# New and Emerging Treatment Options for Neuropathic Pain

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***Abstract***

A large number of neuroanatomical, neurophysiologic, and neurochemical mechanisms are thought to contribute to the development and maintenance of neuropathic pain (NP). As a result, a corresponding wide range of treatments have been employed to treat patients with NP, including antiepileptic drugs, opioid analgesics, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, *N*-methyl-D-aspartate receptor antagonists, cholecystokinin receptor antagonists, adenosine, lipoic acid, cannabinoids, isosorbide dinitrate, dronabinol, capsaicin, protein kinase C inhibitors, aldose reductase inhibitors, and VR-1 receptor modulators. Many of these compounds are limited by marginal efficacy and clinically significant adverse events; few have been evaluated in well-controlled, large-scale clinical trials. At present, the only agents approved for the treatment of painful diabetic peripheral neuropathy and postherpetic neuralgia are lidocaine patches 5%, duloxetine, gabapentin, and pregabalin. Of these, only pregabalin is indicated for both conditions.

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Neuropathic pain (NP) is a complex condition that has been the subject of considerable basic and clinical research. As a result of this effort, considerable progress has been made in our understanding of the pathophysiology underlying NP. Mechanisms now thought to be involved in the development and maintenance of NP include alterations in peripheral nerves, dorsal root ganglia, and the spinal cord. These changes include upregulation and/or downregulation of neuropeptides and neurotransmitters and changes that occur at supraspinal sites and result in facilitation of pain transmission.[1] Given the wide range of neuroanatomical, neurophysiologic, and neurochemical changes thought to be involved in NP, it should not be surprising that a large number of compounds with peripheral and/or central neuronal or non-neuronal targets have been used in the treatment of this condition, including 2 of the most common causes of NP: diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN).

## AGENTS USED TO TREAT NEUROPATHIC PAIN

Many different drugs have been employed for the treatment of NP (**Table**). These include a wide range of antiepileptic drugs (AEDs), including carbamazepine, phenytoin, oxcarbazepine, lamotrigine, valproic acid, gabapentin, topiramate, and pregabalin. AEDs may have multiple actions that provide clinical benefits in the treatment of patients with NP. Agents including carbamazepine, oxcarbazepine, gabapentin, pregabalin, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate reduce high-frequency repetitive firing in neurons via blockade of voltage-dependent sodium and calcium channels. Other agents (eg, phenobarbital, tiagabine, topiramate, vigabatrin, valproate) may either enhance inhibitory neurotransmission or directly interfere with excitatory transmission.[2]

Older AEDs may be limited by pharmacokinetic factors and high risk for adverse

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**Table.** Treatment Options for Neuropathic Pain

| Antidepressants | Anticonvulsants | Opioids | NMDA antagonists | Antiarrhythmics | Topical agents | Cannabinoids | Glycine antagonists |
|---|---|---|---|---|---|---|---|
| Amitriptyline | Carbamazepine | Methadone | Dextromethorphan | Mexiletine | Lidocaine patch | Dronabinol | GV196771 |
| Bupropion | Gabapentin | Morphine | Memantine | | Lidocaine gel | THC 129 | |
| Citalopram | Lamotrigine | Oxycodone | Riluzole | | Capsaicin | CT3 | |
| Clomipramine | Phenytoin | Tramadol | | | | | |
| Desipramine | Pregabalin | | | | | | |
| Duloxetine | Topiramate | | | | | | |
| Fluoxetine | Valproate | | | | | | |
| Imipramine | | | | | | | |
| Maprotiline | | | | | | | |
| Nortriptyline | | | | | | | |
| Paroxetine | | | | | | | |
| Venlafaxine | | | | | | | |

NMDA indicates *N*-methyl-D-aspartate.
*Sources:* Finnerup NB, et al. *Pain.* 2005;118:289-305; Wallace MS, et al. *Neurology.* 2002;59:1694-1700.

