups, with improvements in the active treatment groups compared with the placebo group observed for all three gabapentin enacarbil as early as week one and maintained across all time points. From a numerical standpoint, the gabapentin enacarbil 3,600 mg treatment group had the greatest adjusted mean change from baseline to each week of treatment in pain intensity compared with the other treatment groups. There was a reduction from baseline in pain intensity scores across all treatment groups. The magnitude of the improvement observed was greater in all three gabapentin enacarbil treatment groups than in the placebo treatment group. With the exception of the daytime worst pain endpoint for the gabapentin enacarbil 2,400 mg/day group, the 95% CIs indicated a benefit for the three gabapentin enacarbil treatment groups over placebo. In the time to sustained improvement in pain intensity analysis of the intention-to-treat population at the end of maintenance therapy, the percentage of subjects with sustained improvement was numerically greater for the three gabapentin enacarbil treatment groups (1,200 mg/day = 67%; 2,400 mg/day = 70%; 3,600 mg/day = 76%) compared with the placebo treatment group (57%). There was a numerical reduction from baseline to EOMT across all treatment groups in the adjusted mean for subject-reported sleep interference, nighttime awakenings due to pain, total nighttime

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				awakenings, and percent of days with use of sleep medications as well as an increase in total sleep time. CIs indicate a benefit over placebo in sleep interference for gabapentin enacarbil 1,200 mg/day as well as gabapentin enacarbil 3,600 mg/day and in the total number of nighttime awakenings and the number of nighttime awakenings due to pain for gabapentin enacarbil 3,600 mg/day.
Rosenstock et al[40] 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, adverse events	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). 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[41] 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	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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Survey, adverse events	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[42] Pregabalin 150 to 600 mg/day vs placebo	DB, MC, PG, RCT Chinese patients 18 to 75 years of age with a primary diagnosis of painful diabetic peripheral neuropathy or PHN; patients 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	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 Change	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 vs 52%; *P*=0.041). Secondary: 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-MPQ 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).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	from herpes zoster skin rash, moderate to severe neuropathic pain over 4 consecutive days			
Moon et al[43] Pregabalin 150 to 600 mg/day vs placebo	DB, MC, PC, RCT 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	N=241 10 weeks	Primary: 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	Primary: 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	(type 1 or 2); HbA_{1c} ≤11%; and documented symptoms of diabetic peripheral 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		scores, Daily Sleep Interference Scale, EQ-5D, Medical Outcome Study, HADS, Patient Global Impression of Change, Clinician Global Impression of Change	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 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).
Richter et al (abstract)[44] 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	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Impression of Change, Patient Global Impression of Change, adverse events	Dizziness was the most common adverse reaction.
Dworkin et al[45] 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 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[46] Pregabalin 75, 300, and 600 mg/day administered in divided doses (TID)	DB, MC, PC, RCT Patients with 1- to 5-year history of diabetic	N=338 5 weeks	Primary: Pain score Secondary: Sleep interference	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:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	peripheral neuropathy and average weekly pain score ≥4 on an 11-point numeric pain-rating scale		score, global impression of change, SF-MPQ, SF-36 Health Survey, Patient Global Impression of Change, Clinician Global Impression of Change, adverse events	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 ($P \leq 0.05$ 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[47] Pregabalin flexible-dose regimen of 150, 300, 450, and 600 mg/day with weekly dose escalation based on responses and tolerability vs pregabalin fixed-dose regimen of 300 mg/day for 1 week, followed by 600 mg/day for 11 weeks vs placebo	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 (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 (25.0 vs 17.0 vs 7.7% of placebo group; *P* values not reported).
Skvarc et al[48] Pregabalin 75 to 150 mg BID	DB, PC, PRO, RCT Outpatients 30 to	N=29 3 weeks	Primary: Assessment of pain severity using the 11-	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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	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		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	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.
Siddall et al[49] Pregabalin 150 to 600 mg/day, administered BID vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with a spinal cord injury (paraplegia or tetraplegia) for ≥1 year, in whom it had been nonprogressive for ≥6 months, and chronic (≥3 months or with relapses and remission ≥6 months that started after sustaining the	N=137 12 weeks	Primary: Pain score Secondary: Responder rates, SF-MPQ, sleep interference, mood, patient global measure of change	Primary: Pregabalin significantly reduced pain scores compared to placebo (difference, -1.53; 95% CI, 0.92 to 2.15; *P*<0.001). In the analysis of pain scores by week, scores were significantly lower with pregabalin as early as week one and remained so for the duration of the study. Results were similar when analyzed in patients with complete spinal lesions (difference, 1.79; 95% CI, 0.9 to 2.7; *P*<0.001), incomplete spinal lesions (difference, 1.25; 95% CI, 0.1 to 2.2; *P*<0.05) and in patients with lesions at or below L2 (difference, 1.57; 95% CI, 0.9 to 2.2; *P*<0.001). Secondary: The proportion of patients with ≥30% reduction (42 vs 16; *P*=0.001) and ≥50% reduction (22 vs 8%; *P*<0.05) in pain score from baseline at endpoint were significantly higher with pregabalin compared to placebo. Based on the 30 and 50% responder rate the NNT was 3.9 and 7.1, respectively. At trial end, 15.9 and 43.3% of patients receiving pregabalin and placebo had severe pain (*P* value not reported). Reduction from baseline to trial end on each of the five SF-MPQ scales

