Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society

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BACKGROUND: Neuropathic pain (NeP), redefined as pain caused by a lesion or a disease of the somatosensory system, is a disabling condition that affects approximately two million Canadians.
OBJECTIVE: To review the randomized controlled trials (RCTs) and systematic reviews related to the pharmacological management of NeP to develop a revised evidence-based consensus statement on its management.
METHODS: RCTs, systematic reviews and existing guidelines on the pharmacological management of NeP were evaluated at a consensus meeting in May 2012 and updated until September 2013. Medications were recommended in the consensus statement if their analgesic efficacy was supported by at least one methodologically sound RCT (class I or class II) showing significant benefit relative to placebo or another relevant control group. Recommendations for treatment were based on the degree of evidence of analgesic efficacy, safety and ease of use.
RESULTS: Analgesic agents recommended for first-line treatments are gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors. Tramadol and controlled-release opioid analgesics are recommended as second-line treatments for moderate to severe pain. Cannabinoids are now recommended as third-line treatments. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol and botulinum toxin. There is support for some analgesic combinations in selected NeP conditions.
CONCLUSIONS: These guidelines provide an updated, stepwise approach to the pharmacological management of NeP. Treatment should be individualized for each patient based on efficacy, side-effect profile and drug accessibility, including cost. Additional studies are required to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes and treatment of pediatric, geriatric and central NeP.

Key Words: *Analgesic agents; Neuropathic pain; Randomized controlled trials*

La prise en charge pharmacologique de la douleur neuropathique chronique : une déclaration de consensus révisée de la Société canadienne de la douleur

HISTORIQUE : La douleur neuropathique (DNe), redéfinie comme une douleur causée par une lésion ou une maladie du système somatosensoriel, est un trouble invalidant dont sont affligés environ deux millions de Canadiens.
OBJECTIF : Examiner les essais aléatoires et contrôlés (EAC) et les analyses systématiques liées à la prise en charge pharmacologique de la DNe pour préparer une déclaration de consensus révisée, fondée sur des faits probants, à l'égard de sa prise en charge.
MÉTHODOLOGIE : Les EAC, les analyses systématiques et les lignes directrices sur la prise en charge pharmacologique de la DNe ont été évaluées lors d'une réunion de consensus en mai 2012, puis mises à jour en septembre 2013. Les médicaments étaient recommandés dans le document de consensus si leur efficacité analgésique était soutenue par au moins une EAC solide sur le plan méthodologique (classe I ou II), qui démontrait des avantages marqués par rapport à un placebo ou à un autre groupe témoin pertinent. Les recommandations thérapeutiques reposaient sur la qualité des preuves d'efficacité analgésique, d'innocuité et de facilité d'utilisation.
RÉSULTATS : Les analgésiques recommandés pour le traitement de première intention sont les gabapentinoïdes (gabapentine et prégabaline), les antidépresseurs tricycliques et les inhibiteurs spécifiques du recaptage de la sérotonine et de la noradrénaline. Le tramadol et les opioïdes à libération contrôlée sont recommandés en deuxième intention pour la douleur modérée à grave. Les cannabinoïdes sont désormais recommandés en troisième intention, tandis que la méthadone, les anticonvulsivants dont l'efficacité est moins attestée (p. ex., lamotrigine, lacosamide), le tapentadol et la toxine botulique sont recommandés en quatrième intention. Certaines polythérapies analgésiques sont acceptées pour traiter des troubles de DNe particuliers.
CONCLUSIONS : Ces lignes directrices fournissent une démarche mise à jour et graduelle pour la prise en charge pharmacologique de la DNe. Le traitement devrait être personnalisé en fonction de chaque patient, compte tenu de l'efficacité, du profil d'effets secondaires et de l'accessibilité du médicament, y compris son coût. D'autres études s'imposent pour faire des comparaisons directes entre analgésiques et examiner des combinaisons d'analgésiques, les résultats à long terme et le traitement de la DNe en pédiatrie, de la DNe en gériatrie et de la DNe centrale.