events (AEs); and newer agents have been the focus of recent studies.[3-5] However, there is, at present, insufficient information from controlled clinical trials to support use of most of these agents in patients with NP.[5]

Opioids have also been used to treat patients with NP, and their use is supported by the results of recent clinical trials that have demonstrated the efficacy of oxycodone, morphine, and levorphanol in patients with PHN, DPN, and other neuropathic pain conditions.[6] Aside from butorphanol and nalbuphine, all widely used opioids are selective for μ-opioid receptors. Butorphanol and nalbuphine are selective for κ-opioid receptors, are limited by partial agonist activity, have a high risk for central side effects (eg, dysphoria, sedation, and hallucinations), and are not generally used in the treatment of NP.[7]

Most opioid analgesics are limited by high rates of AEs, including constipation, sedation, and nausea. These drugs should also be used with extreme caution in patients with a history of addictive behavior.[6] Tramadol, an agent that combines opioid receptor antagonist activity with norepinephrine (NE) reuptake inhibition, may have value for the treatment of NP.[3] Results from one small-scale clinical trial have demonstrated the effectiveness of tramadol in patients with polyneuropathy.[8-10]

Tricyclic antidepressants (TCAs) have been used extensively in the treatment of NP. These agents are thought to inhibit pain transmission in the spinal cord by increasing levels of NE and serotonin (5-HT) as a result of their ability to prevent the reuptake of these amines after they are released from synaptic terminals. TCAs might also affect histaminergic, cholinergic, and glutamatergic neurotransmission, and they appear to block sodium channels.[3,11] TCAs are associated with a wide range of AEs, some potentially serious, which include exacerbation of glaucoma, urinary retention, constipation, dry mouth, blurred vision, cognitive changes, tachycardia, weight gain, orthostatic hypotension, and falls.[11]

Selective serotonin reuptake inhibitors are generally believed to be less effective than TCAs for the treatment of NP in some patients, although this is somewhat controversial.[6] Serotonin-NE reuptake inhibitors (SNRIs) have also been used to treat NP; duloxetine and venlafaxine have been shown to be effective in treating and preventing postmastectomy pain syndrome, DPN, and painful polyneuropathy.[12-14] The use of duloxetine is discussed later in this article.

A variety of other therapies are being evaluated in the treatment of NP. These include *N*-methyl-D-aspartate receptor antagonists (ketamine, lidocaine, glycine,

dextromethorphan, amantadine), cholecystokinin receptor antagonists, adenosine, lipoic acid, cannabinoids, isosorbide dinitrate, dronabinol, capsaicin, protein kinase C inhibitors, aldose reductase inhibitors, and VR-1 receptor modulators (Table).[3,15,16]

Antiviral agents, including aciclovir, famciclovir, and valacyclovir, have also been assessed in patients with herpes zoster for their role in the prevention of PHN or lessening its severity. Results of clinical trials indicate that all 3 agents mentioned decrease both zoster pain and the risk of developing PHN.[17] A review of the results for famciclovir indicated that older age, rash severity, and acute pain severity are risk factors for prolonged PHN. In addition, these results demonstrated that treatment of patients with acute herpes zoster with famciclovir significantly reduced both the duration and prevalence of PHN.[18] It may be useful to combine antiviral therapy with treatments directed at PHN pain in patients with herpes zoster infections.