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	spinal cord injury) central neuropathic pain			was greater with pregabalin compared to placebo (*P*≤0.002 for all). Reduction from baseline to trial end on sleep interference score was greater with pregabalin compared to placebo (*P*<0.001). Pregabalin was associated with a greater reduction in the overall sleep problems index compared to placebo at trial end (*P*=0.021). The improvement in sleep quantity (*P*<0.05) and reduction in sleep disturbance (*P*<0.001) on the Medical Outcomes Study-sleep scale were significantly greater with pregabalin compared to placebo. There were no differences between the two treatments on the other five subscales (snoring, awaken short of breath, adequacy, somnolence, proportions of patients with optimal sleep). Reduction from baseline to trial end in the HADS anxiety score was greater with pregabalin compared to placebo (*P*=0.043), but there were no differences in the HADS depression score. A higher proportion of patients receiving pregabalin rated themselves as improved compared to placebo (56.5 vs 21.5%; *P*<0.001).
Vranken et al[50] Pregabalin 150 mg, QD to QID capsules per day (flexible-dose regimen) vs placebo Patients taking concomitant analgesic mediation were allowed to enter the trial if	DB, PC, RCT Patients ≥18 years of age suffering from severe neuropathic pain (described as burning pain, paroxysmal episodes of shooting pain, or pain on light touch), VAS	N=40 4 weeks	Primary: Pain score Secondary: Pain Disability Index, EQ-5D, SF-36	Primary: Pain intensity scores before and after four weeks of treatment changed from 7.4±1.0 to 7.1±2.0 with placebo and from 7.6±0.8 to 5.1±2.9 with pregabalin. Pregabalin significantly decreased pain scores compared to placebo (difference, 2.18; 95% CI, 0.57 to 3.80; *P*=0.01). There was no difference in pain relief with pregabalin between patients with neuropathic pain due to brain injury and spinal cord injury. Secondary: There was no difference between treatments in Pain Disability Index scores. Pregabalin significantly improved EQ-5D utility VAS scores compared to placebo (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
neuropathic pain treatment was on a stable regimen ≥90 days before screening. Previous gabapentin had to be discontinued ≥3 days prior to trial entry.	score >6 caused by lesion or dysfunction of in the central nervous system (brain or spinal cord injury), pain for ≥6 months that started after sustaining the lesion of dysfunction of the central nervous system, and LANSS questionnaire score >12			Pregabalin significantly improved the bodily pain domain of the SF-36 compared to placebo (*P*=0.009). Pregabalin improved the remaining seven domains of the SF-36 compared to placebo, but differences did not reach significance.
Cardenas et al[51] Pregabalin 150 to 600 mg/day, administered BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with C2-T12 spinal cord injury, for ≥12 months and below-level neuropathic pain (type 14 or 15 according to Bryce-Ragnarsson taxonomy) continuously for ≥3 months or remitting/	N=220 17 weeks	Primary: Duration-adjusted average change in pain Secondary: Change in mean pain score, proportion of patients with ≥30% reduction in mean pain score, Patient Global Impression of Change and pain-related	Primary: Patients treated with pregabalin experienced a statistically significant improvement in duration-adjusted average change in pain compared to patients treated with placebo (difference, -0.59; 95% CI, -0.98 to -0.20; *P*=0.003). Secondary: Pain scored were significantly reduced from baseline following treatment with pregabalin compared to placebo (difference, -0.70; 95% CI, -1.20 to -0.20; *P*=0.007). A significantly greater proportion of patients treated with pregabalin compared to placebo achieved ≥30% reduction in pain scores (48 vs 33%; OR, 1.85; 95% CI, 1.03 to 3.33; *P*=0.039). On Patient Global Impression of Change, more patients treated with pregabalin compared to placebo rated themselves as 'very much improved' (7 vs 2%; *P*<0.001) or 'much improved' (33 vs 25.2%;

