

Treatment of Neuropathic Pain: An Overview of Recent Guidelines

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ABSTRACT

A number of different treatments for neuropathic pain have been studied, but the literature is sizable, rapidly evolving, and lacks important information about practical aspects of patient management. Under the auspices of the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG), a consensus process was used to develop evidence-based guidelines for the pharmacologic management of neuropathic pain that take into account clinical efficacy, adverse effects, impact on health-related quality of life, convenience, and costs. On the basis of randomized clinical trials, medications recommended as first-line treatments for neuropathic pain included certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel $\alpha_2\text{-}\delta$ ligands (i.e., gabapentin and pregabalin), and topical lidocaine. Opioid analgesics and tramadol were recommended as second-line treatments that can be considered for first-line use in selected clinical circumstances. Other medications that generally would be used as third-line treatments include certain other antidepressant and antiepileptic medications, topical capsaicin, mexiletine, and *N*-methyl-D-aspartate receptor antagonists. Two other national and international associations recently published pharmacologic treatment guidelines for neuropathic pain, which are summarized and contrasted with the NeuPSIG recommendations. Recent guidelines for the use of neurostimulation for the treatment of neuropathic pain also are summarized. For all treatments for neuropathic pain, long-term studies, head-to-head comparisons, and studies of treatment combinations are a priority for future research.

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Neuropathic pain can be caused by a number of different diseases (e.g., diabetes mellitus, herpes zoster, human immunodeficiency virus [HIV] infection), medical interventions (e.g., chemotherapy, surgery), and injuries (e.g., brachial plexus avulsion). It has recently been defined as “pain arising as a direct consequence of a lesion or disease affect-

ing the somatosensory system”.¹ Neuropathic pain has been shown to impair patients’ overall health-related quality of life (HRQOL), including important aspects of physical and emotional functioning such as mobility and ability to work.^{2–6} It also generates substantial costs to society.^{6–10}

Treatment of neuropathic pain is challenging. Compared with patients with nonneuropathic chronic pain, patients with neuropathic pain seem to have higher average pain scores and lower HRQOL (even after adjusting for pain scores); to require more medications; and to report less pain relief with treatment.^{11,12} In randomized clinical trials (RCTs) assessing efficacious medications for neuropathic pain, typically $\leq 50\%$ of patients experience satisfactory pain relief, and side effects (including inability to tolerate treatment) are common. In real-world settings, several cross-sectional studies have found that patients with neuropathic pain continue to have pain of moderate severity on

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average, despite taking prescribed medications for their condition.⁶ It is likely that a major part of the reason for these findings is generally poor pain management—patients with neuropathic pain are usually not prescribed medications with demonstrated efficacy for their condition, and when they do receive appropriate treatment (e.g., tricyclic antidepressants [TCAs] or gabapentin), they receive dosages that are, on average, far below the dosages with demonstrated efficacy in RCTs.⁶

The literature on neuropathic pain is evolving rapidly. A large number of RCTs of different interventions for various neuropathic pain conditions have been published over the past several years, but substantial gaps in the literature remain. For these reasons, under the auspices of the International Association for the Study of Pain (IASP) Neuropathic Pain Special Interest Group (NeuPSIG), an international consensus process that included a diverse group of pain experts was convened to develop evidence-based guidelines for the pharmacologic treatment of neuropathic pain. These guidelines were endorsed by the American Pain Society, the Canadian Pain Society, the Finnish Pain Society, the Latin American Federation of IASP Chapters, and the Mexican Pain Society.¹³ Additional consensus guidelines for the pharmacologic treatment of neuropathic pain were created simultaneously by the European Federation of Neurological Societies (EFNS)¹⁴ and the Canadian Pain Society.¹⁵ This article describes the NeuPSIG guidelines, contrasts them with the EFNS and Canadian Pain Society guidelines, and also briefly summarizes recent EFNS guidelines for the use of neurostimulation for the treatment of patients with neuropathic pain.

GENERAL CONSIDERATIONS REGARDING GUIDELINES FOR THE TREATMENT OF NEUROPATHIC PAIN

Although consensus guidelines for the treatment of neuropathic pain are based on synthesizing results from RCTs, a large number of gaps in the literature exist. For example, most of the pharmacotherapy trials have investigated patients with postherpetic neuralgia or painful diabetic peripheral neuropathy, yet there are many patients with neuropathic pain who have a different lesion or disease as the cause of their pain. This raises an important concern: to what extent is it reasonable to extrapolate results from an RCT in one neuropathic pain condition to the treatment of another neuropathic pain condition? In addition, the duration of RCTs evaluating medications in neuropathic pain disorders has been relatively short, typically ≤ 3 months. This gives rise to another important question: can efficacy established in short-term trials be reasonably extrapolated to long-term use in neuropathic pain? Most authors have concluded that, in the absence of evidence to the contrary, these extrapolations are reasonable.

