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Reviews and recommendations

Pharmacologic management of neuropathic pain: Evidence-based recommendations

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Abstract

Patients with neuropathic pain (NP) are challenging to manage and evidence-based clinical recommendations for pharmacologic management are needed. Systematic literature reviews, randomized clinical trials, and existing guidelines were evaluated at a consensus meeting. Medications were considered for recommendation if their efficacy was supported by at least one methodologically-sound, randomized clinical trial (RCT) demonstrating superiority to placebo or a relevant comparison treatment. Recommendations were based on the amount and consistency of evidence, degree of efficacy, safety, and clinical experience of the authors. Available RCTs typically evaluated chronic NP of moderate to severe intensity. Recommended first-line treatments include certain antidepressants (i.e., tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel α2-δ ligands (i.e., gabapentin and pregabalin), and topical lidocaine. Opioid analgesics and tramadol are recommended as generally second-line treatments that can be considered for first-line use in select clinical circumstances. Other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances include certain antiepileptic and antidepressant medications, mexiletine, *N*-methyl-D-aspartate receptor antagonists, and topical capsaicin. Medication selection should be individualized, considering side effects, potential beneficial or deleterious effects on comorbidities, and whether prompt onset of pain relief is necessary. To date, no medications have demonstrated efficacy in lumbosacral radiculopathy, which is probably the most common type of NP. Long-term studies, head-to-head comparisons between medications, studies

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involving combinations of medications, and RCTs examining treatment of central NP are lacking and should be a priority for future research.

Keywords: Neuropathic pain; Evidence-based recommendations; Pharmacologic management; Randomized clinical trials

1. Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as pain "initiated or caused by a primary lesion or dysfunction in the nervous system" [74]. It is estimated to afflict millions of people worldwide, although precise figures are not available [7,9,12,44,102]. Many common diseases, injuries, and interventions cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system.

The management of patients with chronic NP is complex and response to existing treatments is often inadequate. Even with well-established NP medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are common. Evidence-based consensus treatment recommendations exist [25], but additional medications have become available since their publication [31]. Because of gaps and controversies in the literature, considerable interpretation of available evidence, judgment, and experience are required to develop treatment approaches that can be used in clinical practice.

The objectives of this article are to: (1) briefly review the results of RCTs examining medications for the treatment of NP; (2) present up-to-date, evidence-based guidelines for the pharmacologic management of NP that take into account clinical efficacy, adverse effects, impact on health-related quality of life, convenience, and costs; and (3) provide specific recommendations for the use of these medications.

2. Methods

The consensus meeting on which these treatment recommendations are based and the preparation of this article were conducted under the auspices of the IASP Neuropathic Pain Special Interest Group with additional support provided by the Neuropathic Pain Institute, both of which have received unrestricted support for their activities from multiple pharmaceutical companies. No individuals employed by pharmaceutical companies were involved in the consensus meeting on which these recommendations are based or in the preparation of this article. Prior to the consensus meeting, all participants were provided with copies of existing treatment guidelines [25,58], systematic reviews and meta-analyses, and recently published RCTs. This literature and the authors' clinical and research experience were reviewed during the consensus meeting. Systematic reviews and RCTs published after the meeting were reviewed subsequently. The treatment recommendations included in this article have been endorsed by the American Pain Society, Canadian Pain Society, Finnish Pain Society, Latinamerican Federation of IASP Chapters, and Mexican Pain Society.

2.1. Search strategy and selection criteria

Relevant publications were identified through Medline searches (1966–2007), examination of reference lists of relevant published articles and book chapters, and personal knowledge of the authors. Only studies of oral or topical pharmacotherapy in adults were considered, and our recommendations do not apply to the treatment of pediatric neuropathic pain. The treatment of trigeminal neuralgia (tic douloureux), for which there are distinct treatment recommendations [3,65], was not considered. On the basis of recent recommendations for the diagnosis of NP [115], conditions for which there is no evidence of lesions affecting nervous system somatosensory pathways (e.g., fibromyalgia, irritable bowel syndrome) were also not considered.

In evaluating the literature and developing recommendations, the Cochrane Database and other recent systematic reviews were emphasized [27,31,33,50,53,68,100,109,119,129]. Efficacy was considered to have been demonstrated if the results of an RCT found statistically significantly greater pain reduction vs. placebo for the primary outcome measure [31] and was evaluated according to the Oxford Centre for Evidence-based Medicine levels of evidence [78]. All medications with efficacy supported by at least one systematic review or positive placebo-controlled or dose-response RCT (levels of evidence criterion 1b or better), [78] in which reduction of chronic NP was a primary or co-primary endpoint were considered for inclusion. Published data, unpublished data (when available), and the clinical experience of the authors were used to evaluate each of these medications in terms of degree of efficacy, safety, tolerability, drug interactions, ease of use, and impact on health-related quality of life.