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	relapsing for ≥6 months		sleep interference scores	*P*<0.001). Scores for sleep interference were significantly improved in the pregabalin treatment group compared to the placebo group (difference, -1.08; 95% CI, -1.60 to -0.56; *P*<0.001).
Roth et al[52] Pregabalin vs placebo	Review (9 trials) 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
Sharma et al[53] Pregabalin 150, 300, or 600 mg/day vs	RETRO (9 MC, PC, RCTs) Adult patients with PHN or diabetic	N=1,982 Duration not specified	Primary: Time to onset for individual treatment arms that statistically separated from	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

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placebo	peripheral neuropathy; patients with PHN were adults with neuropathic pain for ≥6 months after healing of the herpes zoster rash, average daily pain score ≥4; patients with diabetic peripheral neuropathy were adults with type 1 or 2 diabetes, HbA_{1c} ≤11%, painful distal symmetric sensorimotor poly-neuropathy, average daily pain score ≥4, and ≥40 mm score		placebo Secondary: Not reported	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 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 and 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

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Semel et al[54] Pregabalin 150, 300, or 600 mg/day vs placebo	Pooled analysis of 11 PC, RCTs 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

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				improvements with 300 (-0.67; *P*=0.0003) and 600 mg/day (-1.08; *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
Wernicke et al[55] 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.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients randomized to duloxetine therapy experienced higher incidences of palpitations (*P*=0.004), tachycardia (*P*=0.007), orthostatic 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[56] Duloxetine vs placebo or control Only outcomes for painful peripheral neuropathy are reported.	SR (6 RCTs) 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%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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 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 WMD on the mental summary component was significantly greater only with 120 mg/day (2.23; 95% CI, 0.69 to 3.77). The WMD 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 WMD 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.
Wiffen et al[57] Gabapentin vs placebo	MA (15 RCTs) Patients with acute and chronic pain; trials included patients with acute post-operative pain (1 trial), diabetic peripheral neuropathy (7 trials), PHN (2	N=1,468 Duration not specified	Primary: Evaluate analgesic effectiveness and adverse effects of gabapentin for acute and chronic pain Secondary: Not reported	Primary: The study in acute post-operative pain (n=70) showed no benefit for gabapentin compared to placebo for pain at rest. 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

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	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)			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[58] Gabapentin 1,200 mg/day vs placebo, no treatment, or any other AC Only results for PHN are reported (5 trials), when possible.	SR (29 RCTs) Adult patients with 1 of 12 chronic pain conditions; 78% of patients had PHN, painful diabetic neuropathy, or mixed neuropathic pain	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 indicating some improvement, withdrawals due to lack of efficacy, withdrawals due to adverse events	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). 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

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				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).
Chou et al[59] Gabapentin vs placebo (6 trials) and gabapentin vs tricyclic antidepressants (3 trials) and tricyclic antidepressants vs placebo (9 trials)	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 pain or global efficacy on a categorical scale), safety Secondary: Not reported	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). 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[60] Pregabalin	MA of (25 RCTs) Patients with acute and	N=7,652 24 hours acute pain, 4	Primary: Analgesic effectiveness and adverse	Primary: There was no clear evidence of beneficial effects of pregabalin in established acute postoperative pain.