There are very few head-to-head RCTs comparing different treatments in neuropathic pain, which is a major limitation in developing treatment recommendations. An-

other challenge involves comparing RCTs that, even when studying the same condition, differ substantially in research design. For example, many older RCTs of TCAs are cross-over trials, whereas newer medications have typically been assessed using a parallel group research design. In addition, recent trials have often used a run-in period (to ensure adherence) and have required pain of at least moderate baseline severity. The outcomes measured have also differed; newer RCTs have typically measured outcomes more comprehensively and have used measures (such as daily numeric ratings of pain intensity and measures of HRQOL) that were not collected in many older RCTs. One method that is sometimes used to compare the relative efficacy and tolerability of medications from different RCTs examines the numbers needed-to-treat (NNT) and the numbers needed-to-harm (NNH). However, as described above, the fact that the design and outcomes vary significantly among RCTs makes this approach problematic. Nevertheless, the EFNS and Canadian Pain Society guidelines incorporated NNT values into their recommendations.^{14,15} In general, the medications shown to be efficacious for treating neuropathic pain have NNTs between 2 and 6, typically reflecting that as many as 6 patients must be treated for 1 additional patient (relative to placebo) to experience a 50% reduction in pain. Ignoring the response to placebo, most trials of efficacious treatments have found that $\leq 50\%$ of patients achieve satisfactory pain relief.

Given that the existing literature does not allow us to definitively rank medications by efficacy, the choice of medication in an individual patient depends heavily on a number of factors, including the potential for side effects; treatment of other comorbidities (e.g., depression, difficulty sleeping); risk of drug interactions, overdose, or abuse; and cost. All of the guidelines recommend incorporating these factors into the medication choices for an individual patient.

As described below, the 3 pharmacologic guidelines differ from each other in some details. Areas of difference between the guidelines can be considered areas of controversy in the management of neuropathic pain. It is worth noting that all of the guidelines committees attempted to balance specificity with simplicity, and this balance was particularly challenging around topics where gaps in the literature exist. For example, the NeuPSIG and Canadian Pain Society guidelines grouped peripheral neuropathic pain into a single treatment category, whereas the EFNS guidelines split peripheral neuropathic pain into different conditions, including postherpetic neuralgia and painful polyneuropathy. There is basic science and clinical research evidence to support and refute both approaches. In addition, the Canadian Pain Society and EFNS guidelines incorporated rankings of efficacy based on NNTs (as described above), although this, too, is controversial. Despite these differences, the guidelines are generally consistent. It is also worth noting that the NeuPSIG guidelines were endorsed by the Canadian Pain Society, and there were a few experts who were authors of both the NeuPSIG and EFNS guidelines,

indicating that the approaches used by the different guidelines groups are considered acceptable by many experts.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN NEUROPATHIC PAIN SPECIAL INTEREST GROUP GUIDELINES FOR THE TREATMENT OF NEUROPATHIC PAIN

The NeuPSIG guidelines recommend medications as first-line treatment if multiple RCTs have demonstrated consistent efficacy in Neuropathic Pain (Oxford Centre for Evidence-based Medicine grade A recommendation¹⁶) and the authors believed them to be good first choices for patients with neuropathic pain; as second-line if multiple RCTs demonstrated consistent efficacy in neuropathic pain (grade A recommendation) but the authors had reservations about their use relative to the first-line medications; and as third-line if there was only 1 positive RCT or if the results of RCTs were inconsistent (grade B recommendation) but the authors believed that the medication may be a reasonable choice in selected patients.

These consensus guidelines are not applicable to pediatric patients or to patients with trigeminal neuralgia (tic douloureux), for whom there are distinct treatment recommendations.^{14,15} Only oral and topical pharmacologic treatments were considered. Conditions without a clearly demonstrated lesion or disease affecting the somatosensory nervous system (such as fibromyalgia or irritable bowel syndrome) were not considered neuropathic pain.

Three classes of medications were recommended as first-line treatments: antidepressants with both norepinephrine and serotonin reuptake inhibition (TCAs and selective serotonin and norepinephrine reuptake inhibitors [SSNRIs]), calcium channel α_2 - δ ligands (gabapentin and pregabalin), and topical lidocaine (lidocaine patch 5%). Opioids and tramadol were recommended as generally second-line treatments, except in certain specific clinical situations in which it was recommended that first-line use could be considered. A number of medications were considered third-line choices.