New therapies with novel mechanisms of action are also being developed for the management of DPN. Elevated homocysteine has been shown to be an independent risk factor for the development of DPN,[19] and the combination of l-methylfolate, pyridoxal-5'-phosphate, and methylcobalamin has been shown to be effective in lowering homocysteine levels and decreasing the symptoms of diabetic neuropathy.[20]

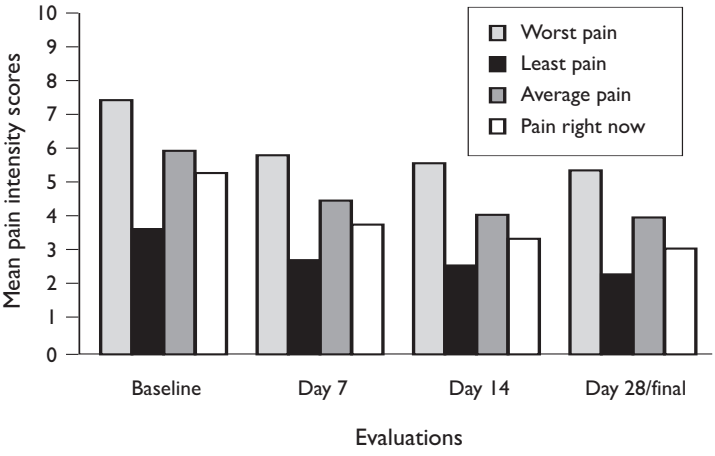
At present, none of these treatments has demonstrated sufficient efficacy in controlled clinical trials to warrant approval for the treatment of NP by the US Food and Drug Administration. In fact, the only agents currently indicated for the treatment of painful DPN are duloxetine and pregabalin, and only lidocaine patches 5%, gabapentin, and pregabalin are approved for the treatment of patients with PHN. Carbamazepine is approved for the treatment of trigeminal neuralgia. The rest of this article reviews the pharmacodynamics (mechanism of action) and pharmacokinetics, clinical efficacy and safety, and dosing regimens for these agents.

### Lidocaine Patches 5%

Lidocaine patches 5% are indicated for the relief of pain associated with PHN.[17] The mechanism of action of lidocaine in the treatment of NP is stabilization of membranes by inhibiting ionic fluxes necessary for the conduction of action potentials.[21] The amount of lidocaine systemically absorbed from lidocaine patches 5% is directly related to both the duration of application and to the surface area over which they are applied. When lidocaine patches 5% are used according to the recommended dosing instructions, only 3% of the applied dose is expected to be absorbed. At least 95% of lidocaine remains in the patch. The peak plasma concentration of lidocaine in subjects treated with these patches in pharmacokinetic studies is approximately 10% of the lidocaine level associated with cardiac activity and 3% of that associated with toxicity.[21,22]

The effectiveness of lidocaine patches 5% in the treatment of patients with PHN has been demonstrated in 2 small-scale, placebo-controlled studies and 1 larger-scale, open trial. In all 3 trials, lidocaine patches 5% provided significant pain relief relative to baseline and/or placebo (**Figure 1**).[23-25] Application site reactions are the AEs most commonly associated with lidocaine patches 5%. They are generally mild to moderate in severity and do not often result in treatment discontinuation.[26]

**Figure 1.** Mean Pain Intensity and Pain Relief Scores in Patients Treated With Lidocaine Patches 5%




*P* = .0001 vs baseline for all pain intensity measures.
*Source:* Reprinted with permission from Reference 25.

Lidocaine patches 5% are applied to intact skin to cover the most painful area. Up to 3 patches may be applied. Patches should be applied only once for up to 12 hours during a 24-hour period.[21]

**Duloxetine**

Duloxetine, a balanced SNRI, is indicated for the management of NP associated with DPN.[27] Although the mechanism of action underlying pain relief with duloxetine is not completely understood, it is thought to be related to its ability to increase NE and 5-HT activity in the central nervous system. As noted above, these actions are also believed to underlie the ability of TCAs to relieve NP.[28]

Absorption of duloxetine is relatively slow, with peak plasma concentrations ($C_{max}$) achieved about 6 hours after dosing. Administration of duloxetine with food slows absorption, and delivery in the evening versus the morning slows absorption and increases clearance by about 33%. Duloxetine is highly protein bound (>90%). After absorption, duloxetine is rapidly metabolized by cytochrome P450 2D6 and 1A2. It has been suggested that the metabolism of duloxetine may result in as many as 25 metabolites, most of which are glucuronide conjugates. Several primary metabolites of duloxetine are active at the 5-HT and/or NE transporters. The elimination half-life of duloxetine is approximately 12 hours.[28,29]