Neuropathic pain (NeP) has been redefined as pain caused by a lesion or a disease of the somatosensory system, and may be generated by either the peripheral or central nervous system, or both (1). Pain may be a manifestation of nerve injury, but there are few predictors to indicate which patients will develop this complication. For example, 50% of diabetic patients develop neuropathy during the course of their illness, but only approximately 15% report actual dysesthesias or pain (2). Similarly, breast surgery with transection of the intercostal brachial nerve results in NeP in up to 50% of patients (3). Previous prevalence estimates indicated that 2% to 3% of the population in the developed world experience NeP (4,5). However, newer studies using population-based questionnaires estimate a higher rate of 4% to 8% (6,7), which suggest that approximately two million Canadians experience this disabling condition. Even more striking is that the prevalence of NeP is likely to increase for a number of reasons. The population is aging, and a pandemic of obesity is occurring in the developed world. These factors are largely responsible for increasing rates of postherpetic neuralgia and painful diabetic neuropathy (8,9). In addition, survival rates are increasing among cancer patients, and many of the medical and surgical interventions used in the treatment of cancer (including chemotherapy) can cause NeP (10).

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METHODS

In 2007, the Canadian Pain Society (CPS) produced the first guidelines on pharmacological management of NeP tailored to the clinical practices of Canadian health professionals including analgesic agents specifically available in Canada (11). A consensus meeting was held in Whistler, British Columbia under the direction of the Neuropathic Pain Special Interest Group of the CPS in May 2012 to update these guidelines, given the plethora of systematic reviews and meta-analyses published since 2007 (Appendix A). There is also recent evidence from community-based studies that management of NeP, including postherpetic neuralgia, is not consistent with evidence-based recommendations (12). Funding for this consensus meeting was provided by the Neuropathic Pain Special Interest Group of the CPS. This involved a multidisciplinary group of individuals with research and clinical expertise relevant to the pathophysiology and management of NeP. This group met to review the randomized controlled trials (RCTs) and systematic reviews related to the pharmacological management of NeP to develop a revised evidence-based consensus statement on the management of NeP (13). Subsequent literature was reviewed by the group until September 2013.

Systematic searches on Medline and Cochrane databases were conducted to identify recent systematic reviews, meta-analyses and treatment recommendations, guidelines and/or consensus statements published since the first 2007 CPS consensus statement. Other selected publications and references were also considered. Medications could be recommended in the consensus statement if their analgesic efficacy was supported by at least one methodologically sound RCT (class I or class II) showing significant benefit relative to placebo or another relevant control group. Trials were excluded if they represented uncontrolled studies, had sample sizes of <10 patients or studied cancer NeP except for well-defined postsurgical pain syndromes (eg, postmastectomy pain syndrome) and chemotherapy-induced NeP. Trials were also excluded if they studied trigeminal or glossopharyngeal neuralgia because these conditions have their own specific medical and surgical treatments (14). The initial draft of the present manuscript was prepared by the first author and subsequent revisions were based on feedback from the other authors until consensus was achieved.

The current guidelines are based on quality of evidence of analgesic efficacy, side-effect profiles and ease of use. Medications were considered to be first line if there was high-quality evidence of efficacy (at least one class I study or two consistent class II studies – level of recommendation grade B or better) (15); positive results in at least two NeP models (16); and if they were considered to be straightforward and of sufficient tolerability to prescribe and monitor. Medications were considered to be second or third line if there was high-quality evidence of efficacy, but the medication required more specialized follow-up and monitoring. Fourth-line treatments had at least one positive RCT, but require further study. A limitation of this algorithmic classification is that grading of tolerability and ease of use was based solely on consensus opinion of the authors.

Target users for these guidelines are physicians, nurse practitioners and other allied health care individuals involved in the management of NeP. These guidelines have been endorsed by the Canadian Pain Coalition, an advocacy group for patients living with chronic pain. The published guidelines will be disseminated through various websites, including the CPS website, and reprints will be made available to undergraduate and postgraduate trainees, and practicing health care workers attending continuing medical education events. They will be updated periodically by the Neuropathic Pain Special Interest Group of the CPS.