The guidelines acknowledge that a combination of medications with efficacy for neuropathic pain may provide greater analgesia than use of individual medications as monotherapy,¹⁷ although such combination therapy will often be associated with increased side effects,¹⁷ inconvenience, risk of drug interactions, and cost. Nevertheless, because $\leq 50\%$ of patients in Neuropathic Pain trials of efficacious medications typically achieve satisfactory pain relief, many patients in clinical practice will require treatment with a combination of medications. Such combination therapy was incorporated into a stepwise management strategy for patients with partial responses to treatment with first-line medications (Table 1).¹³

FIRST-LINE MEDICATIONS

Antidepressants with Both Norepinephrine and Serotonin Reuptake Inhibition (TCAs and SSNRIs)

Numerous placebo-controlled RCTs have established the efficacy of TCAs for treating a variety of types of neuropathic pain (Table 2). However, RCTs in some neuropathic pain conditions, such as painful HIV and chemotherapy peripheral neuropathies, have been negative.^{13,18}

The biggest advantages of TCAs are their low cost, once-daily dosing, and beneficial effects on depression, which is a common comorbidity with neuropathic pain. Importantly, TCAs appear to have equivalent analgesic benefits in both depressed and nondepressed patients with neuropathic pain. The biggest disadvantage of TCAs is the risk of anticholinergic side effects (such as dry mouth, constipation, and urinary retention) and orthostatic hypotension. Of the TCAs, secondary amine TCAs, including nortriptyline and desipramine, are recommended because they provide pain relief that is comparable to amitriptyline and other tertiary amine TCAs while causing fewer side effects.

Cardiac toxicity is also possible with TCAs. A small RCT found an increase in sinus tachycardia and ventricular ectopy in patients with a history of ischemic heart disease¹⁹; however, a systematic review involving a much greater number of patients with cardiovascular disease did not find an increased risk of adverse cardiovascular outcomes.²⁰ Concerns that TCAs may be associated with the development of myocardial infarction²¹ have been contradicted by much larger studies.^{22,23} Finally, a large retrospective cohort analysis found an association between sudden death and TCAs at dosages of ≥ 100 mg/day; however, dosages < 100 mg/day were not associated with sudden death (odds ratio < 1 with tight confidence intervals).²⁴ Given these data, the NeuPSIG guidelines recommend using TCAs with caution in patients with cardiac disease, checking a screening electrocardiogram for patients > 40 years of age with Neuropathic Pain, and using dosages < 100 mg/day whenever possible.

In general, TCAs should be started at low dosages, administered at night, and titrated slowly (e.g., increase dose by 25 mg every 3 to 7 days as tolerated). An adequate trial of a TCA can take 6 to 8 weeks, including 2 weeks at the maximum tolerated dosage (Table 3).¹³

Two SSNRIs, duloxetine and venlafaxine, have demonstrated efficacy in RCTs in patients with peripheral neuropathic pain. A third SSNRI, milnacipran, has been studied in RCTs in patients with fibromyalgia, but has not been evaluated in patients with neuropathic pain.

Duloxetine has consistently demonstrated efficacy in painful diabetic peripheral neuropathy,¹³ and its efficacy has been shown to be sustained over 1 year in an open-label extension of an RCT.²⁵ Unfortunately, duloxetine has not been studied in other types of neuropathic pain, and so its efficacy in such conditions is uncertain.

Table 1 Stepwise Pharmacologic Management of Neuropathic Pain**Step 1**

- Assess pain and establish the diagnosis of NP (Dworkin et al., 2003; Cruccu et al., 2004); if uncertain about the diagnosis, refer to a pain specialist or neurologist
- Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist
- Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy
- Explain the diagnosis and treatment plan to the patient, and establish realistic expectations

Step 2

- Initiate therapy of the disease causing NP, if applicable
- Initiate symptom treatment with one or more of the following:
 - Antidepressant medication: either secondary amine TCA (nortriptyline, desipramine) or SSNRI (duloxetine, venlafaxine)
 - Calcium channel α_2 - δ ligand: either gabapentin or pregabalin
 - For patients with localized peripheral NP: topical lidocaine used alone or in combination with 1 of the other first-line therapies
 - For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies
- Evaluate patient for nonpharmacologic treatments, and initiate if appropriate

Step 3

- Reassess pain and health-related quality of life frequently
- If substantial pain relief (e.g., average pain reduced to NRS $\leq 3/10$) and tolerable side effects, continue treatment.
- If partial pain relief (e.g., average pain remains NRS $\geq 4/10$) after an adequate trial (see Table 3), add 1 of the other first-line medications
- If no or inadequate pain relief (e.g., $<30\%$ reduction) at target dosage after an adequate trial (see Table 3), switch to an alternative first-line medication