Approval of duloxetine for the treatment of NP secondary to DPN is based on results from 2 large-scale, randomized, double-blind, placebo-controlled, 12-week trials in patients with DPN and pain. These 2 trials enrolled a total of 791 patients with type 1 or 2 diabetes with a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for ≥6 months. The patients had a baseline pain score of ≥4 on an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain). Both studies compared duloxetine 60 mg once daily or 60 mg twice daily with placebo. Treatment with both of these duloxetine doses significantly improved end point mean pain scores from baseline and increased the proportion of patients with ≥50% reductions in pain scores from baseline. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study (**Figure 2**).[27,30,31]

Duloxetine is generally well-tolerated. The AEs observed most often in clinical trials of patients with DPN involved the gastrointestinal system and the nervous system. These included nausea, constipation, decreased appetite, somnolence, headache, dizziness, insomnia, fatigue, and dry mouth.[27] Discontinuations due to AEs occurred in about 4% of patients treated with 60 mg/day of duloxetine and 12% to 19% of those who received 120 mg/day of duloxetine.[30,31]

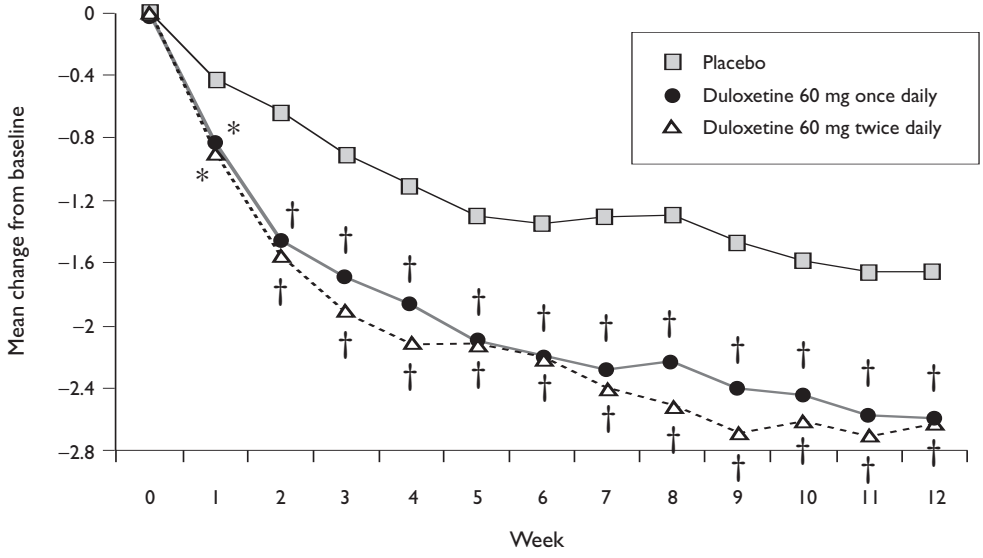
Duloxetine should be administered once daily at a dose of 60 mg, without regard to meals. Although a dose of 120 mg/day was shown to be safe and effective, there is no evidence that doses higher than 60 mg/day confer additional significant benefit, and the higher dose is clearly less well-tolerated. Because diabetes is frequently complicated by renal disease, a lower starting dose and gradual titration should be considered for patients with renal impairment.[27]

**Gabapentin**

Gabapentin is indicated for the management of PHN in adults. This molecule is structurally related to the neurotransmitter gamma-aminobutyric acid, but it does not interact significantly with this or other neurotransmitter systems.[32] Although the mechanism underlying the ability of gabapentin to relieve PHN is not understood, available information suggests that it may be binding to high-affinity sites on $\alpha_2\delta$ subunits of voltage-activated calcium channels. This binding is thought to decrease $Ca^{2+}$ influx into nerve terminals and reduce the release of neurotransmitters, including glutamate and NE.[33,34]