CLINICAL CHARACTERISTICS AND DIFFERENTIAL DIAGNOSES OF NeP

The clinical features of NeP can be divided into spontaneous pain and stimulus-evoked pain. Spontaneous pain is commonly described as burning or intense tightness with superimposed shooting or lancinating pain. Stimulus-evoked pain includes allodynia, defined as painful sensations in response to a normally nonpainful stimulus, and hyperalgesia, defined as increased pain sensitivity in response to a normally painful stimulus. Superimposed autonomic features, such as alterations in temperature, colour and sweating as well as the development of trophic changes, suggest a diagnosis of reflex sympathetic dystrophy or complex regional pain syndrome (17).

The differential diagnosis of NeP is extensive and includes central and peripheral causes. Examples of central NeP include poststroke pain ('thalamic pain syndrome'), pain related to multiple sclerosis and pain due to spinal cord injury. Common causes of peripheral NeP include painful diabetic neuropathy, postherpetic neuralgia and surgically induced NeP, following thoracotomy, amputation, breast surgery and back surgery sometimes associated with nerve root fibrosis.

The diagnosis of NeP is based primarily on the patient's history and physical examination. Postherpetic neuralgia and painful diabetic neuropathy are typically easy to diagnose when there is a history of shingles and diabetes mellitus, respectively. However, pain radiating into an extremity can be either referred myofascial pain or NeP, and these can be much more challenging to diagnose. Simple questionnaires based on sensory descriptors and sensory examination have been developed to differentiate between somatic pain and NeP. Instruments such as the *Douleur Neuropathique 4* and the Leeds Assessment of Neuropathic Symptoms and Signs have been shown to be valid and reliable discriminators of NeP (18,19). In addition, the presence of true weakness (sometimes difficult to differentiate from pain-related or antalgic weakness), reduced or absent reflexes, allodynia and hyperalgesia all favour a diagnosis of NeP. Electromyography and nerve conduction studies are sometimes useful to provide more objective evidence of nerve injury, although electromyography study results are often normal in small-fibre neuropathies. Guidelines are available to determine the diagnostic certainty of NeP (possible, probable or definite) based on history, sensory signs, neurophysiological testing and neuroimaging (1).

GENERAL CONSIDERATIONS

Because NeP can be severe and unrelenting, it is important to recognize and treat comorbidities such as anxiety and depression. It is also important to recognize secondary treatment goals such as improving sleep, ability to function and overall quality of life. However, treatment goals must be realistic. Caregivers should validate the patient's pain to gain their trust and should set realistic treatment goals. This is typically straightforward from the caregiver's point of view because most NeP states are based on well-defined injuries to the nervous system. The primary goal in most cases is to make the pain 'bearable' or 'tolerable' – not to eliminate the pain. Such goal setting can make a considerable difference in patient satisfaction when pharmacological treatments are instituted.

Due to the lack of head-to-head trials to guide treatment choices, one approach to estimate the relative efficacy of analgesic agents in RCTs is to use the number needed to treat (NNT) – the number of patients that need to be treated with a certain drug to provide one additional patient with at least 50% pain relief relative to the comparator group. The NNT is used to estimate treatment efficacy, recognizing that there are limitations to this methodology including variability in RCTs (eg, crossover versus parallel design) and the short-term nature of most RCTs. Another approach to estimate efficacy is to determine the effect size – defined as the mean difference between active agent and placebo divided by the SD. The effect size can be classified as small (<0.5), medium (0.5 to <0.8) or large (≥0.8) (20).

Appendix A summarizes the results of a systematic search of systematic reviews, meta-analyses and treatment recommendations, guidelines and/or consensus statements published since the first 2007 CPS consensus statement. These results were reviewed and approved by two coauthors (DEM and IG) and provide the basis for the consensus statement presented here.

FIRST-LINE ANALGESICS

Two classes of medications are recommended for first-line treatment in the management of NeP – anticonvulsants and certain antidepressants.

Anticonvulsants

The gabapentinoids, gabapentin and pregabalin, bind to presynaptic voltage-gated calcium channels in the dorsal horn, reducing the release of excitatory neurotransmitters such as glutamate and substance P (21). These agents have been studied in large clinical trials, although mainly in the management of painful diabetic neuropathy and postherpetic neuralgia. Gabapentin has shown efficacy in three trials involving painful diabetic neuropathy and two trials involving postherpetic neuralgia (22); however, four RCTs involving gabapentin have been negative, including a trial of gabapentin in chemotherapy-induced painful neuropathy (23-26). The combined NNTs for gabapentin in the management of painful polyneuropathy and postherpetic neuralgia were 6.4 and 4.3, respectively (27).