Step 4

- If trials of first-line medications alone and in combination fail, consider second-line medications or referral to a pain specialist or multidisciplinary pain center

NP = neuropathic pain; NRS = numeric rating scale; SSNRI = selective serotonin and norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant. Reprinted with permission from *Pain*.¹³

The advantages of duloxetine are that it also effectively treats depression and its dosing is straightforward, with a 60 mg once-daily dosage appearing to be as effective as the 60 mg twice-daily maximum. Nausea is the most common side effect, but its frequency seems to be reduced by starting at 30 mg once daily for 1 week before increasing to 60 mg once daily. Duloxetine appears to be safe from a cardiovascular standpoint.²⁶ A recent review concluded that the risk of hepatotoxicity is similar to that for other antidepressants and that no aminotransferase monitoring is necessary.²⁷

Venlafaxine is another SSNRI that has shown efficacy at higher dosages in painful diabetic peripheral neuropathy and painful polyneuropathies of different etiologies, but not in postherpetic neuralgia.¹³ Additional RCTs have not found lower dosages of venlafaxine to be superior to placebo in trials involving neuropathic pain of other etiologies (Table 2). Venlafaxine is available in short- and long-acting preparations, and generally requires 2 to 4 weeks to titrate to an efficacious dosage (Table 3). It has been associated with cardiac conduction abnormalities in a small number of patients,²⁸ so caution should be used in patients with significant cardiovascular disease. A withdrawal syndrome has also been described. Venlafaxine should therefore be tapered when treatment is being discontinued.²⁹

A recent report in the literature has suggested a link between antidepressant treatment and thoughts of suicide, with the strongest evidence for selective serotonin reuptake inhibitors (SSRIs) in children and adolescents.³⁰ Thus, in patients with neuropathic pain, potential concerns about the risks of TCAs and SSNRIs must be balanced against the benefits of pain relief.

Calcium Channel α_2 - δ Ligands (Gabapentin and Pregabalin)

Gabapentin and pregabalin are medications that bind to voltage-gated calcium channels (at the α_2 - δ subunit), producing changes in neurotransmitter release. Both drugs have been found to be efficacious compared with placebo in several neuropathic pain conditions, although the results of some RCTs have been negative (Table 2).¹³ These medications can produce dose-related dizziness and sedation that can be ameliorated by starting with low dosages and titrating cautiously. Gabapentin and pregabalin have few drug interactions, but require dosage reduction in patients with renal insufficiency.

Gabapentin has complicated, nonlinear pharmacokinetics and is administered 3 times daily. Administration

Table 2 Summary of the Results of Randomized Clinical Trials Involving First- and Second-Line Medications for Patients With Neuropathic Pain^{*13,18}

	Antidepressants			Calcium Channel Ligands		Topical Lidocaine Patch 5%	Opioid Receptor Agonists	
	Tricyclic Antidepressants	Duloxetine	Venlafaxine	Gabapentin	Pregabalin		Opioid Analgesics	Tramadol
Peripheral NP								
Painful DPN	Positive	Positive	Positive	Both	Both	—	Positive	Positive
PHN	Positive	—	Negative	Positive	Both	Positive [†]	Positive	Positive
Painful polyneuropathy	Positive	—	Positive	Positive	—	Positive [†]	Positive	Positive
Phantom limb pain	Negative	—	—	Both	—	—	Positive	Positive
Postmastectomy pain	Positive	—	Negative	—	—	—	—	—
Guillain-Barré syndrome	—	—	—	Positive	—	—	—	—
Neuropathic cancer pain	Negative	—	—	Positive	—	—	—	—
Complex regional pain syndrome (type I)	—	—	—	Negative	—	—	—	—
Chronic lumbar root pain	Negative	—	—	—	—	—	Negative	—
Chemotherapy-induced neuropathy	Negative	—	—	Negative	—	—	—	—
HIV neuropathy	Negative	—	—	Negative	—	—	—	—
Central NP								
Central poststroke pain	Positive	—	—	—	Positive	—	—	—
Spinal cord injury pain	Negative	—	—	Positive	Positive	—	—	—

DPN = diabetic painful neuropathy; HIV = human immunodeficiency virus; NP = neuropathic pain; PHN = postherpetic neuralgia.

*“Positive” indicates that ≥ 1 trial demonstrated statistically significant pain relief for the primary outcome (compared with placebo); “negative” indicates that ≥ 1 trial failed to demonstrate statistically significant pain relief for the primary outcome (compared with placebo); and “both” indicates that ≥ 1 trial was positive and ≥ 1 trial was negative. Not all medications were tested in every NP condition.