Gabapentin is rapidly absorbed after oral administration. Absorption is mediated, at least in part, by a transport mechanism that becomes saturated at higher doses. This reduces the bioavailability of gabapentin as the dose is increased. For example, the bioavailability of gabapentin at a dose of 300 mg is about 60%, and this falls to 40% with a 600-mg dose. The $C_{max}$ for gabapentin is reached 3.2 hours after oral administration, and the drug does not exhibit significant

**Figure 2.** Mean Change in 24-hour Average Pain Severity Score




*$P \leq .01$ vs placebo.
†$P \leq .001$ vs placebo in patients treated with duloxetine or placebo.
*Source:* Reprinted with permission from Reference 30.

protein binding. Gabapentin is eliminated as an unchanged drug via the kidneys and has no interactions with hepatic enzymes. The elimination half-life for gabapentin is 6 to 8 hours.[35]

The indication for gabapentin in patients with PHN is supported by results from 2 multicenter, randomized, double-blind, placebo-controlled trials that included a total of 563 patients with PHN, which was defined as pain for >3 months after healing of the herpes zoster skin rash. Each trial included a 1-week baseline phase followed by 7 or 8 weeks of double-blind treatment. The target doses for gabapentin in the 7-week trial were 1800 mg/day and 2400 mg/day, and the maximum dose in the 8-week trial was 3600 mg/day. Results from these 2 studies indicated significant superiority of gabapentin over placebo at all evaluated doses. Significant reductions in weekly mean pain scores were apparent at the end of the first week of treatment and were maintained until the end of the study (**Figure 3**).[32,36,37]

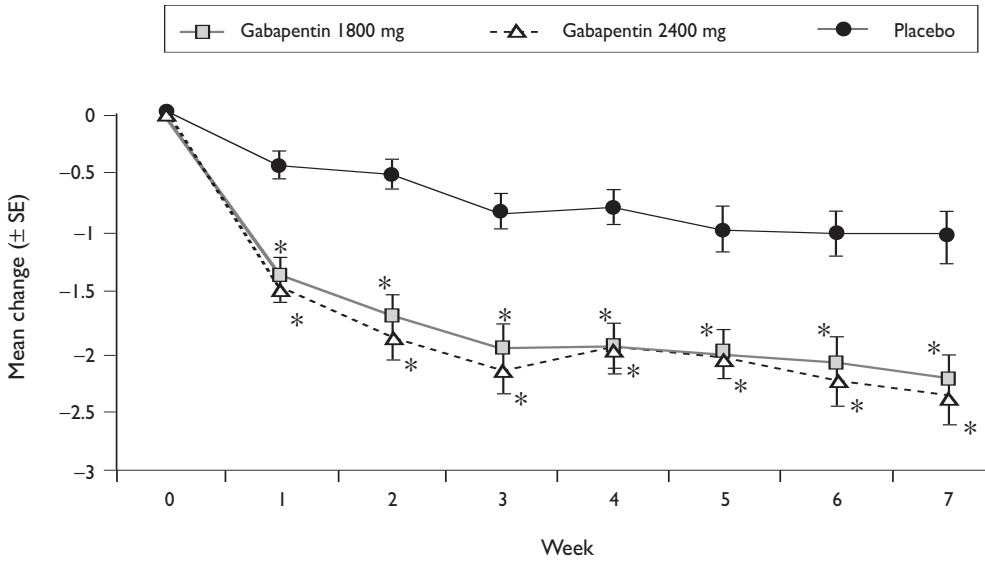
The AEs observed most often in clinical trials of patients with PHN who were treated with gabapentin and not seen with the same frequency in subjects who received placebo included dizziness, somnolence, and peripheral edema. Discontinuation due to AEs occurred in 16% of patients who received gabapentin and 9% of those treated with placebo in these studies.[32]