Recommendations for first-line treatments are consistent with the results of multiple RCTs (Oxford Centre for Evidence-based Medicine grade A recommendation), [78] and the clinical experience of the authors. Recommendations for opioid analgesics and tramadol as generally second-line treatments are consistent with the results of multiple RCTs (grade A recommendation), the clinical experience of the authors, and published guidelines and recommendations for their use. Recommendations for other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances are based on a single positive RCT or inconsistent results from multiple trials (grade B recommendation) and the authors' clinical experience.

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3. General management considerations and recommendations

Appropriate diagnosis and assessment are critical to the successful treatment of NP. The diagnosis of NP can often be challenging, diagnostic criteria are evolving, and NP commonly coexists with other types of pain (e.g., low back pain associated with both radiculopathy and musculoskeletal abnormalities). Assessment of NP should focus on identifying and treating the underlying disease processes and peripheral or central nervous system lesions, response to prior therapies, and comorbid conditions that can be affected by therapy. Particular attention should be paid to identifying coexisting depression, anxiety, sleep disturbances, and other adverse impacts of NP on health-related quality of life [56,75], and both pain and its adverse effects should be reassessed frequently. Patient education and support are critical components of the successful management of NP. Careful explanation of the cause of NP and the treatment plan are essential. Patient and provider expectations regarding treatment effectiveness and tolerability must be discussed, and realistic treatment goals should be established with patients. Non-pharmacologic methods of coping with pain should be discussed, including the importance of stress reduction, good sleep hygiene, physical therapy, and other potentially useful interventions. Additional information about the diagnosis of NP and recommendations for its assessment can be found elsewhere [20,25,47,85].

The majority of the RCTs of patients with NP have examined either PHN or painful diabetic peripheral neuropathy (DPN). Although the extent to which the results of RCTs of one type of NP apply to other types is unknown, the extrapolation of efficacy from first-line medications that have demonstrated efficacy in one or more types of NP to other types of NP is reasonable and often clinically necessary. Medications that have demonstrated efficacy in several different NP conditions may have the greatest probability of being efficacious in additional, as yet unstudied, conditions [46]. However, it is possible that some types of NP respond differently to treatment [3]. Although few clinical trials have been conducted, no medications have demonstrated efficacy in patients with lumbosacral radiculopathy, which is probably the most common type of NP.

The methodology used in RCTs of NP varies, and there are few head-to-head comparisons of different medications, making it difficult to compare the relative efficacy and safety of many medications. Little is known regarding the treatment response of patients with mild-to-moderate NP because RCTs have typically evaluated chronic NP of moderate to severe intensity. Moreover, treatment duration has generally not exceeded three months in the RCTs of any treatments for NP, and knowledge of the long-term benefits and risks of treatment is therefore inadequate. Unfortunately, there is insufficient evidence to rank first-line medications for NP by their degree of efficacy or safety. Given these limitations, clinicians must consider several other factors when selecting a specific medication for a patient with NP, including: (1) the potential for adverse outcomes associated with medication-related side effects; (2) potential drug interactions; (3) comorbidities that may also be relieved by the non-analgesic effects of the medication (e.g., sleep disturbance, depression, anxiety); (4) costs associated with therapy; (5) the potential risks of medication abuse; and (6) the risks of intentional and unintentional overdose. These potentially competing factors must be prioritized according to the specific needs of each patient with NP.

Individual variation in the response to the medications used to treat NP is substantial and unpredictable. Although evidence-based recommendations encourage the use of specific medications, the overall approach should be recognized as a stepwise process intended to identify the medication, or medication combination, that provides the greatest pain relief and fewest side effects for a given patient (Table 1). If an adequate trial of one medication fails to adequately relieve pain or causes intolerable side effects, treatment should be discontinued and a different medication should be selected for a trial. If a medication is well tolerated and provides partial pain relief, it should be continued and a second medication with a distinct mechanism of action added.

In addition to potential additive analgesic benefits, combination therapy may provide analgesia more quickly by combining a medication with a rapid onset of effect with one that requires several weeks of treatment before maximum benefit is achieved. These potential advantages of combination therapy must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen. In one of the first RCTs of combination therapy in NP, gabapentin and morphine in combination provided superior pain relief to either medication alone and to placebo [36]. However, a recent RCT evaluating nortriptyline, morphine, and their combination in patients with chronic lumbar root pain found no greater efficacy with the combination than with either medication alone or placebo [60].