†Trial only included patients with allodynia.

should begin with a low initial dose, with gradual titration until pain relief, dose-limiting side effects, or a dosage of 3,600 mg/day is achieved (Table 3). Because of slow titration requirements and potentially delayed onset of full analgesia, an adequate therapeutic trial can take 2 months.

Pregabalin seems to have similar efficacy and tolerability as gabapentin, but its pharmacokinetics and dosing are more straightforward. Dosing can start at 150 mg/day (which has been shown to be efficacious in some RCTs), given in 2 or 3 divided doses, and titrated up to 300 mg/day after 1 to 2 weeks (Table 3). Because of its shorter titration period and potentially efficacious starting dosage, pregabalin appears to be faster than gabapentin at providing analgesia. Dosages as high as 600 mg/day have been used, but higher dosages are not consistently more effective than 300 mg/day and are associated with a greater rate of side effects.

As with antidepressants, there is some evidence supporting a link between antiepileptic drugs and thoughts of suicide, though the link seems to be strongest for phenytoin and phenobarbital in patients with epilepsy.³¹ We have found no literature linking gabapentin or pregabalin to increased risk for suicide.

Topical Lidocaine

The lidocaine patch 5% has been found to be efficacious in RCTs involving patients with postherpetic neuralgia and allodynia, and in patients with allodynia due to different types of peripheral neuropathic pain.^{13,18} The primary advantage of this treatment approach is that it is very well tolerated—the most common side effects are mild local reactions, and systemic side effects are unusual.

Lidocaine gel 5% has also been shown to be efficacious in patients with postherpetic neuralgia and allodynia, but not in patients with HIV neuropathy.¹³ Lidocaine gel is less expensive than the lidocaine patch.

Application of topical lidocaine is typically most appropriate when neuropathic pain is well localized; it is unlikely to have efficacy in central neuropathic pain.

SECOND-LINE MEDICATIONS APPROPRIATE FOR FIRST-LINE USE IN CERTAIN CIRCUMSTANCES

Opioid analgesics and tramadol have been found to be efficacious in several high-quality RCTs in patients with various types of neuropathic pain (grade A recommendation). However, owing to concerns over their long-term safety (relative to first-line medications), they are recommended

Table 3 Prescribing Recommendations for First-Line Medications and for Opioid Agonists*

Medication Class	Starting Dosage	Titration	Maximum Dosage	Duration of Adequate Trial	Major Side Effects	Precautions	Other Benefits
Antidepressant medications							
Secondary amine TCAs							
Nortriptyline [†]	25 mg at bedtime	Increase by 25 mg daily every 3-7 days, as tolerated, until pain relief	150 mg daily; if blood level of active drug and its metabolite is <100 ng/mL (mg/mL), continue titration with caution	6-8 wk with ≥2 wk at maximum tolerated dosage	Sedation, dry mouth, blurred vision, weight gain, urinary retention	Cardiac disease, glaucoma, suicide risk, seizure disorder, concomitant use of tramadol	Improvement of depression, improvement of insomnia, low cost
Desipramine [†]							
SSNRIs							
Duloxetine	30 mg once daily	Increase to 60 mg once daily after 1 wk	60 mg twice daily	4 wk	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol	Improvement of depression
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week, as tolerated until pain relief	225 mg daily	4-6 wk	Nausea	Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation	Improvement of depression
Calcium channel α_2-δ ligands							
Gabapentin [†]	100-300 mg at bedtime or 100-300 mg 3 times daily	Increase by 100-300 mg 3 times daily every 1-7 days, as tolerated, until pain relief	3,600 mg daily (1,200 mg 3 times daily); reduce if impaired renal function	3-8 wk for titration + 2 weeks at maximum dose	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, no clinically significant drug interactions
Pregabalin [†]	50 mg 3 times daily or 75 mg twice daily	Increase to 300 mg daily after 3-7 days, then by 150 mg/day every 3-7 days, as tolerated, until pain relief	600 mg daily (200 mg 3 times daily or 300 mg twice daily); reduce if impaired renal function	4 wk	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions
Topical lidocaine							
5% lidocaine patch	Maximum of 3 patches daily for a maximum of 12 hr	None needed	Maximum of 3 patches daily for a maximum of 12-18 hr	3 wk	Local erythema, rash	None	No systemic side effects
Opioid agonists [‡]							
Morphine, oxycodone, methadone, levorphanol [†]	10-15 mg morphine every 4 hr or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1-2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed	No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (e.g., 120-180 mg morphine daily; equianalgesic dosages should be used for other opioid analgesics)	4-6 wk	Nausea/vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, driving impairment during treatment initiation	Rapid onset of analgesic benefit