In adults with PHN, gabapentin therapy may be initiated as a single 300-mg dose on day 1, 600 mg/day on day 2 (divided into 2 doses), and 900 mg/day on day 3 (divided into 3 doses). The dose can be titrated up as needed for pain relief to a maximum daily dose of 1800 to 3600 mg (divided into 3 doses). The dose of gabapentin should be reduced in patients with renal impairment and in the elderly.[32]

**Pregabalin**

Pregabalin is indicated for the treatment of NP associated with DPN and for PHN. The mechanism of action for pregabalin, insofar as it is currently understood, appears to be the same as that for gabapentin. It binds with high affinity to $\alpha_2\delta$ subunits of voltage-activated calcium channels, blocks $Ca^{2+}$ influx into nerve terminals, and decreases transmitter release.[38-40] Thus, the mechanism of action of pregabalin appears to be

**Figure 3.** Change From Baseline in Average Daily Pain Scores in Patients Treated With Gabapentin or Placebo




*$P$ <.01 vs placebo.
SE indicates standard error.
*Source:* Reprinted with permission from Reference 37.

identical to that of gabapentin. Currently available information supports the view that the pharmacologic profiles for these drugs are indistinguishable: both exert their effects via inhibition of calcium currents mediated by high-voltage–activated channels that include the $\alpha_2\delta$-1 subunit. This leads to reduced neurotransmitter release and attenuation of postsynaptic excitability.[41]

Pregabalin is well-absorbed after oral administration, with a time to $C_{max}$ of 1.5 hours and bioavailability >90%. The rate of pregabalin absorption is decreased when given with food, but there is no clinically relevant effect on the total absorption. Unlike that of gabapentin, the pharmacokinetic profile of pregabalin is linear and dose proportional at doses up to 900 mg/day. Pregabalin does not bind to plasma proteins, and it is eliminated primarily via renal excretion, with a half-life of about 6 hours; and as for gabapentin, it does not undergo significant metabolism.[38,39] The lack of significant hepatic metabolism for both pregabalin and gabapentin contrasts with the extensive oxidative hepatic metabolism of duloxetine.

The indication of pregabalin in painful DPN is based on results from 3 multicenter, randomized, double-blind, placebo-controlled trials that enrolled a total of 729 patients with type 1 or type 2 diabetes and a diagnosis of painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. Patients enrolled in these 2 studies had a minimum mean baseline pain score of ≥4 on an 11-point numerical pain rating scale. In the first trial, pregabalin was dosed at 75, 300, or 600 mg/day; in the second trial, the pregabalin dose was 300 mg/day; and in the third, it was 150 or 600 mg/day. Results from the 3 trials indicated significant superiority of pregabalin doses ≥300 mg/day over placebo in decreasing mean pain scores. Pregabalin was significantly superior to placebo by the end of week 1, and this benefit was maintained for the duration of each study (**Figure 4**). Patients treated with pregabalin also had significantly decreased sleep interference scores.[38,42-44]

