# Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society

DE Moulin MD[1], AJ Clark MD[2], I Gilron MD MSc[3], MA Ware MD[4], CPN Watson MD[5], BJ Sessle MDS PhD[5], T Coderre PhD[4], PK Morley-Forster MD[1], J Stinson RN PhD[6], A Boulanger MD[7], P Peng MBBS[5,8], GA Finley MD[9,10], P Taenzer PhD[2], P Squire MD[11], D Dion MD MSc[7], A Cholkan CA[12], A Gilani MD[13], A Gordon MD[5,12], J Henry PhD[13], R Jovey MD[5], M Lynch MD[9], A Mailis-Gagnon MD MSc[5], A Panju MB ChB[13], GB Rollman PhD[1], A Velly DDS PhD[14]

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Neuropathic pain (NeP), generated by disorders of the peripheral and central nervous system, can be particularly severe and disabling. Prevalence estimates indicate that 2% to 3% of the population in the developed world suffer from NeP, which suggests that up to one million Canadians have this disabling condition. Evidence-based guidelines for the pharmacological management of NeP are therefore urgently needed. Randomized, controlled trials, systematic reviews and existing guidelines focusing on the pharmacological management of NeP were evaluated at a consensus meeting. Medications are recommended in the guidelines if their analgesic efficacy was supported by at least one methodologically sound, randomized, controlled trial showing significant benefit relative to placebo or another relevant control group. Recommendations for treatment are based on degree of evidence of analgesic efficacy, safety, ease of use and cost-effectiveness. Analgesic agents recommended for first-line treatments are certain antidepressants (tricyclics) and anticonvulsants (gabapentin and pregabalin). Second-line treatments recommended are serotonin noradrenaline reuptake inhibitors and topical lidocaine. Tramadol and controlled-release opioid analgesics are recommended as third-line treatments for moderate to severe pain. Recommended fourth-line treatments include cannabinoids, methadone and anticonvulsants with lesser evidence of efficacy, such as lamotrigine, topiramate and valproic acid. Treatment must be individualized for each patient based on efficacy, side-effect profile and drug accessibility, including cost. Further studies are required to examine head-to-head comparisons among analgesics, combinations of analgesics, long-term outcomes, and treatment of pediatric and central NeP.

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

## Le traitement pharmacologique de la douleur neuropathique chronique : Déclaration et lignes directrices consensuelles de la Société canadienne pour le traitement de la douleur

La douleur neuropathique (DNE), causée par des troubles du système nerveux périphérique et du système nerveux central, peut être particulièrement marquée et invalidante. D'après les estimations de prévalence, de 2 % à 3 % de la population du monde industrialisé en souffrent, ce qui laisse supposer que jusqu'à un million de Canadiens seraient atteints de ce trouble invalidant. Des lignes directrices probantes pour le traitement pharmacologique de la DNE s'imposent donc instamment. Des essais aléatoires et contrôlés, des analyses systématiques et les lignes directrices courantes sur le traitement pharmacologique de la DNE ont fait l'objet d'une évaluation à une réunion consensuelle. Les médicaments sont recommandés dans les lignes directrices si leur efficacité analgésique est étayée par au moins un essai aléatoire et contrôlé à la méthodologie solide, qui démontre des avantages importants par rapport à un placebo ou à un groupe témoin pertinent. Les recommandations de traitement se fondent sur les degrés probants d'efficacité analgésique, d'innocuité, de facilité d'utilisation et de rentabilité. Les analgésiques recommandés en première ligne sont certains antidépresseurs (tricycliques) et anticonvulsivants (gabapentine et prégabaline). Les traitements de deuxième ligne recommandés sont les inhibiteurs du recaptage de la sérotonine et de la noradrénaline et la lidocaïne topique. Le tramadol et les analgésiques opioïdes à libération contrôlée sont recommandés comme traitements de troisième ligne pour des douleurs moyennes à graves. Les traitements de quatrième ligne recommandés sont les cannabinoïdes, la méthadone et des anticonvulsivants dont l'efficacité est moins démontrée, tels que la lamotrigine, le topiramate et l'acide valproïque. Il faut adapter le traitement à chaque patient d'après l'efficacité, le profil d'effets secondaires et l'accessibilité du médicament, y compris le coût. D'autres études devront être menées pour examiner les comparaisons directes entre les analgésiques, les associations d'analgésiques, les issues à long terme et le traitement de la DNE pédiatrique et centrale.