Table 3 Continued

Medication Class	Starting Dosage	Titration	Maximum Dosage	Duration of Adequate Trial	Major Side Effects	Precautions	Other Benefits
Tramadol [§]	50 mg once or twice daily	Increase by 50-100 mg daily in divided doses every 3-7 days, as tolerated, until pain relief	400 mg daily (100 mg daily); in patients aged >75 yr, 300 mg daily.	4 wk	Nausea/vomiting, constipation, drowsiness, dizziness, seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SSNRI, or TCA	Rapid onset of analgesic benefit

SSNRI = selective serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant. (use tertiary amine TCA only if a secondary amine TCA is not available).

*Opioid agonists generally considered second-line drugs but can be used for first-line treatment in select clinical circumstances.

†Consider lower starting dosages and slower titration in geriatric patients.

‡First-line only in certain circumstances; see text.

§Consider lower starting dosages and slower titration in geriatric patients; dosages given are for short-acting formulation.

Adapted with permission from *Pain*.¹³

principally for patients who have not responded to the first-line medications, except in certain clinical circumstances (i.e., for the treatment of acute neuropathic pain, episodic exacerbations of severe neuropathic pain, neuropathic cancer pain, and during titration of a first-line medication when prompt relief of pain is needed).

Opioid Analgesics

In RCTs lasting 1 to 8 weeks, opioid analgesics have produced greater pain relief than placebo in several neuropathic pain conditions (Table 2), and, when compared with TCAs and gabapentin, they have produced at least as much analgesia.¹³ However, opioids are not recommended for routine first-line use primarily because of concerns over long-term safety. Opioids produced side effects more frequently than TCAs and gabapentin in head-to-head trials.^{17,32} Additional concerns about long-term opioid use that are based on an evolving literature and that require future investigation include the risks of immunologic changes, hypogonadism, and opioid-associated hyperalgesia.¹³ Finally, the risk of opioid misuse, abuse, or addiction in patients with chronic pain cannot be ignored; estimates of the frequency of these problems have varied widely, from <5% to 50%.¹³ Given the established efficacy of the first-line medications, opioids generally should be reserved for patients who fail to respond to first-line medications, a recommendation that is consistent with published guidelines for the use of opioids in chronic noncancer pain.³³

Opioids, however, are unique among neuropathic pain medications in having the potential to provide immediate pain relief. For this reason, opioids can be considered for first-line use in certain clinical situations. Patients with neuropathic pain who require prompt pain relief can be treated with opioid analgesics while their first-line medication is being titrated to an effective dosage. Patients with acute neuropathic pain are also appropriately treated with opioids, recognizing that if their pain becomes chronic, their treatment should be transitioned to a first-line medication. Additionally, some patients with chronic neuropathic pain will have episodic exacerbations of their pain (e.g., during specific activities); in these patients, short-acting opioids, taken as soon as possible after the onset of an acute exacerbation of pain, can be very helpful. Finally, patients with neuropathic cancer pain can be appropriately treated with opioids.¹³

In patients for whom opioids are being considered, clinicians should address risk factors for abuse, which include active or previous substance abuse and family history of substance abuse. Guidelines for prescribing opioids for chronic noncancer pain should be followed, including using the lowest effective dose and monitoring for signs of misuse.³³

The most common side effects of opioids are constipation, nausea, and sedation. Although nausea and sedation can be reduced with gradual titration and typically improve over time, constipation usually does not; in general, patients should be simultaneously treated with a bowel regimen, and

their bowel function should be monitored. Opioids can also impair cognitive function and gait in older patients. Physical dependence develops in patients treated chronically with opioids; dosages therefore should be gradually tapered when discontinuing treatment, and patients should be instructed not to stop taking opioids abruptly.

Opioids require individualized titration because the effective dosage varies considerably for individual patients. In general, long-acting opioids administered in fixed dosages are preferred over short-acting opioid preparations for long-term use. Opioids can be initiated with a short-acting preparation during opioid dosage titration, followed by conversion to a long-acting preparation once the effective total daily opioid dosage has been determined. Alternatively, treatment can be initiated with low dosages of long-acting opioids, with gradual titration to an effective dosage, recognizing that excessive initial doses or overly rapid titration can lead to significant adverse events. As with other medications recommended for neuropathic pain, if a treatment trial does not demonstrate clear symptom benefits, the medication should be tapered and discontinued and another medication initiated.