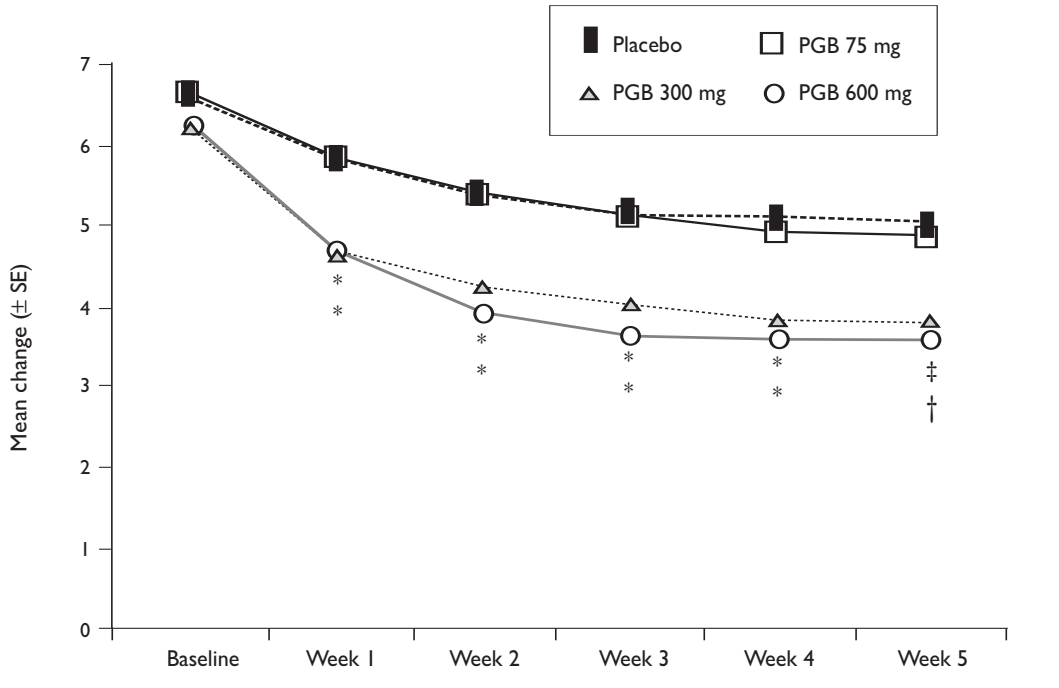
The efficacy of pregabalin for the treatment of PHN was established in 3 double-blind, placebo-controlled, multicenter studies that enrolled a total of 779 patients with neural-

gia persisting for ≥3 months after healing of herpes zoster rash and a minimum baseline score of ≥4 on an 11-point numerical pain rating scale. In the first of these trials, pregabalin was dosed at 150 or 300 mg/day; in the second, patients received 300 or 600 mg/day based on creatinine clearance; and in the third, patients received 150, 300, or 300/600 mg/day based on creatinine clearance. Results from these trials indicated that all pregabalin doses were significantly superior to placebo in decreasing pain scores and that active treatment was also significantly superior to placebo in improving sleep. The superior efficacy of pregabalin over placebo was apparent by the first week of treatment and was sustained for the duration of each study (**Figure 5**).[38,45,46]

Pregabalin was well-tolerated in patients with painful DPN or PHN. The most common AEs were dizziness, somnolence, and peripheral edema.[38] These AEs are similar to those reported most often for gabapentin. Additional studies with pregabalin have demonstrated the effectiveness of flexible dosing with this agent,[47] and high completion rates in clinical trials suggest that its use should promote high adherence in routine clinical practice.