4. First-line medications

Three medications or medication classes are recommended as first-line treatment for patients with NP (grade A recommendation). Table 2 summarizes treatment selection considerations. Prescribing information for each of these medications – including starting dosage, titration requirements, target dosage, and duration of an adequate trial – is provided in Table 3.

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Table 1
Stepwise pharmacologic management of neuropathic pain (NP)

Step 1

Assess pain and establish the diagnosis of NP [25,20]; 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:

- A secondary amine TCA (nortriptyline, desipramine) or an SSNRI (duloxetine, venlafaxine)
- A calcium channel α2-δ ligand, either gabapentin or pregabalin
- For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies
- For patients with acute neuropathic pain, 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 one of the first-line therapies

Evaluate patient for non-pharmacologic 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 $\leqslant 3/10$) and tolerable side effects, continue treatment

If partial pain relief (e.g., average pain remains $\geqslant 4/10$) after an adequate trial (see Table 3), add one 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- and third-line medications or referral to a pain specialist or multidisciplinary pain center

TCA, tricyclic antidepressant; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.

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Table 2
Treatment selection considerations for first-line medications and for opioid agonists

Medication class	Therapeutic index[a]	Major side effects	Precautions	Other benefits	Cost[b]
Secondary amine TCAs					
Nortriptyline, desipramine (use a tertiary amine TCA only if a secondary amine TCA is not available)	+	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	$
SSNRIs					
Duloxetine[c]	++	Nausea	Hepatic dysfunction, renal insufficiency, alcohol abuse, concomitant use of tramadol	Improvement of depression	$$
Venlafaxine	+	Nausea	Concomitant use of tramadol, cardiac disease, withdrawal syndrome with abrupt discontinuation	Improvement of depression	$/$$
Calcium channel α2-δ ligands					
Gabapentin	++	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, no clinically significant drug interactions	$/$$
Pregabalin[c]	++	Sedation, dizziness, peripheral edema	Renal insufficiency	Improvement of sleep disturbance, improvement of anxiety, no clinically significant drug interactions	$$
Topical lidocaine	++	Local erythema, rash	None	No systemic side effects	$$ (patch) $ (gel)
Opioid agonists[d]					
Morphine, oxycodone, methadone, levorphanol	+	Nausea/vomiting, constipation, drowsiness, dizziness	History of substance abuse, suicide risk, driving impairment during treatment initiation	Rapid onset of analgesic benefit	$/$$
Tramadol	+	Nausea/vomiting, constipation, drowsiness, dizziness seizures	History of substance abuse, suicide risk, driving impairment during treatment initiation, seizure disorder, concomitant use of SSRI, SSNRI, TCA	Rapid onset of analgesic benefit	$/$$

TCA, tricyclic antidepressants; SSNRI, selective serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a] Refers to the likelihood of pain relief relative to the likelihood of side effects, with "++" being more favorable.
[b] Cost varies by region but is estimated on the basis of availability and cost of generic formulations, with "$$" being relatively more expensive.
[c] Lack long-term clinical experience and safety data because new to market.
[d] First-line only in certain circumstances; see text.

4.1. Tricyclic antidepressants (TCAs) and selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)

Systematic reviews have consistently concluded that placebo-controlled trials have provided support for the efficacy of TCAs in the treatment of patients with NP, especially PHN and painful DPN [31,50,100,109]. A substantial percentage of patients do not respond favorably to treatment with TCAs, as is also true of the other medications recommended for the treatment of NP, with no more than 40–60% of patients obtaining partial relief of their pain. TCAs have not differed significantly from placebo in RCTs of patients with HIV neuropathy [62,105], spinal cord injury [15], cisplatin neuropathy [45], neuropathic cancer pain [73], phantom limb pain [91], and chronic lumbar root pain [60].