Tramadol

Tramadol is an agonist of the opioid μ -receptor, but it also inhibits reuptake of serotonin and norepinephrine. It has demonstrated efficacy in several neuropathic pain conditions (Table 2), but it may be less efficacious than strong μ -agonists such as morphine and oxycodone.¹⁸ As with opioid analgesics, tramadol carries a risk of abuse, although the overall risk appears to be lower.¹³ Tramadol is also similar to opioids in providing prompt pain relief, and so is recommended as an appropriate first-line treatment in the same situations as described for opioids.

The side effects of tramadol are largely similar to opioids, except that tramadol can also lower the seizure threshold and precipitate the serotonin syndrome in combination with certain other medications, such as SSNRIs and SSRIs. The serotonin syndrome is a potentially fatal and highly variable reaction that can produce cognitive impairment, autonomic dysfunction, and neuromuscular hyperactivity.³⁴

Tramadol can be started at 50 mg once or twice daily, and increased gradually to a maximum of 400 mg/day in patients without renal or hepatic dysfunction or 300 mg/day in older patients (Table 3). It is available in short- and long-acting preparations.

THIRD-LINE MEDICATIONS

A number of other medications have shown efficacy in neuropathic pain in a single RCT or inconsistent results in different RCTs (grade B recommendation). In general, these medications should be reserved for patients who do not tolerate or respond to the first- and second-line medications, or for whom the first- and second-line medications are contraindicated.

Several additional antidepressant medications have been studied for treatment of neuropathic pain.¹⁸ Single RCTs

have shown efficacy for bupropion, citalopram, and paroxetine, which are therefore recommended for patients with neuropathic pain who would benefit from an antidepressant other than a TCA or an SSNRI.

Besides gabapentin and pregabalin, a number of antiepileptic drugs have been studied in neuropathic pain. Carbamazepine is known to be effective for trigeminal neuralgia, but RCTs performed in other types of neuropathic pain have been of variable quality and produced mixed results.¹⁸ For lamotrigine, oxcarbazepine, topiramate, and valproic acid, there is generally inconsistent evidence of efficacy.^{13,18}

Inconsistent RCT results have been obtained for topical capsaicin, dextromethorphan, memantine, and mexiletine^{13,18} each of which can be considered for third-line treatment on the basis of individual circumstances.

CENTRAL NEUROPATHIC PAIN

The NeuPSIG guidelines note that few medications have been found to be efficacious in neuropathic pain originating from a lesion in the central nervous system. RCTs have demonstrated efficacy for TCAs in central poststroke pain, and for calcium channel α_2 - δ ligands in spinal cord injury and poststroke central neuropathic pain (Table 2).^{13,35}

Cannabinoids have demonstrated efficacy in pain associated with multiple sclerosis, but their use is limited by availability and concerns over long-term tolerability, risk of abuse, and potential to precipitate psychosis, especially in individuals at high risk.^{13,36}

For patients with central neuropathic pain who cannot tolerate or do not respond to the above medications, the other first- and second-line medications, except for topical lidocaine, can be recommended.

CANADIAN PAIN SOCIETY GUIDELINES

The Canadian Pain Society created 4 levels of recommendation, with first- and second-line medications differentiated by "the quality of evidence and the evidence of efficacy" based on NNTs.¹⁵ Medications were classified as third-line treatments if they have good evidence of efficacy, but require specialized monitoring and follow-up not required of drugs at the other levels. Fourth-line medications were described as having "at least 1 positive RCT, but required further study".¹⁵

The authors recommended TCAs, gabapentin, and pregabalin as first-line treatments for neuropathic pain in general (Table 4). They also recommended carbamazepine as first-line treatment specifically for trigeminal neuralgia. The recommended second-line treatments were topical lidocaine (for localized peripheral neuropathic pain), duloxetine, and venlafaxine. Tramadol and opioid analgesics were recommended as third-line treatments, while the fourth-line treatments were cannabinoids, methadone, SSRIs, lamotrigine, topiramate, valproic acid, mexiletine, and clonidine. Similar to the NeuPSIG guidelines, the Canadian Pain Society guidelines acknowledge the appropriate use of opioids for severe pain during titration of first- or second-line treat-

Table 4 Comparison of Neuropathic Pain Treatment Guidelines, Excluding Trigeminal Neuralgia*