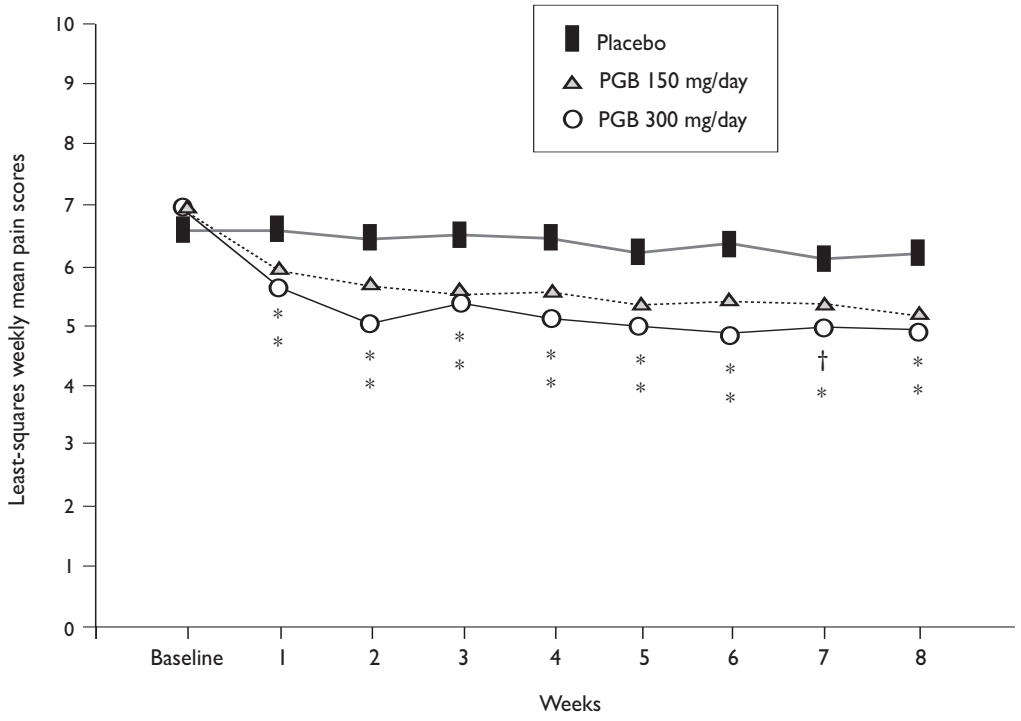
For patients with painful DPN, the maximum recommended dose of pregabalin is 100 mg 3 times daily (300 mg/day). In patients with creatinine clearance ≥60 mL/min, dosing should begin at 50 mg 3 times daily (150 mg/day) and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. The dose of pregabalin should be adjusted for patients with reduced renal function. For patients with PHN, the recommended dose of pregabalin is 75 to 150 mg twice daily, or 50 to 100 mg 3 times daily (150-300 mg/day). In patients with creatinine clearance ≥60 mL/min, dosing should begin at

**Figure 4.** Least-squares Mean Pain Scores by Week for Pregabalin or Placebo




*$P$ = .001.
†$P$ <.005.
‡$P$ <.001.
PGB indicates pregabalin; SE, standard error.
*Source:* Reprinted with permission from Reference 42.

**Figure 5.** Weekly Least-squares Mean Pain Scores for Pregabalin Versus Placebo




*$P$ <.01.
†$P$ <.05.
PGB indicates pregabalin.
*Source:* Reprinted with permission from Reference 45.

75 mg twice daily, or 50 mg 3 times daily (150 mg/day), and may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief after 2 to 4 weeks of treatment with 300 mg/day pregabalin may be treated with up to 600 mg/day in divided doses.[38]

## CONCLUSION

A wide range of medications with an equally broad spectrum of mechanisms of action, efficacy, and tolerability profiles have been employed for the treatment of NP. Newer antiepileptic drugs appear to have several distinct advantages over older agents in this class and medications from other classes as therapy for NP. Two of the more recently developed antiepileptic drugs, gabapentin and pregabalin, appear to have a single specific mechanism of action. In addition, neither of these drugs undergoes significant metabolism, thus eliminating potential problems that may be associated with active metabolites that have unfavorable pharmacokinetic or pharmacodynamic profiles. The lack of hepatic metabolism for these drugs may also decrease the risk for clinically important pharmacokinetic interactions.

Although pregabalin and gabapentin are very similar in many respects, the pharmacokinetic profile for pregabalin confers an important advantage over gabapentin. The linear pharmacokinetics for pregabalin result in predictable changes in plasma drug concentrations when the dose is increased or decreased. This is not the case for gabapentin, which has nonlinear pharmacokinetics with decreasing absorption at higher doses. Pregabalin is approved for the treatment of both painful DPN and PHN and it appears to fill previously unmet needs in

the management of patients with NP. Pregabalin will require further observation and phase 4 trials to determine if it meets this need.

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