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Table 3
Prescribing recommendations for first-line medications and for opioid agonists

Medication class	Starting dosage	Titration	Maximum dosage	Duration of adequate trial
Secondary amine TCAs				
Nortriptyline, desipramine[a] (use a tertiary amine TCA only if a secondary amine TCA is not available)	25 mg at bedtime	Increase by 25 mg daily every 3–7 days as tolerated	150 mg daily; if blood level of active medication and its metabolite is below 100 ng/ml (mg/ml), continue titration with caution	6–8 weeks with at least 2 weeks at maximum tolerated dosage
SSNRIs				
Duloxetine	30 mg once daily	Increase to 60 mg once daily after one week	60 mg twice daily	4 weeks
Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg each week	225 mg daily	4–6 weeks
Calcium channel α2-δ ligands				
Gabapentin[a]	100–300 mg at bedtime or 100–300 mg three times daily	Increase by 100–300 mg three times daily every 1–7 days as tolerated	3600 mg daily (1200 mg three times daily); reduce if impaired renal function	3–8 weeks for titration plus 2 weeks at maximum dosage
Pregabalin[a]	50 mg tid or 75 mg bid	Increase to 300 mg daily after 3–7 days, then by 150 mg/d every 3–7 days as tolerated	600 mg daily (200 mg three times or 300 mg twice daily); reduce if impaired renal function	4 weeks
Topical lidocaine				
5% lidocaine patch	Maximum of 3 patches daily for a maximum of 12 h	None needed	Maximum of 3 patches daily for a maximum of 12–18 h	3 weeks
Opioid agonists[b]				
Morphine, oxycodone, methadone, levorphanol[a]	10–15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)	After 1–2 weeks, 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 weeks
Tramadol[c]	50 mg once or twice daily	Increase by 50–100 mg daily in divided doses every 3–7 days as tolerated	400 mg daily (100 mg four times daily); in patients older than 75, 300 mg daily	4 weeks

TCA, tricyclic antidepressants; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.
[a] Consider lower starting dosages and slower titration in geriatric patients.
[b] First-line only in certain circumstances; see text.
[c] Consider lower starting dosages and slower titration in geriatric patients; dosages given are for short-acting formulation.

TCAs are typically inexpensive and usually administered once daily. The presence of depression is not required for the analgesic effects of these medications [69], although they may be particularly useful in patients with inadequately treated depression. The most common side effects of TCAs include sedation, anticholinergic effects (e.g., dry mouth, constipation, and urinary retention), and orthostatic hypotension. Secondary amine TCAs (nortriptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) but have comparable analgesic efficacy [70,98,126]. Amitriptyline in particular should be avoided in elderly patients.

The decision to start a TCA should also consider the possibility of cardiac toxicity. Nortriptyline was associated with sinus tachycardia and increased ventricular ectopy in an RCT that examined patients with a history of depression and ischemic heart disease [92].

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An increased risk of myocardial infarction with TCAs compared to selective serotonin reuptake inhibitors (SSRIs) has been reported [19], but subsequent, larger studies did not confirm this finding [51,113]. Finally, a large, retrospective cohort analysis found an increased risk of sudden cardiac death at dosages of 100 mg/day or higher [86].

Taken together, these data suggest that the lowest effective dosage of a TCA should be used in all patients with NP, and that TCAs should be avoided in patients who have ischemic heart disease or an increased risk of sudden cardiac death. A screening electrocardiogram (ECG) is recommended before beginning treatment with TCAs in patients over 40 years of age [25]. TCAs should be used cautiously in patients at risk for suicide or accidental death from overdose. They can cause or exacerbate cognitive impairment and gait disturbances in elderly patients, and may predispose to falls. Toxic TCA levels may result if TCAs are administered together with medications that inhibit cytochrome P450 2D6, such as SSRIs.

Starting doses of TCAs should be low, and the dosage should be titrated slowly until pain is adequately controlled or side effects limit continued titration (Table 3). Although monitoring medication levels is not usually necessary, it may reduce the risk of cardiac toxicity at dosages greater than 150 mg/day.

Duloxetine is an SSNRI that inhibits the reuptake of both serotonin and norepinephrine. It has demonstrated significantly greater pain relief compared with placebo in three RCTs in patients with painful DPN [38,82,128], but it has not been studied in other types of NP. Although duloxetine is also an efficacious antidepressant and anxiolytic, these effects do not account for its analgesic benefits in painful DPN [38]. Safety and effectiveness have also been demonstrated in open-label treatment of patients with painful DPN extending over 52 weeks [83], and meta-analyses showed modest increases in fasting plasma glucose in the patients with DPN [49] but no clinically meaningful ECG changes relative to placebo in depressed patients [116].

Duloxetine has a generally favorable side effect profile and dosing is simple. Nausea is the most common side effect, but it occurs less frequently if treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day [23], an efficacious dosage at which pain relief can occur within one week (Table 3). In RCTs in painful DPN, 60 mg once daily appears to be as efficacious as 60 mg twice daily and is associated with fewer side effects. As a new medication, there is limited long-term safety information and efficacy data are limited to studies of painful DPN.

Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages. RCTs in patients with painful DPN [96] and painful polyneuropathies of various types including DPN [108] demonstrated efficacy at dosages of 150–225 mg/day. RCTs in other populations, including those with post-mastectomy pain [112], various peripheral and central NP conditions [133], and PHN [42], demonstrated inconsistent or negative results. Two of these trials used lower dosages of venlafaxine [112,133], which may account for some of the differences in efficacy.

In one RCT, 5% of venlafaxine-treated patients developed ECG changes [96], and monitoring is therefore recommended in patients with cardiovascular risk factors. Venlafaxine is available in both short- and long-acting formulations. Two-to-four weeks is often required to titrate to an effective dosage, and patients should be tapered gradually from venlafaxine because of the risk of discontinuation syndrome (Table 3) [29].

4.2. Calcium channel α2-δ ligands

Gabapentin and pregabalin both bind to the α2-δ subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P [114]. Pain reduction has been greater with gabapentin than with placebo in RCTs of PHN, painful DPN, phantom limb pain, diverse peripheral NP conditions, Guillain-Barré syndrome, neuropathic cancer pain, and acute and chronic spinal cord injury pain [4,10,14,39,64,79,87,97,104,111]. In some RCTs, treatment with gabapentin was also associated with improvement in sleep and various components of mood and health-related quality of life. Negative trials of gabapentin include an unpublished study in painful DPN [5] and recent studies of complex regional pain syndrome, type I [121], painful HIV neuropathy [43], chronic phantom and residual limb pain [110], and chemotherapy-induced neuropathy [132].

Gabapentin is generally safe, has no clinically important drug interactions, and is available in generic formulations. The main dose-limiting side effects are somnolence and dizziness, which are reduced by gradual dosage titration, and peripheral edema. In some patients, particularly the elderly, gabapentin can cause or exacerbate cognitive or gait impairment.

Several weeks can be required to reach an effective dosage, which is usually between 1800 and 3600 mg/day (administered in three divided doses, increasing the night-time dose preferentially). Dosage reduction is necessary in patients with renal insufficiency. The onset of activity can be seen as early as the second week of therapy when titration is rapid, but peak effect usually occurs approximately two weeks after a therapeutic dosage is achieved. Therefore, an adequate trial may require two months or more (Table 3).

Pregabalin has demonstrated efficacy in three RCTs in PHN [26,101,122], in three RCTs in painful DPN [63,93,89], and in one RCT that enrolled patients with

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either of these types of NP [32]. An RCT in patients with spinal cord injury neuropathic pain also demonstrated greater pain relief with pregabalin than with placebo [106]. An unpublished trial in patients with DPN also showed evidence of efficacy, but in two unpublished trials, pregabalin did not differ significantly from placebo in patients with PHN and with DPN [24].

Pregabalin produces dose-dependent side effects similar to those of gabapentin. It has also demonstrated anxiolytic effects in RCTs of generalized anxiety disorder [76,90], which may provide additional benefit in patients with chronic pain. Like gabapentin, it has no clinically important drug interactions but requires dosage reduction in patients with renal impairment. Studies indicate that treatment can be initiated at 150 mg/day (in either two or three divided doses), although a starting dose of 75 mg at bedtime is used by some clinicians to reduce the likelihood of early side effects in elderly patients and in others especially prone to side effects (Table 3). The potential for twice daily dosing and the linear pharmacokinetics of pregabalin may contribute to relatively greater ease of use compared with gabapentin, but the overall efficacy and tolerability of these two medications appear similar. However, onset of pain relief with pregabalin can be more rapid than with gabapentin because its starting dosage of 150 mg/day is efficacious [26]. Upward dosage titration can reach 300 mg/day within one to two weeks, and the maximum benefits typically occur after two weeks of treatment at target dosages of 300–600 mg/day. Because it is a new medication, long-term safety of pregabalin is not as well established as it is for gabapentin.

4.3. Topical lidocaine

RCTs have demonstrated significantly greater pain relief with lidocaine patch 5% than with vehicle-controlled patches in patients with PHN and allodynia [34,95] and in patients with diverse peripheral NP conditions and allodynia [72], including a subgroup without PHN [71]. As a topical preparation, it is recommended for patients with localized peripheral NP but not for patients with central NP.

When used as recommended, the only side effects that occur with the lidocaine patch 5% are mild skin reactions (e.g., erythema and localized rash). Blood levels are minimal with the approved maximum dosing of three patches/day applied for 12 h and also when four patches/day are applied for 18 h [35]. Nonetheless, use of the lidocaine patch 5% should be avoided in patients receiving oral Class I antiarrhythmic medications (e.g., mexiletine) and in patients with severe hepatic dysfunction, in whom excessive blood concentrations are theoretically possible.