[1]*University of Western Ontario, London, Ontario;* [2]*University of Calgary, Calgary, Alberta;* [3]*Queen's University, Kingston, Ontario;* [4]*McGill University, Montreal, Quebec;* [5]*University of Toronto;* [6]*The Hospital for Sick Children, Toronto, Ontario;* [7]*Universite de Montreal, Montreal, Quebec;* [8]*University Health Network, Toronto, Ontario;* [9]*Dalhousie University;* [10]*IWK Health Centre, Halifax, Nova Scotia;* [11]*University of British Columbia, Vancouver, British Columbia;* [12]*Wasser Pain Management Centre, Mount Sinai Hospital, Toronto, Ontario;* [13]*McMaster University, Hamilton, Ontario;* [14]*University of Minnesota, Minneapolis, Minnesota, USA*

*Please see appendix for complete author affiliations*

*Correspondence: Dr Dwight Moulin, London Regional Cancer Program, 790 Commissioners Road East, London, Ontario N6A 4L6. Telephone 519-685-8661, fax 519-685-8636, e-mail dwight.moulin@lhsc.on.ca*

  

Neuropathic pain (NeP), defined by the International Association for the Study of Pain as pain "initiated or caused by a primary lesion or dysfunction in the nervous system" (1), is a challenging clinical problem because the pain is often severe and disabling (2). It can be caused by lesions of the peripheral or central nervous system, or both. Pain can be a manifestation of nerve injury, but there are few predictors to indicate which patients will develop this complication. For instance, 50% of diabetics develop neuropathy during the course of their illness, but only approximately 10% report actual dysesthesias or pain (3). Similarly, breast surgery with transection of the intercostal brachial nerve results in NeP in up to 50% of patients (4). Prevalence estimates indicate that 2% to 3% of the population in the developed world suffer from NeP (5), which suggests that up to one million Canadians have this disabling condition. However, the prevalence of NeP is increasing because the population is aging and several NeP syndromes including painful diabetic neuropathy and postherpetic neuralgia are more common in the elderly (6).

## METHODS

A consensus meeting was held under the direction of the Neuropathic Pain Special Interest Group of the Canadian Pain Society. This involved a multidisciplinary group of individuals with research and clinical expertise relevant to the pathophysiology and management of NeP. Another individual is a patient advocate for the management of NeP. This group met to review the randomized, controlled trials (RCTs) related to the pharmacological management of NeP to develop evidence-based guidelines that are applicable to the clinical practices of Canadian health professionals.

Relevant publications were identified through searches of Medline and the Cochrane Database, screening of references from published peer-reviewed articles, reviews of existing guidelines and individual knowledge of the authors. Medications were recommended in the guidelines if their analgesic efficacy was supported by at least one positive, methodologically sound RCT (level of evidence Grade 1B or better) (7) written in English. Trials were excluded if they represented uncontrolled studies, had samples of fewer than 10 patients or were taken from cancer NeP studies, except for well-defined postsurgical pain syndromes (eg, postmastectomy pain syndrome). 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.

These guidelines are based on quality of evidence of analgesic efficacy, side-effect profiles, ease of use and cost. More specifically, medications were considered first- or second-line if there was high-quality evidence of efficacy and if they were considered straightforward to prescribe and monitor. First-line analgesics were separated from second-line analgesics based on quality of evidence and evidence of efficacy. Medications were considered third-line if there was good evidence of efficacy, but more specialized follow-up and monitoring was required. Fourth-line treatments had at least one positive RCT, but required further study.

## CLINICAL FEATURES 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, which is pain in response to a normally nonpainful stimulus, and hyperalgesia, defined as increased pain 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 (8).

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 radicular pain due to nerve root fibrosis following failed back surgery. In fact, chronic back pain on a nociceptive basis frequently coexists with radicular pain in the setting of failed back syndrome.