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vs placebo	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)	to 26 weeks chronic pain	effects of pregabalin for acute and chronic pain Secondary: Not reported	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 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[61]	MA and SR (12 RCTs)	N=not specified	Primary: Percentage	Primary: The difference in the percentage reduction in pain intensity varied from

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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	Patients with PHN	6 to 13 weeks	reduction in pain intensity Secondary: RR of withdrawal due to lack of efficacy, RR of withdrawal due to adverse events	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.
Quilici et al[62] Duloxetine vs pregabalin and gabapentin Placebo was used a common comparator.	MA (11 RCTs; duloxetine, 3 trials; pregabalin, 6 trials; gabapentin, 2 trials) 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 duloxetine, a difference that reached significant (95% CI, 0.016 to 1.060).

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				Secondary: Not reported
Ney et al[63] Duloxetine, Dextromethorphan-quinidine, lacosamide, pregabalin, oxcarbazepine, topiramate or zonisamide vs placebo	MA (17 RCTs) Patients with peripheral neuropathic pain	N=5,975 ≥12 weeks	Primary: Reduction in pain at ≥12 weeks or pain at ≥12 weeks Secondary: Sleep interference score, ≥50% reduction in pain and global improvement measure	Primary: The greatest reduction in pain at ≥12 weeks compared to placebo occurred with duloxetine 120 mg (-1.17; 95% CI, 0.77 to 1.58; *P*<0.001), pregabalin 600 mg (-1.11; 95% CI, 0.77 to 1.45; *P*<0.001) and duloxetine 60 mg (-1.08; 95% CI, 0.70 to 1.46; *P*<0.001). There was no statistically significant difference in pain between placebo and treatment with zonisamide 540 mg (*P*=0.13), pregabalin 150 mg (*P*=0.10), oxcarbazepine 1,200 mg (*P*=0.20), topiramate 100 mg (*P*=1.00), 200 mg (*P*=0.01), 400 mg (*P*=0.08) or lacosamide 200 mg (*P*=0.09). Secondary: The greatest change in sleep interference scores compared to placebo occurred with pregabalin 600 mg (1.1; 95% CI, 0.7 to 1.6; *P*<0.001) and lacosamide (1.0; 95% CI, 0.3 to 1.6; *P*=0.003). Duloxetine 60 mg and pregabalin 300 mg each improved scores by 0.9 points compared to placebo (*P*<0.001 for both). The NNT for a single 50% improvement in pain was 3.7 with zonisamide 540 mg and dextromethorphan-quinidine 90/60 mg (*P*<0.001 for both), 4.1 with pregabalin 600 mg (*P*<0.001), 4.9 with duloxetine 120 mg (*P*<0.001), 5.1 with duloxetine 60 mg (*P*<0.001), six with oxcarbazepine 1,800 mg (*P*<0.02) 6.9 with topiramate 400 mg (*P*<0.004) and nine for pregabalin 300 mg (*P*=0.017). Improvements with other strengths of these agents were not statistically significant. The number needed for a single greater than-minimal improvement was 4.5 and 4.6 with duloxetine 120 and 60 mg, respectively (*P*<0.001 for both), followed by 4.7 with lacosamide 600 mg (*P*=0.006), 5.1 with