The efficacy of lidocaine gel was demonstrated in patients with PHN and allodynia [94], but not in patients with HIV neuropathy [28]. Because of its safety and ease of use, lidocaine gel can be considered when the lidocaine patch 5% is not available, application of a patch is problematic, or the cost of the lidocaine patch 5% precludes its use.

5. Second-line medications that can be used for first-line treatment in select clinical circumstances

Opioid analgesics and tramadol have demonstrated efficacy in multiple RCTs in patients with NP, and when patients do not have a satisfactory response to the first-line medications alone or in combination, opioid agonists can be used as second-line treatment alone or in combination with the first-line medications (grade A recommendation).

In select clinical circumstances, opioid analgesics and tramadol can also be considered for first-line use (Table 4). These circumstances include when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, and for episodic exacerbations of severe pain, acute neuropathic pain, and neuropathic cancer pain.

5.1. Opioid analgesics

Oral opioid analgesics have demonstrated efficacy in RCTs ranging from eight days to eight weeks in duration in patients with a variety of peripheral and central NP conditions, including painful DPN, PHN, and phantom limb pain [37,54,77,80,99,124,125]; however, morphine did not differ from placebo in a recent RCT for chronic nerve root pain [60]. These trials have examined different opioids, including oxycodone, morphine, methadone, and levorphanol. The magnitude of pain reduction associated with opioid analgesics is at least as great as that obtained with other treatments for NP [27,31,36,80].

Although opioid analgesics have demonstrated efficacy in multiple RCTs in patients with NP, they are generally considered a second-line treatment for several reasons. First, in head-to-head comparisons, opioids have produced side effects more frequently than TCAs [60,80] and gabapentin [36], and some of these side effects can persist throughout long-term treatment [127]. Second, the long-term safety of opioid treatment has not been systematically studied [27,33], and evidence

Table 4
Circumstances in which opioid analgesics and tramadol can be considered for first-line treatment of neuropathic pain

During titration of a first-line medication to an efficacious dosage for prompt pain relief
Episodic exacerbations of severe pain
Acute neuropathic pain
Neuropathic cancer pain

that long-term opioid use is associated with the development of immunologic changes and hypogonadism [21,81,120] suggests that clinicians should not be guided by the assumption that safety is intrinsically better for opioids than other medications. Third, experimental data suggest that opioid treatment can be associated with hyperalgesia [2,16,17,131]; like tolerance, opioid-induced hyperalgesia could potentially alter the risk-benefit ratio of long-term therapy in patients with various types of acute and chronic pain. There are no studies of opioid-induced hyperalgesia in patients with chronic NP, however, and future studies must evaluate the clinical significance of this phenomenon and also systematically distinguish opioid-induced hyperalgesia from tolerance [2,17] and from exacerbation of the underlying pain condition.

Finally, the results of recent studies using a variety of methods and patient samples have provided estimates of the frequency of opioid analgesic misuse or addiction that range widely from less than 5% to as much as 50% [1,6,52,55,66,67]. Although the risk that opioid analgesics will be misused or abused has not been determined for patients with chronic NP, these recent estimates cannot be ignored when initiating opioid treatment. Recent recommendations have emphasized the need for clinical skills in risk assessment and management as a prerequisite to safe and effective opioid prescribing [6,52,59].

Because of these problematic aspects of opioid treatment, and given the efficacy of the first-line medications discussed above, treatment of chronic NP with opioid agonists should generally be reserved for patients who have failed to respond to or cannot tolerate the first-line medications. This recommendation is consistent with published guidelines for the use of opioids in chronic non-cancer pain that have been prepared by various groups [52]. Of existing medications with efficacy in NP, however, opioid analgesics may be most likely to provide prompt pain relief. For this reason, and because of their established efficacy in NP, opioids can be considered for first-line use in select clinical circumstances (see Table 4). Typically, such first-line use of opioids should be reserved for circumstances in which suitable alternatives cannot be identified and should be on a short-term basis to the extent possible.

Before initiating treatment with opioid analgesics, clinicians should identify and address risk factors for abuse, which include active substance abuse, prior history of opioid or other drug abuse, other major psychiatric pathology, and family history of substance abuse [6,52,135]. Response to treatment, side effects, and signs of opioid misuse or abuse should be monitored on a regular basis, as has been described in guidelines for opioid use in chronic non-cancer pain [6,52,57,58,117]. It is recommended that clinicians without opioid expertise obtain consultation from appropriate specialists in developing a treatment plan for challenging patients.