The diagnosis of NeP is based primarily on the patient's history and physical examination. Postherpetic neuralgia and painful diabetic neuropathy are usually 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 or NeP, and these can be much more challenging. Simple questionnaires based on sensory descriptors and sensory examination have been developed to differentiate between somatic and NeP. Such instruments have been shown to be valid and reliable discriminators of NeP (9,10). 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 condition studies are sometimes useful to provide more objective evidence of nerve injury, although electromyography study results are often normal in small fibre neuropathies.

## GENERAL CONSIDERATIONS IN THE MANAGEMENT OF NeP

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. To accomplish this, it is important for caregivers to validate the patient's pain to gain trust. This is usually straightforward from the caregiver's point of view, because most NeP states are based on well-defined injuries to the nervous system. It is also important to convey that the primary goal in most cases is to make the pain 'bearable' or 'tolerable' – not to eliminate the pain. This can make a huge difference in patient satisfaction when pharmacological treatments are instituted.

Because there is a lack of head-to-head trials to guide treatment choices, one approach to estimate the relative efficacy of analgesic agents in RCTs is to utilize the number needed to treat (NNT) – the number of patients that need to be treated with a certain drug to obtain one patient with at least 50% pain relief. 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.

## FIRST-LINE ANALGESICS

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

**Tricyclic antidepressants**

The tricyclic antidepressants (TCAs) provide the best evidence of efficacy in the management of NeP. Although the definitive mechanism of action of tricyclic analgesia is unknown, these drugs block the reuptake of noradrenaline and serotonin, block hyperalgesia induced by N-methyl-D-aspartate agonists and also have sodium channel blocking properties (11). The TCAs, therefore, have analgesic properties independent of their antidepressant effects.

Two systematic reviews of antidepressants in NeP revealed a total of 17 RCTs involving 10 antidepressants (12,13). The NNT was approximately 2.5. There was no difference in the NNT between TCAs with balanced inhibition of reuptake of serotonin and noradrenaline (amitriptyline, imipramine) and those with relatively selective inhibition of noradrenaline uptake (desipramine, nortriptyline). Similarly, in terms of the NNT, the efficacy for TCAs was nearly identical regardless of the underlying condition: diabetes mellitus, herpes zoster, traumatic nerve injury or stroke.

**Anticonvulsants**

Gabapentin and pregabalin bind to presynaptic voltage-gated calcium channels in the dorsal horn, resulting in a decrease in the release of excitatory neurotransmitters such as glutamate and substance P (14). In two studies of painful diabetic neuropathy (15) and postherpetic neuralgia (16), gabapentin produced significant pain relief relative to placebo, and significant improvement in measures of quality of life and mood. The combined NNT for gabapentin in the management of NeP is approximately 4 (17).

Pregabalin is an analogue of gabapentin with the same mechanism of action, but manifests linear pharmacokinetics and has higher affinity for the presynaptic calcium channel. Large RCTs have shown that pregabalin provides significant pain relief and improved quality of sleep in postherpetic neuralgia (18,19), painful diabetic neuropathy (20-22) or both (23). The overall NNT for pregabalin in these conditions is 4.2 (17). Pregabalin has also been studied in chronic central NeP following spinal cord injury, with resulting evidence of significant pain relief (24).

Carbamazepine remains the drug of first choice for tic douloureux (idiopathic trigeminal neuralgia) but otherwise is not recommended for the management of NeP (5).

## SECOND-LINE ANALGESICS

**Serotonin noradrenaline reuptake inhibitors**

The newer mixed serotonin noradrenaline reuptake inhibitors (SNRIs), venlafaxine and duloxetine, have NNTs of approximately 4.6 and 5.2, respectively (25). Duloxetine has demonstrated significant pain relief relative to placebo in three RCTs involving patients with painful diabetic neuropathy (26-28) but is not presently available in Canada. Venlafaxine has shown efficacy in trials involving painful diabetic neuropathy (29) and mixed painful polyneuropathy (30) at doses of 150 mg to 225 mg per day. However, the latter trial also compared venlafaxine with imipramine, and imipramine showed a higher proportion of responders (30).