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				oxcarbazepine 1,800 mg (*P*=0.004) and pregabalin 600 mg (*P*<0.001). The NNT for improvement was 6.8 with lacosamide 400 mg (*P*=0.022) and 8.5 with topiramate 400 mg (*P*=0.022). Improvements with other evaluated doses were not statistically significant.
Snedecor et al[64] pharmacological treatment vs placebo	MA (58 RCTs) Patients ≥18 years of age with painful diabetic peripheral neuropathy	N=11,883 ≥4 weeks	Primary: Treatment efficacy (Numerical Rating Scale), daily pain (VAS), proportion of patients achieving ≥30% or ≥50% reductions in Numerical Rating Scale or VAS Secondary: Adverse events, discontinuation, EQ-5D	Primary: The greatest reduction in Numerical Rating Scale score compared to placebo was achieved with sodium valproate treatment (-3.29; 95% CI, -4.22 to -2.36). Significant improvements compared to placebo were also observed with venlafaxine (-2.20), oxycodone (-1.45), tapentadol (-1.40), gabapentin (-1.30), tramadol (-1.13), lidocaine 5% (-1.08), pregabalin ≥300 mg (-1.06) and duloxetine ≥40 mg (-0.96). Smaller yet significant improvements occurred with lamotrigine (-0.53), lacosamide (-0.52), pregabalin ≤150 mg (-0.41), and duloxetine ≤20 mg (-0.39). No statistically significant improvements in Numerical Rating Scale occurred following treatment with zonisamide, pentoxifylline, amitriptyline, lanepitant or sativex (*P* values not reported). There was no statistically significant difference in Numerical Rating Scale score between patients treated with amitriptyline compared to gabapentin (difference, -0.007; 95% CI, -5.06 to 5.04) or pregabalin ≥300 mg compared to lidocaine (difference, 0.007; 95% CI, -5.238 to 5.235). Treatment with ≥300 mg pregabalin was associated with the greatest reduction in VAS for pain (-21.88; 95% CI, -27.06 to -16.68), followed by mexiletine (-18.84), amitriptyline (-15.53), tramadol (-13.39), gabapentin (-13.38) and topical capsaicin (-12.56). Significant reductions in VAS were also reported following treatment with zonisamide (-10.72), venlafaxine (-9.43), lacosamide (-6.92), oxcarbazepine (-5.93) and topiramate (-3.09).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference in VAS score between patients treated with amitriptyline compared to lidocaine (-2.763; 95% CI, -86.94 to 81.44). The probabilities of ≥30% reduction in pain were not significantly different compared to placebo for sativex (RR, 0.78; 95% CI, 0.19 to 1.66), lamotrigine (RR, 1.02; 95% CI, 0.80 to 1.25) and duloxetine ≤20 mg/day (RR, 1.24; 95% CI, 0.89 to 1.60). Lidocaine treatment had the highest probability of ≥30% reduction (RR, 1.84; 95% CI, 1.39 to 2.21). The risk of ≥50% pain reduction ranged from 0.98 (95% CI, 0.56 to 1.52) with amitriptyline to 2.25 (95% CI, 1.51 to 3.00) with alpha-lipoic acid 600 to 1,800 mg). Secondary: Treatment with imipramine had the highest discontinuation rate (RR, 3.96; 95% CI, 3.06 to 4.28), followed by zonisamide (RR, 3.44) and alpha lipoic acid (RR, 2.70). Tramadol was associated with the lowest risk of discontinuation compared to placebo (RR, 0.71; 95% CI, 0.49 to 0.98). No pharmacologic treatments were associated with significantly lower rates of adverse events compared to placebo. Oxycodone, pregabalin ≥300 mg, amitriptyline and duloxetine ≥40 mg were associated with significantly higher rates of adverse events compared to placebo (*P* values not reported).

Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, ES=extension study, ITT=intention-to-treat, MA=meta-analysis, MC=multicenter, NI=non inferiority, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, 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: AUC=area under the curve, BPI-MSF=Brief Pain Inventory Modified Short Form, BID=twice-daily, CrCl=creatinine clearance, DBP=diastolic blood pressure, 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, LANSS=Leeds assessment of neuropathic symptoms and signs, MDD=major depressive disorder, PHN=postherpetic neuralgia, PI-NRS=point pain intensity numerical rating scale, POMS=Profile of Mood States, QD=once-daily, QID=four times daily, SF-36=Short Form 36, SF-MPQ=Short Form-McGill Pain Questionnaire, SBP=systolic blood pressure, TID=three times daily, VAS=visual analog scale, WMD=weighted mean difference