Pregabalin is an analogue of gabapentin, with the same mechanism of action, but it manifests linear pharmacokinetics and has higher affinity for the presynaptic calcium channel. Four studies have shown that pregabalin provides significant pain relief and improved quality of life in painful diabetic neuropathy (28) and an additional four trials have shown efficacy in postherpetic neuralgia (22). The combined NNTs for pregabalin in the management of painful diabetic neuropathy and postherpetic neuralgia were 4.5 and 4.2, respectively (27). Pregabalin has also been studied in chronic central NeP following spinal cord injury, with evidence of significant pain relief (29,30). However, a study investigating pregabalin in the treatment of NeP associated with chronic lumbosacral radiculopathy was negative (31), as was a recent trial involving refractory painful diabetic neuropathy (32). A study investigating the safety and efficacy of pregabalin in patients with central poststroke pain showed no significant improvement in the primary end point of pain intensity; however, there were some improvements in secondary end points including sleep and anxiety (33).

Carbamazepine remains the drug of first choice for tic douloureux (idiopathic trigeminal neuralgia), but otherwise is not recommended for the management of NeP (14). Anecdotally, it may also be useful in the management of glossopharyngeal neuralgia (14).

Antidepressant agents

The tricyclic antidepressants (TCAs) have been shown to provide significant pain relief in various NeP conditions in many clinical trials, although the sample sizes have tended to be relatively small and most of these trials have used a crossover design (34). The combined NNTs for TCAs in the management of painful diabetic neuropathy and postherpetic neuralgia were 2.1 and 2.8, respectively (27).

The serotonin noradrenaline reuptake inhibitors (SNRIs), duloxetine and venlafaxine, have mainly been studied in painful diabetic neuropathy. Duloxetine has demonstrated significant pain relief relative to placebo in three RCTs (28), with a combined NNT of 5.0 (27). A recent study investigating duloxetine in the management of chemotherapy-induced painful peripheral neuropathy showed a significant reduction in pain intensity relative to placebo, with a moderate effect size of 0.51 (35). However, duloxetine has also been studied in patients with central NeP due to spinal cord injury or stroke, and the results of this trial were negative (36).

Venlafaxine has shown efficacy in trials involving painful diabetic neuropathy (37) and mixed painful polyneuropathy (38) at doses of 150 mg to 225 mg daily. However, the latter trial, comparing venlafaxine with imipramine, showed a higher proportion of responders in the venlafaxine group. Another trial investigating venlafaxine plus gabapentin in the management of painful diabetic neuropathy showed significant pain relief relative to placebo plus gabapentin (39).

SECOND-LINE ANALGESICS

Two opioid-type medications are recommended for second-line treatment in the management of NeP.

Tramadol

Tramadol is a weak opioid agonist and mimics some of the properties of the TCAs in that it inhibits reuptake of noradrenalin and serotonin (40). Tramadol has shown significant benefit in three RCTs investigating painful diabetic neuropathy and mixed NeP syndromes, and has an overall NNT of 4.9 (27). Tramadol leads to less constipation and nausea than other weak opioid analgesics, such as codeine (41), but is more expensive in Canada. Tramadol should be used with caution in conjunction with selective serotonin reuptake inhibitors (SSRIs) because of increased risk of confusion and serotonin syndrome, especially among elderly patients (42).

Opioid analgesics

A recent meta-analysis of opioids for chronic noncancer pain included 16 randomized trials for chronic NeP (43). Most of these trials investigated painful diabetic neuropathy and postherpetic neuralgia; however, other trials focused on postamputation pain, sciatica and spinal cord injury pain. The authors found that opioids were more effective than placebo, with a moderate effect size (0.56) for pain. There was a small effect size (0.24) in favour of opioids for function in 13 of these RCTs. The combined NNT for opioids in the management of painful polyneuropathy and postherpetic neuralgia was 2.6 (27).

THIRD-LINE ANALGESICS

One class of medication is recommended for third-line treatment in the management of NeP – cannabinoids.