The most common opioid-related side effects are nausea, constipation, and sedation [27,33]. Although nausea and sedation typically decrease after several weeks of treatment, constipation may not; it usually requires concurrent management, especially in the elderly or other groups with risk factors for this problem. Opioids should be used cautiously in patients at risk for suicide or accidental death from overdose. In elderly patients, opioids can also cause or exacerbate cognitive impairment and gait disturbances, increasing the risk of falls. In contrast to abuse or addiction, physical dependence develops in all patients chronically treated with opioid analgesics, and patients must be advised that they should not discontinue these medications on their own.

The effective opioid dosage varies widely among patients, and either of two strategies for the initiation of treatment can be used depending on the specific clinical circumstances. For opioid-naïve patients, treatment can be initiated with an oral immediate-release opioid at a dose equivalent to 10–15 mg of morphine every 4 h or on an as needed basis, with conversion to a long-acting opioid after a few days, when the approximate daily dosage has been identified (Table 3). Treatment can also be initiated with a long-acting opioid (e.g., extended-release oral morphine or oxycodone, or transdermal fentanyl). Fixed-schedule dosing with a long-acting opioid is generally preferred, although RCTs in patients with NP are needed to compare the efficacy and safety of short- vs. long-acting opioids. Titration should continue until satisfactory pain relief is achieved or unacceptable side effects persist despite attempts to improve tolerability (e.g., laxatives for constipation). Treatment with a short-acting opioid on an as needed basis may be appropriate to continue in selected patients with NP who have episodes of markedly increased pain; until the role of such ''rescue'' treatment has been more adequately characterized for patients with NP, treatment approaches used for patients with other types of chronic pain, including cancer pain, can be followed [57,58,117]. As with all of the medications recommended for NP, the lowest effective dosages of opioid analgesics should be used. If an adequate trial of therapy has not produced clinically meaningful pain relief, patients should be tapered off their opioid analgesic and an alternative treatment administered.

5.2. Tramadol

Tramadol is a weak μ-opioid agonist that also inhibits the reuptake of norepinephrine and serotonin. The results of RCTs in patients with PHN, painful DPN, painful polyneuropathies of different etiologies, and post-amputation pain demonstrated that tramadol reduced pain and improved some aspects of health-

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related quality of life [11,48,53,107,130]. As with opioids, tramadol is associated with abuse potential; although rates of tramadol abuse have remained very low despite new branded and generic formulations [18], some recent reports suggest that the rate of recreational tramadol use may be rising [134].

The most common side effects of tramadol are somnolence, constipation, dizziness, nausea, and orthostatic hypotension, which occur more frequently with rapid dosage escalation. Tramadol can cause or exacerbate cognitive impairment and gait disturbances in elderly patients. It can also precipitate seizures in patients with a history of seizures or in those receiving medications that reduce seizure threshold. Concurrent use of other serotonergic medications (including SSRIs and SSNRIs) may increase the risk of serotonin syndrome, and combination therapy with these medications must be undertaken cautiously.

Tramadol may be somewhat less efficacious than stronger opioid analgesics in patients with NP [31]. As for opioid analgesics, tramadol is recommended primarily for patients who have not responded to the first-line medications but it can also be considered for first-line use in select clinical circumstances (Table 4). Tramadol is available in both short- and long-acting formulations; for the short-acting formulation, the starting dosage is 50 mg once or twice daily, with gradual titration to a maximum of 400 mg/day. Dosage reduction is necessary in patients with renal or hepatic disease and in the elderly (Table 3).

6. Generally third-line medications

There are a number of other medications that would generally be used as third-line treatments but that could also be used as second-line treatments in some circumstances (e.g., when treatment with an opioid agonist is not indicated or when the patient's treatment history suggests greater potential for their effectiveness). These medications – for which there is substantially less evidence of efficacy than exists for TCAs, SSNRIs, calcium channel α2-δ ligands, topical lidocaine, opioid analgesics, and tramadol – include certain other antiepileptic (carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid) and antidepressant (bupropion, citalopram, paroxetine) medications, mexiletine, *N*-methyl-D-aspartate (NMDA) receptor antagonists, and topical capsaicin. Recommendations for their use are based on efficacy in a single RCT or inconsistent results from multiple RCTs and the clinical experience of the authors (grade B recommendation).

6.1. Antiepileptic medications

In contrast to its established efficacy in trigeminal neuralgia, carbamazepine has yielded inconsistent results in RCTs of other types of neuropathic pain [31]. These studies generally had limited methodological quality. Three positive trials of valproic acid in painful DPN or PHN were reported from a single center but an RCT conducted in patients with painful polyneuropathies by a different research group was negative [31].