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 (creatinine clearance <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. Approved for use in the treatment of partial seizures 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	Dose adjustment may be required in the elderly depending on renal function. 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 lability	-	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	-	-	-	-	-	✔
Hypoesthesia	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
Lightheadedness	-	-	-	-	✔	-
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	-	-	-	-	-	✔
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	-	-
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	-	-	-	-	-	✔
Cervicitis	-	-	-	-	-	✔
Cystitis	-	✔	-	-	-	-
Decreased libido	3 to 6	✔	-	<2	-	✔
Dysmenorrhea	-	✔	-	-	-	✔
Dyspareunia	-	-	-	-	-	✔
Dysuria	1	✔	-	-	-	✔
Ejaculation delayed	<3	-	-	-	-	-
Ejaculation dysfunction	<3	-	-	-	-	-
Erectile dysfunction	1 to 4	-	-	-	-	-
Epididymitis	-	-	-	-	-	✔
Female lactation	-	-	-	-	-	✔
Glomerulitis	-	-	-	-	-	✔
Gynecomastia	-	✔	-	-	-	-
Hematuria	-	✔	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
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	-	-	-	-	-	✔
Leukocytosis	-	-	-	-	-	✔
Leukopenia	<1	1.1	-	-	-	✔
Lymphadenopathy	<1	✔	-	-	-	✔
Myelofibrosis	-	-	-	-	-	✔
Polycythemia	-	-	-	-	-	✔
Prothrombin decreased	-	✔	-	-	-	✔
Purpura	-	✔	-	-	-	✔
Thrombocythemia	-	-	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
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
Gamma-glutamyl transpeptidase elevated	-	✔	-	-	-	-
Glucose tolerance decrease	-	-	-	-	-	✔
Gout	-	✔	-	-	-	-
Hepatic steatosis	<1	-	-	-	-	-
Hot flashes	2	-	-	-	-	-
Hypercholesterolemia	<1	-	-	-	-	-
Hyperglycemia	-	1.2	-	-	-	-
Hyperlipidemia	<1	-	-	-	-	-
Hypoglycemia	1	✔	-	-	-	1 to 3
Hyponatremia	<1	-	-	-	-	-
Lactic dehydrogenase increase	-	✔	-	-	-	-
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
Arthritis	-	✔	-	-	-	-
Arthrosis	-	✔	-	-	-	✔
Back pain	3	1.8	1.7	-	-	1 to 4
Breast pain	-	✔	-	-	-	-
Chondrodystrophy	-	-	-	-	-	✔
Fracture	-	1.1	-	-	-	-
Generalized spasm	-	-	-	-	-	✔
Joint swelling	-	-	✔	-	-	-

Adverse Event	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
Leg cramps	-	✔	-	-	-	✔
Muscle cramp	4 to 5	-	-	-	-	-
Muscle spasms	3	-	-	-	-	2 to 4
Muscle tightness	1	-	-	-	-	-
Myalgia	1 to 3	2.0	-	-	-	✔
Myasthenia	-	✔	-	-	-	1
Neck pain	-	✔	-	-	-	-
Neck rigidity	-	-	-	-	-	✔
Neuropathy	-	-	-	-	-	2 to 9
Pain in extremity	-	-	1.9	-	-	-
Paraesthesia	2	-	-	-	-	-
Pelvic pain	-	✔	-	-	-	✔
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
Hiccups	-	✔	-	-	-	✔
Hoarseness	-	✔	-	-	-	-
Hyperventilation	-	✔	-	-	-	-
Hypoxia	-	-	-	-	-	-
Laryngitis	-	✔	-	-	-	-
Laryngismus	-	-	-	-	-	✔
Lung edema	-	✔	-	-	-	✔
Lung fibrosis	-	-	-	-	-	✔
Mucositis	-	✔	-	-	-	-
Nasal obstruction	-	✔	-	-	-	-