Cannabinoids

The cannabinoids are analgesic agents with increasing evidence of efficacy in central NeP states, with a combined NNT of 3.4 (27). Dronabinol produced modest analgesia in a trial investigating central pain in multiple sclerosis (44). A 50/50 mixture of tetrahydrocannabinol and cannabidiol in the form of an oral mucosal spray provided significant benefit in another trial investigating central pain in multiple sclerosis (45). A recent systematic review of clinical trials investigating cannabinoids in chronic pain determined that, since 2006, there have been seven high-quality (class I and II) studies investigating NeP, and all of these studies except one were positive (46). Four of these studies involved smoked cannabis for the management of HIV neuropathy (two studies), posttraumatic or postsurgical NeP, and combined central and peripheral NeP states. Two trials involved the cannabinoid oral mucosal spray in the management of multiple peripheral NeP states with allodynia and painful diabetic neuropathy. The single negative trial compared the synthetic cannabinoid nabilone with dihydrocodeine in peripheral NeP conditions, and found that dihydrocodeine was superior to nabilone. A more recent trial found that nabilone was effective in relieving symptoms of painful diabetic neuropathy, and also improved disturbed sleep and overall quality of life using an enriched enrollment withdrawal design (47).

FOURTH-LINE ANALGESICS

Several classes of medications can be considered to be fourth-line treatments for NeP – SSRIs, other anticonvulsants, methadone, topical lidocaine and miscellaneous agents.

SSRIs

SSRIs appear to have a weak analgesic effect in the management of NeP. Citalopram (48), paroxetine (49) and escitalopram (50) have been found to be efficacious in the management of painful diabetic neuropathy and painful polyneuropathy independent of their antidepressant effects, but fluoxetine has not (51). However, the combined NNT for all four studies was 6.8 (27). SSRIs used primarily for depression may inhibit the metabolism of TCAs and may increase the risk for serotonin syndrome (52).

Other anticonvulsants

Lamotrigine has been studied in a variety of peripheral and central NeP conditions, with variable results. Four studies investigating painful diabetic neuropathy, two studies investigating mixed NeP and single studies investigating chemotherapy-induced NeP and spinal cord injury pain were negative. Positive trials investigating HIV-related neuropathy, trigeminal neuralgia and central poststroke pain were reported; however, the sample sizes tended to be small, with significant dropout rates (53).

Lacosamide is an anticonvulsant agent with sodium channel-blocking properties. Lacosamide has been studied in five RCTs investigating painful diabetic neuropathy. There was modest benefit in each trial, with an NNT in the range of 10 to 12. Lacosamide, therefore, has limited efficacy in the treatment of painful diabetic neuropathy (54).

Topiramate and valproic acid have produced mixed results in NeP trials (27).

Methadone

Methadone is a synthetic opioid analgesic that may be useful in the management of NeP related to its *N*-methyl-D-aspartate antagonist properties (55). Two small RCTs demonstrated benefit from methadone in chronic NeP (56,57) and survey data suggested efficacy in mixed NeP conditions (58). Methadone has excellent oral bioavailability and a duration of action of at least 8 h with repetitive dosing. It has an elimination half-life of 24 h to 36 h, which requires close observation during the titration phase. There are no high-quality RCTs to support the use of methadone in the management of NeP, although guidelines for the use of methadone in the management of chronic pain are available (59). An RCT comparing methadone with other oral opioids is urgently needed.

Topical lidocaine

Topical lidocaine, as a sodium channel blocker, may be useful in the management of NeP. Systemic side effects are extremely rare as a result of negligible blood levels (60). Topical lidocaine is most practical for patients with localized peripheral NeP, such as postherpetic neuralgia, and remains a second-line agent for this condition based on three positive RCTs investigating lidocaine patch 5% in the management of postherpetic neuralgia (27). However, recent trials of lidocaine cream or patch 5% failed to provide benefit in patients with postsurgical peripheral nerve injury (61) or in mixed NeP (62). Therefore, there are conflicting results among placebo-controlled trials investigating topical lidocaine for NeP.

Miscellaneous agents

Tapentadol is a novel analgesic that has recently become available in Canada. It is pharmacologically similar to tramadol in that it has a dual mechanism of action, but has higher affinity for the mu opioid receptor and has only noradrenergic activity as a monoamine reuptake inhibitor. Tapentadol is approximately one-fifth as potent as oxycodone and has shown efficacy in the management of painful diabetic neuropathy, with greater tolerability (63).