**Topical lidocaine**

Topical lidocaine, a sodium channel blocker, is useful in the management of NeP; systemic side effects are extremely rare as a result of minimal blood levels (31). Topical lidocaine is most practical for patients with localized peripheral NeP such as postherpetic neuralgia. Lidocaine patch 5% has been shown to be useful in the management of a variety of focal NeP syndromes, with an NNT of 4.4 (17). However, all of these trials were of short duration (up to three weeks) and had other limitations. One trial (32) used an enriched enrolment design (only patients who responded to open-label treatment were included) and two other studies (33,34) were derived from post hoc analyses of larger trials involving multiple NeP states. The 5% lidocaine patch is not available in Canada, but gel or cream at a concentration of 5% or 10% can be compounded by pharmacists. Lidocaine gel (5%) has demonstrated significant pain relief for up to 8 h in postherpetic neuralgia (35).

## THIRD-LINE ANALGESICS

**Tramadol**

Tramadol is a unique analgesic agent that demonstrates low-affinity binding for the mu opioid receptor, and inhibits reuptake of noradrenaline and serotonin (36). Tramadol is a weak opioid agonist and mimics some of the properties of the TCAs. Tramadol has shown significant benefit in three RCTs of painful diabetic neuropathy and mixed NeP syndromes, and provides an overall NNT of 3.9 (17). Tramadol produces less constipation and nausea than other weak opioid analgesics such as codeine (37), but is much more expensive.

**Opioid analgesics**

A recent systematic review of eight high-quality RCTs of up to eight weeks' duration demonstrated clinically important analgesia in NeP states (38). Three trials involved morphine, three involved oxycodone, and single trials involved methadone and levorphanol. All these trials demonstrated significant benefit relative to placebo or a dose-dependent analgesic response. On average, these studies demonstrated a 20% to 30% reduction in pain intensity. RCTs in patients with postherpetic neuralgia given controlled-release oxycodone (39) or controlled-release morphine (40) showed a significant reduction in pain intensity, with variable improvement in sleep and disability. Trials of controlled-release oxycodone in painful diabetic neuropathy showed more consistent improvement in pain, sleep and ability to function relative to placebo (41,42). The NNT for morphine and oxycodone was approximately 2.5 (17).

## FOURTH-LINE ANALGESICS

**Cannabinoids**

The cannabinoids are analgesic agents with strong evidence of efficacy in animal models and increasing evidence of efficacy in NeP states. Dronabinol produced modest analgesia in a RCT of central pain in multiple sclerosis (43). A 50/50 mixture of tetrahydrocannabinol and cannabidiol in the form of an oral mucosal spray provided significant benefit in a trial of central pain in multiple sclerosis (44).

**Methadone**

Methadone is a synthetic opioid analgesic that may be useful in the management of NeP because it has N-methyl-D-aspartate antagonist properties (45). Two small RCTs demonstrated benefit from methadone in chronic NeP (46,47), and survey data suggested efficacy in mixed NeP conditions (48). Methadone has excellent oral bioavailability and a duration of action of

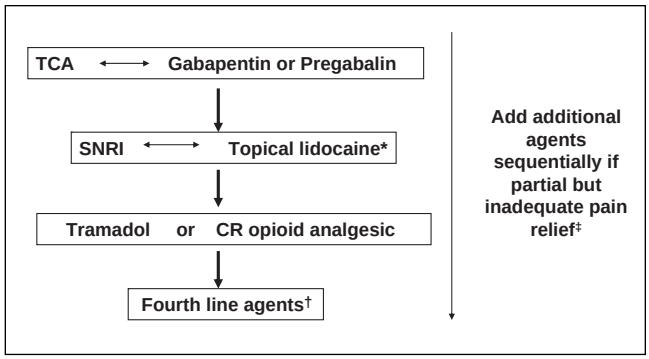


**Figure 1)** *Stepwise pharmacological management of neuropathic pain. *5% gel or cream – useful for focal neuropathy such as postherpetic neuralgia (the lidocaine patch is not available in Canada); †Cannabinoids, methadone, lamotrigine, topiramate, valproic acid; ‡Do not add serotonin noradrenaline reuptake inhibitors (SNRIs) to tricylic antidepressants (TCAs). CR Controlled-release*

at least 8 h with repetitive dosing. However, it has an elimination half-life of 24 h to 36 h, which requires close observation during the titration phase. Because methadone is challenging to titrate, lacks high quality evidence of efficacy, and requires special approval from federal and provincial regulators in Canada, it is relegated to fourth-line status as an analgesic for NeP. Guidelines for the use of methadone in the management of chronic pain are available (49).