Adverse Event	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
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	-	-	-	-
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
Ear infection	-	1.2	-	-	-	✔
Ear pain	-	✔	-	-	-	-
Epistaxis	-	✔	-	-	-	-
Exophthalmoses	-	-	-	-	-	✔
Extraocular palsy	-	-	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
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
Gingivitis	<1	✔	-	-	-	-
Glaucoma	<1	✔	-	-	-	-
Glossitis	-	✔	-	-	-	-
Granuloma	-	-	-	-	-	✔
Gum hemorrhage	-	✔	-	-	-	-
Hangover effect	-	✔	-	-	-	✔
Hepatitis	<1	✔	-	-	-	-
Hepatomegaly	-	✔	-	-	-	-
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	-	-	-	-	-	✔
Nephropathy	<1	-	-	-	-	-
Night blindness	-	-	-	-	-	✔
Ophthalmoplegia	-	-	-	-	-	✔

Adverse Event	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
Orgasm abnormality	2	-	-	-	-	-
Oropharyngeal edema	<1	-	-	-	-	-
Otic atrophy	-	-	-	-	-	✔
Overdose	-	-	-	-	-	✔
Pain	-	-	1.1	-	-	4 to 5
Pancreatitis	-	✔	-	-	-	✔
Papilledema	-	-	-	-	-	✔
Parosmia	-	-	-	-	-	✔
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	Gabapentin Enacarbil	Lidocaine Patch	Pre-gabalin
Concomitant use with monoamine oxidase inhibitors	✔*	-	-	-	-	-
History of sensitivity to amide-type anesthetics	-	-	-	-	✔	-
Hypersensitivity to the drug or its ingredients	✔	✔	✔	✔	✔	✔

*Contraindicated when used with monoamine oxidase inhibitors intended to treat psychiatric disorders or within 14 days of stopping a monoamine oxidase inhibitor intended to treat psychiatric disorders is also contraindicated.

Boxed Warnings

Boxed Warning for Cymbalta® (duloxetine)[1]

WARNING
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients.

Warnings/Precautions

Table 8. Warnings and Precautions[1-8]

Warning/Precaution	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
Abnormal bleeding; the risk is higher with concomitant administration of aspirin, nonsteroidal anti-inflammatory drugs and anticoagulants	✔	-	-	-	-	-
Abrupt discontinuation; symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea have been reported without tapering the dose down over one week	✔	-	-	✔	-	✔
Accidental exposure in children; small children or pets may suffer serious adverse effects from chewing or ingesting a new or used patch.	-	-	-	-	✔	-
Activation of mania/hypomania; use with caution in patients with a history of mania.	✔	-	-	-	-	-
Angioedema; has been reported during initial and maintenance treatment	-	-	-	-	-	✔
Angle-closure glaucoma may occur in patients due to pupillary dilation resulting in an angle closure attack in patients with anatomically narrow angles who does not have a patent iridectomy.	✔	-	-	-	-	-
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; discontinue treatment if marked elevations occur	-	-	-	-	-	✔
Decreased platelet count; has been reported	-	-	-	-	-	✔

Warning/Precaution	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
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 throughout treatment.	✔	-	-	-	-	-
Excessive dosing; application to larger areas or for a longer duration than recommended may result in increased lidocaine absorption and risk of adverse events.	-	-	-	-	✔	-
External heat sources; the placement of external 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; reported with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors	✔	-	-	-	-	-
Neuropsychiatric effects; use in children three 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	-	✔	✔	✔	-	-
Ophthalmological effects; have been reported (primarily blurred vision)	-	-	-	-	-	✔
Orthostatic hypotension and syncope have been	✔	-	-	-	-	-