Medication Class	NeuPSIG Guidelines	CPS Guidelines	EFNS Guidelines
Tricyclic antidepressants	First line	First line	First line for PPN, PHN, and CP
Calcium channel α_2 - δ ligands (gabapentin and pregabalin)	First line	First line	First line for PPN, PHN, and CP
SSNRIs (duloxetine and venlafaxine)	First line	Second line	Second line for PPN
Topical lidocaine	First line for localized peripheral NP	Second line for localized peripheral NP	First line for PHN if small area of pain/allodynia
Opioid analgesics	Second line except in selected circumstances [†]	Third line	Second-third-line for PPN, PHN, and CP
Tramadol	Second line except in selected circumstances [†]	Third line	Second-third-line for PPN and PHN

CP = central pain; CPS = Canadian Pain Society; EFNS = European Federation of Neurological Societies; NeuPSIG = Neuropathic Pain Special Interest Group; NP = neuropathic pain; PHN = postherpetic neuralgia; PPN = painful polyneuropathy; SSNRIs = selective serotonin and norepinephrine reuptake inhibitors.

*Only medications considered first or second-line in 1 of the guidelines are presented.

[†]Opioid analgesics and tramadol were considered first-line options in the following circumstances: for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.

ments, and recognize the need for combination therapy in many patients.¹⁵

EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES PHARMACOLOGICAL TREATMENT GUIDELINES

As with the NeuPSIG and Canadian Pain Society guidelines, the EFNS guidelines grade the level of evidence for different available treatments. However, unlike the other 2 sets of guidelines, separate recommendations were made for the treatment of patients with painful polyneuropathies (including painful diabetic peripheral neuropathy), postherpetic neuralgia, trigeminal neuralgia, and central neuropathic pain.¹⁴

Consistent with the NeuPSIG and Canadian Pain Society guidelines, the EFNS guidelines recommended gabapentin, pregabalin, and TCAs as first-line treatments for painful polyneuropathies, postherpetic neuralgia, and central neuropathic pain (Table 4). Other EFNS recommendations for painful polyneuropathies were duloxetine and venlafaxine as second-line treatment (“because of moderate efficacy”), and opioids, tramadol, and lamotrigine as “second-/third-line therapy.” Additional recommendations for postherpetic neuralgia were topical lidocaine as a first-line treatment for patients with localized pain and allodynia, and opioids, tramadol, capsaicin, and valproic acid as second-line treatment options (Table 4). “Second-/third-line” treatment options for patients with central neuropathic pain were lamotrigine, opioids, and cannabinoids¹⁴ (Table 4).

EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES GUIDELINES FOR NEUROSTIMULATION THERAPY IN PATIENTS WITH NEUROPATHIC PAIN

An EFNS task force recently reviewed the literature on neurostimulation therapy and developed guidelines for its use in neuropathic pain. In general, the quality of evidence

was inadequate to make specific recommendations for many types of neuropathic pain. One noteworthy problem in many studies assessing neurostimulation interventions, which are typically only applied to patients who are refractory to pharmacologic treatment, is the absence of a good control or comparator (e.g., a placebo or sham treatment group).³⁷

Reasonable evidence was found in support of the use of spinal cord stimulation for failed back surgery syndrome and complex regional pain syndrome type I. It was also noted that spinal cord stimulation seems to produce positive results in other neuropathic pain conditions, but that “confirmatory comparative trials” are needed before “unreservedly” recommending its use in such conditions.³⁷ Some evidence was found that motor cortex stimulation provides substantial benefit in patients with central poststroke pain and neuropathic facial pain. However, other neurostimulation therapies either lacked sufficient evidence on which to base recommendations or seemed to provide only marginal or short-lived benefits relative to placebo.³⁷

SUMMARY

Three evidence-based consensus guidelines for the pharmacologic treatment of neuropathic pain have been published recently. These guidelines all recommend TCAs, gabapentin, and pregabalin as first-line treatment options for patients with neuropathic pain (excluding trigeminal neuralgia). They also recommend reserving opioid analgesics and tramadol as second- or third-line options in most cases, despite evidence of efficacy in neuropathic pain. In 2 of the guidelines, topical lidocaine is recommended as a first-line treatment for patients with localized peripheral neuropathic pain (particularly in patients with postherpetic neuralgia and allodynia), whereas the other guideline considers it a second-line treatment. The NeuPSIG guidelines recommend duloxetine and venlafaxine as first-line treatment options, but the Canadian Pain Society and EFNS guidelines recommend

these SSNRIs as second-line options for patients with painful polyneuropathies.

The array of medications and other treatment interventions with demonstrated efficacy in neuropathic pain is expanding. Future research must not only clarify the optimal use of existing medications alone and in combination, but must also identify medications that increase the magnitude of pain reduction or the likelihood of a beneficial response. Until such advances become available, these consensus guidelines provide up-to-date and comprehensive evidence-based treatment recommendations for improving the care of patients with neuropathic pain.

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