**Selective serotonin reuptake inhibitors**

The role of selective serotonin reuptake inhibitors (SSRIs) in the management of NeP is unclear. Citalopram (50) and paroxetine (51) have been found to be efficacious in the management of painful diabetic neuropathy independent of their antidepressant effects, but fluoxetine has not (52). However, the combined NNT for all three studies was 6.7 (53); thus, SSRIs do not appear to be as efficacious as TCAs or SNRIs. SSRIs used primarily for depression may inhibit the metabolism of TCAs and increase the risk of serotonin syndrome (54).

**Other anticonvulsants**

Lamotrigine is a novel anticonvulsant agent that may act through voltage-gated cation channels to produce inhibition of glutamate release. Lamotrigine has been found to be useful in the management of trigeminal neuralgia (55) and painful diabetic neuropathy (56). However, lamotrigine was not found to be useful in the management of a variety of peripheral NeP states (57). Lamotrigine also requires slow and careful titration and carries a risk of Stevens-Johnson syndrome.

Topiramate and valproic acid have produced mixed results in NeP trials (17).

**Miscellaneous agents**

Mexiletine is a class 1B local anesthetic antiarrhythmic agent whose mechanism of action is blockade of sodium channels. Local anesthetics suppress ectopic neural pacemaker sites at lower concentrations than required for conduction block along the nerve and therefore may have a prolonged duration of action. An intravenous infusion of lidocaine 5 mg/kg over 30 min to 60 min may produce analgesia that lasts several hours or longer (58). This response has been the basis for starting an oral sodium channel blocker such as mexiletine and there is evidence that an intravenous lidocaine infusion can predict subsequent response to oral mexiletine (59). However, mexiletine has produced positive results in only two of seven NeP trials (17).

Clonidine, an alpha$_2$-agonist sympathetic blocker, showed benefit in a subset of patients with painful diabetic neuropathy in an enriched enrolment trial (60).

## STEPWISE PHARMACOLOGICAL APPROACH TO THE MANAGEMENT OF NeP

Figure 1 provides an 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 also important to improve outcomes.

TCAs, gabapentin and pregabalin are all considered first-line agents in the management of chronic NeP. It is reasonable to initiate treatment with either a TCA or an anticonvulsant such as gabapentin or pregabalin. Secondary amine TCAs (nortriptyline and desipramine) are better tolerated than tertiary amine TCAs (amitriptyline and imipramine) and have comparable analgesic efficacy. Amitriptyline, because of its tendency to produce sedation, constipation and urinary retention, should generally be avoided in elderly patients. All antidepressants take approximately two weeks to exert their full analgesic effect at any particular dose, and this needs to be communicated to patients to optimize compliance.

Gabapentin and pregabalin appear similar in terms of their mechanisms of action, efficacies and side-effect profiles, and allow for more rapid titration than antidepressant agents. Pregabalin carries the advantage of twice daily dosing and linear pharmokinetics relative to gabapentin.

If a TCA fails, switch to an anticonvulsant or vice versa. If a TCA provides only partial pain relief, add an anticonvulsant. The SNRIs are considered to be second line to TCAs because the latter agents provide more robust evidence of efficacy and are much less expensive. However, the TCAs have a more challenging side effect profile and are relatively contraindicated in patients with significant cardiovascular disease (17,25).

Topical lidocaine is a good second-line analgesic for an elderly patient with a focal painful neuropathy like postherpetic neuralgia because side effects are usually negligible.

When first-line and second-line medications have failed, tramadol or a conventional opioid analgesic may be useful as third-line treatment. It is reasonable to consider a short-acting opioid such as oxycodone with acetaminophen (Percocet, Bristol-Myers Squibb Canada) for breakthrough pain during titration of first-line and second-line agents, if needed. If there is an inadequate response, the total daily dose of the short-acting opioid may provide guidance as to the initial maintenance dose of a controlled-release opioid analgesic. Intractable pain may require treatment with the combination of an antidepressant, an anticonvulsant and an opioid analgesic. Support for combination pharmacotherapy comes from a recent study reporting enhanced analgesia with a morphine-gabapentin combination relative to either drug alone (61).