Topical capsaicin may have utility in the management of localized NeP such as postherpetic neuralgia. Following application to the skin, capsaicin initially causes enhanced sensitivity of nociceptors, followed by persistent desensitization after repeated application of low-concentration (<1%) capsaicin or a single application of high-concentration (8%) capsaicin. Several older studies involving small sample sizes indicate that low-concentration capsaicin provides minimal benefit relative to placebo creams (64). On the other hand, high-concentration capsaicin has recently been studied in four trials investigating postherpetic neuralgia and two trials investigating painful HIV neuropathy using 0.04% topical capsaicin as the control to maintain blinding. All of these studies showed significant benefit relative to the control for up to 12 weeks after a single application. The NNT for the postherpetic neuralgia studies was in the range of eight to 10 and, for the HIV-neuropathy studies, was approximately 6.2 (65). High-concentration capsaicin requires preapplication of local anesthetic because of the intense burning sensation it produces. This agent is quite expensive and only available in Canada through compassionate release from Health Canada.

Botulinum toxin has been studied in two RCTs involving NeP. Both studies were positive, with significant reduction in pain intensity for 12 to 14 weeks, but these studies were likely underpowered due to small sample sizes. A crossover trial involving patients with painful diabetic neuropathy included only 18 patients (66) and a parallel design trial involving patients with focal painful neuropathies included only 29 patients (67). Evidence for the role of botulinum toxin in the management of NeP, therefore, remains preliminary.

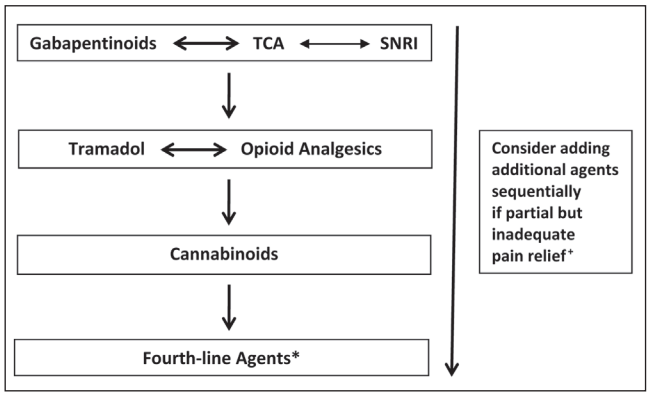

Figure 1) *Algorithm for the pharmacological management of neuropathic pain. *Topical lidocaine (second line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, botulinum toxin; +Limited randomized controlled trial evidence to support add-on combination therapy. TCA Tricyclic antidepressants; SNRI Serotonin noradrenaline reuptake inhibitors*

Combination pharmacotherapy

Combining ≥2 analgesic agents in the management of NeP is an attractive option because combination pharmacotherapy may improve analgesic efficacy and has the potential to reduce the overall side effect profile if synergistic effects allow for dose reductions of combined drugs (68). A recent Cochrane review of combination pharmacotherapy for the treatment of NeP in adults identified 21 eligible studies (69). The majority of these studies evaluated the combination of an opioid with gabapentin, pregabalin or a TCA, the combination of gabapentin and nortriptyline, and various topical medications. Meta-analysis was possible for only one combination – gabapentin plus opioid versus gabapentin alone. The meta-analysis demonstrated modest superiority of gabapentin plus opioid versus gabapentin alone, although the combination produced significantly more dropouts due to accentuated side effects related to combination treatments. A recent RCT comparing a combination of standard doses of duloxetine (60 mg daily) and pregabalin (300 mg daily) with high-dose monotherapy (duloxetine 120mg daily or pregabalin 600 mg daily) found no significant difference in 24 h average pain, although side effects were comparable (70). Available studies do not support a recommendation of any one specific drug combination for NeP, although these studies do provide a rationale for combination pharmacotherapy.

STEPWISE PHARMACOLOGICAL MANAGEMENT OF NeP

Figure 1 provides an updated algorithm for the pharmacological management of NeP, and Table 1 provides dosing guidelines for selected agents. Nonpharmacological interventions, including physiotherapy, exercise programs and psychological treatment modalities, are essential to enhance outcome.