In several relatively small RCTs, lamotrigine showed evidence of efficacy in several types of NP or in subgroups of patients with these conditions [31]. However, intention-to-treat analyses were negative in three large recent RCTs, two of which were in painful DPN [40,123]. Slow titration from a low initial dosage is required with lamotrigine to reduce the risk of potentially serious cutaneous hypersensitivity reactions.

Three placebo-controlled RCTs have been published of oxcarbazepine in patients with painful DPN, one of which was positive [22], but two of which were negative [8,41]. In patients with painful DPN, topiramate showed efficacy in one RCT [84] but not in three others [118], and its efficacy was equivocal in a trial of chronic lumbar radicular pain [61]. Based on the results of these studies of first- and second-generation antiepileptic medications, carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid can be considered options for patients who have not responded to the first-and second-line medications.

6.2. Antidepressant medications

The SSRIs citalopram and paroxetine showed limited evidence of efficacy in RCTs in painful DPN but fluoxetine did not [31]. Bupropion, which inhibits the reuptake of norepinephrine and dopamine, was efficacious in various peripheral and central NP conditions [31]. Based on the results of these trials, bupropion, citalopram, and paroxetine are options for patients who have not responded to an adequate trial of a TCA or SSNRI when additional treatment with a medication with analgesic and antidepressant effects is being considered.

6.3. Mexiletine, NMDA receptor antagonists, and topical capsaicin

Mexiletine is an orally administered lidocaine analogue, and RCTs in patients with painful DPN and other types of NP have shown either modest benefits or no differences compared to placebo [31,119]. When evidence of efficacy was found in these trials, it was at higher dosages, which are often poorly tolerated because of side effects.

Dextromethorphan and memantine block the NMDA receptor. A few early RCTs showed evidence of efficacy, but later trials have provided limited or no evidence of efficacy [31].

The results of RCTs that compared topical capsaicin with placebo in patients with painful DPN, PHN, and

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post-mastectomy pain have been inconsistent [31,68]. Interpretation of efficacy is problematic in these studies because the burning associated with capsaicin use may have compromised blinding in the trials in which superiority to placebo was found.

7. Additional recommendations for central NP

Based on the results of a small number of RCTs [30,31,88], the following specific medications should be considered for patients with central NP: TCAs for central post-stroke pain; calcium channel α2-δ ligands for spinal cord injury pain; and cannabinoids for NP associated with multiple sclerosis (grade B recommendation). Lack of long-term follow-up data, limited availability, and concerns over precipitating psychosis or schizophrenia, especially in individuals with environmental or genetic risk factors [103], restrict the use of cannabinoids to second-line therapy for patients with multiple sclerosis NP at present, and additional trials are needed to further establish their efficacy and safety.

Many patients with central NP either do not have one of these diagnoses or require alternative therapy. In these situations, the first- and second-line medications recommended for peripheral NP can be considered for the treatment of central NP (except for topical lidocaine). However, it must be acknowledged that the evidence base for such treatment is limited.

8. Conclusions

TCAs, SSNRIs, calcium channel α2-δ ligands, and topical lidocaine have demonstrated efficacy in NP and are recommended as first-line medications. In patients who have failed to respond to these first-line medications alone and in combination, opioid analgesics or tramadol can be used as a second-line treatment alone or in combination with one of the first-line medications. Opioid analgesics and tramadol can also be considered for first-line use in select clinical circumstances (Table 4).

Patients who have not responded adequately to these medications used alone and in combination can be treated with one or more other recommended medications. For patients who have not responded adequately to pharmacologic management or those who have pain that is associated with challenging comorbidities or with a high level of disability or distress, prompt consultation with a pain specialist or multidisciplinary pain management center is recommended, including consideration of a broad array of non-pharmacologic therapies and invasive treatments.

It is important to emphasize that pharmacologic management of the patient with chronic NP should be considered an integral component of a more comprehensive approach that also includes non-pharmacologic treatments. Non-pharmacologic treatments for NP require increased attention and evaluation in controlled trials in which they are administered alone and also in combination with pharmacologic therapies.

Existing pharmacologic treatments for NP are limited, with no more than 40–60% of patients obtaining partial relief of their pain. Continued development of new medications for NP, additional trials involving existing medications alone and in combination to identify characteristics of treatment responders, identification of efficacious non-pharmacologic treatments for NP, and the development of strategies to prevent NP are therefore needed to advance the management of NP [13]. The management of NP is expected to rapidly evolve because of ongoing translational studies, and these evidence-based management recommendations should be updated within five years.

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