**TABLE 1**
**Dosing regimens for selected agents for neuropathic pain**

| Agent | Starting dose and titration | Usual maintenance dose | Adverse effects | Comments |
|---|---|---|---|---|
| Tricyclic antidepressants | | | | |
| Amitriptyline<br>Nortriptyline<br>Desipramine<br>Imipramine | 10–25 mg/day; increase weekly by 10 mg/day | 50–150 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, constipation | Dosage adjustments required in renal failure |
| Duloxetine | 60 mg/day | 60–120 mg/day | Sedation, nausea, constipation, ataxia, dry mouth | Contraindicated in patients with glaucoma; duloxetine not available in Canada |
| Anticonvulsants | | | | |
| Gabapentin | 300 mg/day; increase weekly by 300 mg/day | 300–1200 mg three times daily | Drowsiness, dizziness, peripheral edema, visual blurring | Dosage adjustments required in renal failure |
| Pregabalin | 75–150 mg/day; increase weekly by 50–150 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, might interfere with activity of other drugs like warfarin; monitoring of blood counts and liver function tests recommended |
| Controlled-release opioid analgesics | | | | |
| Morphine<br>Oxycodone<br>Fentanyl | 15 mg every 12 h<br>10 mg every 12 h<br>25 µg/h patch | 30–120 mg every 12 h<br>20–60 mg every 12 h<br>25–100 µg/h patch | Nausea, vomiting, sedation, dizziness, urinary retention, constipation | Constipation requires concurrent bowel regimen; addiction is unusual unless there is a past history of substance abuse |
| Others | | | | |
| Tramadol | 50 mg/day; increase weekly by 50 mg/day | 50–150 mg four times daily | Ataxia, sedation, constipation, seizures, orthostatic hypotension | May lower seizure threshold: use with caution in epilepsy; in combination with acetaminophen, keep maximal dose of acetaminophen at 4 g to avoid hepatic toxicity |
| 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 |
| Dronabinol | 2.5 mg twice daily | 2.5–10 mg twice daily | Dizziness, drowsiness, euphoria | Causes positive urine drug testing for cannabinoids |
| Tetrahydrocannabinol/ cannabidiol | 1–2 sprays every 4 h, maximum four sprays on day 1, titrate slowly | 2 sprays four times daily | Dizziness, fatigue, nausea euphoria | Conditionally approved for neuropathic pain associated with multiple sclerosis; causes positive urine drug testing for cannabinoids; monitor application site (oral mucosa) |

Although opioid analgesics have a NNT comparable to that of TCAs and perhaps better NNT than anticonvulsants, there are several reasons for their relegation to third-line analgesics for the management of NeP. Although tolerance often occurs to sedation, nausea and vomiting (and these latter side effects can be treated with antiemetics), there is very little tolerance to constipation and almost all patients placed on long-term opioid analgesics require a bowel regimen with continued monitoring of bowel function. In addition, periodic monitoring of risk of substance abuse and careful documentation of opioid prescriptions should be undertaken. Canadian guidelines for the use of opioid analgesics for the treatment of chronic noncancer pain are available (62).

Fourth-line agents for the management of NeP include cannabinoids, methadone and anticonvulsants with lesser evidence of efficacy such as lamotrigine, topiramate and valproic acid. These should be considered when other options have failed or are not possible. They may be considered adjunctive therapies if there are no concerns regarding polypharmacy or drug interactions.

## INVASIVE TECHNIQUES IN THE MANAGEMENT OF NEP

Although interventional techniques for NeP management are beyond the scope of the present article, they are usually considered when standard pharmacological treatments fail and psychological screening shows emotional stability. Evidence of efficacy for these techniques is generally less than for pharmacological interventions. Intravenous lidocaine infusions are generally safe and can provide significant pain relief for two to three weeks at a time. Other interventional techniques are costly and labour-intensive. Continuous spinal infusion of an opioid or clonidine via an implantable pump may be beneficial (63). Longitudinal studies of spinal cord stimulation have consistently shown significant pain relief in 50% to 60% of patients with extremity NeP (64).