Relative to the previous guidelines for management of NeP published in 2007 (9), duloxetine has been upgraded from a second-line to a first-line agent based on recent evidence of efficacy in the management of chemotherapy-induced painful neuropathy (35) in addition to previously established efficacy in painful diabetic neuropathy.

TCAs, gabapentinoids and SNRIs are, therefore, now all considered to be first-line agents in the management of chronic NeP. TCAs have the advantage of low cost and once-daily dosing, but can produce drowsiness and significant anticholinergic side effects, including dry mouth, constipation and urinary retention, and are, thus, poorly tolerated in the elderly. Secondary amine TCAs (nortriptyline

TABLE 1
Dosing regimens for selected agents for neuropathic pain

Agent	Starting dose and titration	Usual maintenance dose	Adverse effects	Comments
Tricyclic antidepressants				
Amitriptyline Nortriptyline Desipramine	10–25 mg/day; increase weekly by 10 mg/day	10–100 mg/day	Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention, weight gain, arrhythmia	Amitriptyline more likely to produce drowsiness and anticholinergic side effects; contraindicated in patients with glaucoma, symptomatic prostatism and significant cardiovascular disease
Serotonin noradrenaline reuptake inhibitors				
Venlafaxine	37.5 mg/day; increase weekly by 37.5 mg/day	150–225 mg/day	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
Duloxetine	30 mg/day; increase weekly by 30 mg/day	60–120 mg/day	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Anticonvulsants				
Gabapentin	100–300 mg/day; increase weekly by 100–300 mg/day	300–1200 mg three times daily	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderly patients
Pregabalin	25–150 mg/day; increase weekly by 25–150 mg/day	150–300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
Carbamazepine	100 mg once daily; increase weekly by 100–200 mg/day	200–400 mg three times daily	Drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash	Drug of first choice for tic douloureux (idiopathic trigeminal neuralgia); as an enzyme inducer, may interfere with activity of other drugs such as warfarin; monitoring of blood counts and liver function tests recommended
Controlled-release opioid analgesics				
Morphine	15 mg every 12 h	30–120 mg every 12 h	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for addiction
Oxycodone	10 mg every 12 h	20–60 mg every 12 h		
Fentanyl	12–25 µg/h patch	25–100 µg/h patch		
Hydromorphone	3 mg every 12h	6–24 mg every 12 h		
Others				
Tramadol	50 mg/day; increase weekly by 50 mg/day	50–100 mg four times daily or 100–400 mg daily (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypotension	May lower seizure threshold; use with caution in patients with epilepsy
Lidocaine		5% patches or gel applied to painful areas for 12 h in a 24 h period		Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
Tetrahydro-cannabinol/ cannabidiol (nabiximols)	1–2 sprays every 4 h, maximum 4 sprays on day 1, titrate slowly	Two sprays four times daily	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug testing for cannabinoids; monitor application site (oral mucosa)
Nabilone	0.25–0.5 mg at night; increase weekly by 0.5 mg/day	3 mg twice daily	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not test positive for cannabinoids on routine urine drug testing

and desipramine) are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) with comparable analgesic efficacy (71). Cardiac toxicity is also a risk factor with TCAs, which are relatively contraindicated in patients with a history of arrhythmia (72).

Gabapentin and pregabalin appear to be similar in their mechanisms of action and side-effect profiles, and allow for more rapid titration than antidepressant agents. Pregabalin carries the advantage of twice-daily dosing and linear pharmacokinetics relative to gabapentin. Gabapentinoids in general have few drug interactions, but are dependent on renal excretion and, therefore, require dosage reductions in patients with renal insufficiency (72).

If a TCA fails or is contraindicated, the use of a gabapentinoid or an SNRI, such as duloxetine, should be considered. If one of the latter agents provides only partial pain relief, it is reasonable to add the other agent because there is evidence that combination pharmacotherapy can be helpful (68).