Warning/Precaution	Duloxetine	Gabapentin	Gabapentin Extended-Release	Gabapentin Enacarbil	Lidocaine Patch	Pregabalin
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; not evaluated in 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; clinically important changes in blood pressure have not been reported; however, the long-term cardiovascular effect is 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	Management of fibromyalgia: Capsule: initial, 30 mg QD; maintenance, 60 mg QD; maximum, 60 mg QD Management of chronic musculoskeletal pain: Capsule: initial, 30 mg 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 Treatment of major depressive disorder: Capsule: initial, 40 to 60 mg/day divided BID or 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	Adjunctive therapy in the treatment of partial seizures in pediatric patients five 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	Capsule: 100 mg 300 mg 400 mg Solution: 250 mg/5 mL Tablet: 600 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Management of postherpetic neuralgia: Capsule, solution, tablet: initial, 300 mg QD for one day, 300 mg BID for one day, and 300 mg TID for one day; maintenance, 600 mg TID; note: additional benefit of using doses >1,800 mg daily was not demonstrated	Adjunctive therapy in the treatment of partial seizures in pediatric patients three to four years of age: Capsule, solution, tablet: initial, 10 to 15 mg/kg/day divided TID for three days; maintenance, 40 mg/kg/day divided TID	800 mg
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	Safety and efficacy in children have not been	Capsule: 25 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	seizures: Capsule: initial, 150 mg/day 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, 300 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/day 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, management of neuropathic pain associated with spinal cord injury: Capsule: initial, 150 mg/day divided BID or TID; maintenance, 300 mg/day divided BID or TID; maximum, 600 mg/day divided BID or TID	established.	50 mg 75 mg 100 mg 150 mg 200 mg 225 mg 300 mg Oral solution: 20 mg/mL

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

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
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. • 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.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[11]	<u>Painful polyneuropathy</u> • 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. • 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	<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.

Clinical Guideline	Recommendations
Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[12]	• Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants • 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. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options • 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. Nonpharmacologic options • Percutaneous electrical nerve stimulation should be considered for 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 Developing a Diabetes Mellitus Comprehensive Care Plan (2011)**[13]	Diabetic neuropathy • Diabetic painful neuropathy is diagnosed clinically and must be differentiated from other painful conditions. • Interventions that reduce oxidative stress, improve glycemic control, and/or improve dyslipidemia and hypertension might have a beneficial effect on diabetic neuropathy. • Exercise and balance training may also be beneficial. • Tricyclic antidepressants, anticonvulsants, and serotonin and norepinephrine reuptake inhibitors are useful treatments. • Large-fiber neuropathies are managed with strength, gait, and balance training; pain management; orthotics to treat and prevent foot deformities; tendon lengthening for pes equinus from Achilles tendon shortening; and/or surgical reconstruction and full contact casting as needed. • Small-fiber neuropathies are managed with foot protection (e.g., padded socks), supportive shoes with orthotics if necessary, regular foot and shoe inspection, prevention of heat injury, and use of emollient creams; however, for pain management, the medications mentioned above must be used.
American Diabetes Association: **Diabetic**	Algorithm for the management of symptoms diabetic polyneuropathy • Exclude nondiabetic etiologies, followed by,

Clinical Guideline	Recommendations
Neuropathies (2005)[14]	• 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 Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[15]	Diabetic Neuropathy: • All patients should be screened for distal symmetric polyneuropathy starting at diagnosis of type 2 diabetes and five years after the diagnosis of type 1 diabetes and at least annually thereafter. • Medications for the relief of specific symptoms related to painful DPN and autonomic neuropathy are recommended because they may reduce pain. • There is limited clinical evidence regarding the most effective treatments for individual patient needs given the wide range of available medications. • Neither pregabalin nor duloxetine affords complete relief, even when used in combination. Venlafaxine, amitriptyline, gabapentin, valproate and opioids (morphine sulfate, tramadol, and oxycodone controlled-release) may also be effective and could be considered for treatment of painful DPN. • Given the range of partially effective treatment options, a tailored and step-wise pharmacological strategy with careful attention to relative symptom improvement, medication adherence, and medication side effects is recommended to achieve pain reduction and improve quality of life.

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. Only gabapentin immediate-release is available generically in various formulations. Pregabalin is the only agent within this review that is classified as a Schedule V controlled substance.

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.[16] 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 (SF)-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.[17,18] Duloxetine was non-inferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin.[19] 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.[62]

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 and American Diabetes Association state that tricyclic antidepressants, duloxetine, gabapentin, pregabalin, sodium valproate and venlafaxine should be considered.[12,14,15]

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