## SUMMARY

The present guidelines provide a stepwise pharmacological approach to the management of NeP. They are based on quality of evidence of analgesic efficacy, side effect profile, ease of use and cost-effectiveness. It is also important to address co-morbidities such as anxiety and depression and to provide non-pharmacological treatments such as psychological support when available. TCAs, the anticonvulsants gabapentin and pregabalin, and SNRIs provide first-line and second-line treatments for NeP. Topical lidocaine is a useful addition for a focal neuropathy such as postherpetic neuralgia. When adjuvant analgesics fail, opioid analgesics provide important avenues of treatment. 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 treatment of pediatric and central NeP.

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## APPENDIX


**Author affiliations**

| | |
|---|---|
| DE Moulin | Professor and Earl Russell Chair in Pain Research, Departments of Clinical Neurological Sciences and Oncology, University of Western Ontario, London, Ontario |
| AJ Clark | Clinical Professor, Department of Anesthesia, University of Calgary, Calgary, Alberta |
| I Gilron | Associate Professor and Director of Clinical Pain Research, Departments of Anesthesiology and Pharmacology and Toxicology, Queen's University, Kingston, Ontario |
| MA Ware | Assistant Professor, Departments of Family Medicine and Anesthesia, McGill University, Montreal, Quebec |
| CPN Watson | Assistant Professor, Department of Medicine, University of Toronto, Toronto, Ontario |
| BJ Sessle | Professor and Canada Research Chair, Centre for the Study of Pain, University of Toronto, Toronto, Ontario |
| T Coderre | Departments of Anesthesia, Neurology & Neurosurgery and Psychology and Centre for Research on Pain, McGill University, Montreal, Quebec |
| PK Morley-Forster | Associate Professor, Department Anesthesia and Perioperative Medicine, Schulich School of Medicine, Interdisciplinary Pain Program, University of Western Ontario, London, Ontario |
| J Stinson | Assistant Professor, University of Toronto; Nurse Practitioner, Chronic Pain Program, The Hospital for Sick Children, Toronto, Ontario |
| A Boulanger | Associate Professor, Department of Anesthesia, Université de Montréal, Montreal, Quebec |
| P Peng | Assistant Professor and Director, Anesthesia Chronic Pain Program, University Health Network, University of Toronto, Toronto, Ontario |
| GA Finley | Professor Anesthesia and Psychology, Dalhousie University; Medical Director, Pediatric Pain Management, IWK Health Centre, Halifax, Nova Scotia |
| P Taenzer | Adjunct Clinical Assistant Professor, Departments of Psychiatry, Medicine and Oncology, University of Calgary, Calgary, Alberta |
| P Squire | Clinical Instructor, Department of Family Medicine, University of British Columbia, Vancouver, British Columbia |
| D Dion | Department of Family Medicine, Université de Montréal, Montreal, Quebec |
| A Cholkan | Patient Advisory Group of the Wasser Pain Management Centre, Mount Sinai Hospital, Toronto, Ontario |
| A Gilani | Assistant Professor, Department of Medicine/Neurology, McMaster University, Hamilton, Ontario |
| A Gordon | Associate Professor, University of Toronto; Neurologist and Director, Wasser Pain Management Centre, Mount Sinai Hospital, Toronto, Ontario |
| J Henry | Professor of Psychiatry and Behavioural Neurosciences, Anesthesia, McMaster University, Hamilton, Ontario |
| R Jovey | Clinical Instructor, Interfaculty Pain Curriculum, University of Toronto, Toronto, Ontario |
| M Lynch | Professor of Psychiatry, Anesthesia and Pharmacology, Dalhousie University, Halifax, Nova Scotia |
| A Mailis-Gagnon | Professor and Director, Comprehensive Pain Program, University of Toronto, Toronto, Ontario |
| A Panju | Professor of Medicine, Medical Director, Michael DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Ontario |
| GB Rollman | Professor Psychology, University of Western Ontario, London, Ontario |
| A Velly | Epidemiologist, Department of Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, Minnesota, USA |


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