When first-line medications fail or provide inadequate pain relief, tramadol or a conventional opioid analgesic may be useful as a second-line treatment. It is also reasonable to consider a short-acting opioid, such as codeine or oxycodone (sometimes combined with acetaminophen), for breakthrough pain during titration of a first-line agent if needed for severe pain. Controlled-release opioid analgesics are considered to be second-line agents in the management of NeP because of their extensive side-effect profile and the risk of opioid misuse, abuse and addiction leading to cautionary prescribing and monitoring. A recent meta-analysis of 62 RCTs found that the most common adverse effects associated with opioids were nausea (28%), constipation (25%), drowsiness (24%), dizziness (18%) and vomiting (15%) (43). Although tolerance may occur to several of these side effects, there is very little tolerance to constipation and almost all patients placed on a controlled-release opioid analgesic require a bowel regimen with continued monitoring of bowel function. Potential long-term complications of opioid

analgesia include opioid-induced hyperalgesia (73) and opioid-induced endocrinopathy (74,75). Endocrine effects manifest as hypogonadism and increased risk for osteopenia. Monitoring for risk for opioid addiction is also challenging. A review suggested that aberrant drug-related behaviours and illicit drug use occurred in 10% to 15% of patients receiving chronic opioid therapy (76). Canadian guidelines for the safe and effective use of opioids for chronic noncancer pain, including monitoring for addiction, are strongly recommended (77).

The cannabinoids have now advanced to third-line agents in the management of chronic NeP based on increasing evidence of efficacy in multiple pain models including HIV neuropathy, post-traumatic and postsurgical NeP, painful diabetic neuropathy and spinal cord injury pain (46,47). However, the cannabinoids also require close monitoring, are contraindicated in patients with a history of psychosis and most of these agents, including the oral mucosal spray, are expensive.

Fourth-line agents in the management of NeP include methadone, tapentadol and anticonvulsants, with lesser evidence of efficacy such as lacosamide, lamotrigine and topiramate. Topical lidocaine has been relegated to fourth-line status because of conflicting evidence of efficacy except in the management of postherpetic neuralgia, for which it remains a second-line option.

It is more challenging to provide a stepwise systematic approach to the management of central NeP because of the relative paucity of high-quality studies and conflicting evidence of efficacy. For instance, lamotrigine was found to be useful in the management of central poststroke pain, but not for spinal cord injury pain (53). Similarly, pregabalin has been found to be efficacious in the management of spinal cord injury pain (29,30), but not in central poststroke pain (33). However, it is reasonable to consider the gabapentinoids and cannabinoids as first-line agents for the management of spinal cord injury pain (78), and TCAs (79) and lamotrigine (53) in the management of central poststroke pain.

INVASIVE TECHNIQUES IN THE MANAGEMENT OF NeP

Although interventional techniques for NeP management are beyond the scope of the present consensus statement, they are usually considered when standard pharmacological treatments fail and psychological screening shows emotional stability. Intravenous lidocaine infusions are generally safe, but evidence of efficacy is limited to one to two weeks postinfusion (80). Two recent comprehensive reviews of interventional management of NeP concluded that weak recommendations could be made for epidural steroid injections for radiculopathy, and spinal cord stimulation for failed back surgery syndrome and complex regional pain syndrome type 1 (81,82).

SUMMARY

The present updated consensus statement provides a stepwise pharmacological approach to the management of NeP. Gabapentinoids, TCAs and SNRIs represent first-line treatments for NeP either individually or in combination. When these agents fail, conventional opioid analgesics and tramadol provide important avenues of treatment, bearing in mind their associated risks and adverse effect profiles. Cannabinoids are now considered to be third-line agents based on recent evidence of efficacy, but also require judicious prescribing practices. Novel treatment approaches are required to improve our management of NeP and further studies are necessary to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes and treatments of pediatric, geriatric and central NeP.

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APPENDIX A: SYSTEMATIC LITERATURE SEARCH RESULTS

Results from Medline and Cochrane databases for pharmacological management of neuropathic pain using TITLE terms 'systematic reviews', 'meta-analyses' and 'guideline OR statement OR recommendation OR consensus' (English language literature since 2007) were tabulated. Articles related to nonpharmacological interventions, cancer pain due to tumour infiltration of nerve, and prevention and epidemiology of neuropathic pain were excluded. A total of 87 systematic reviews and meta-analyses, and 21 consensus statements/guidelines were reviewed. A full list of the included references is available from the authors on request.

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