Pharmacologic management of chronic neuropathic pain

Review of the Canadian Pain Society consensus statement

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Abstract

Objective To provide family physicians with a practical clinical summary of the Canadian Pain Society (CPS) revised consensus statement on the pharmacologic management of neuropathic pain.

Quality of evidence A multidisciplinary interest group within the CPS conducted a systematic review of the literature on the current treatments of neuropathic pain in drafting the revised consensus statement.

Main message Gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors are the first-line agents for treating neuropathic pain. Tramadol and other opioids are recommended as second-line agents, while cannabinoids are newly recommended as third-line agents. Other anticonvulsants, methadone, tapentadol, topical lidocaine, and botulinum toxin are recommended as fourth-line agents.

Conclusion Many pharmacologic analgesics exist for the treatment of neuropathic pain. Through evidence-based recommendations, the CPS revised consensus statement helps guide family physicians in the management of patients with neuropathic pain.

EDITOR'S KEY POINTS

- Gabapentinoids and tricyclic antidepressants play an important role in first-line management of neuropathic pain (NeP). Evidence published since the 2007 Canadian Pain Society consensus statement on treatment of NeP shows that serotonin-norepinephrine reuptake inhibitors should now also be among the first-line agents.
- Tramadol and opioids are considered second-line treatments owing to their increased complexity of follow-up and monitoring, plus their potential for adverse side effects, medical complications, and abuse. Cannabinoids are currently recommended as third-line agents, as sufficient-quality studies are currently lacking. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol, and botulinum toxin. There is some support for analgesic combinations in selected NeP conditions.
- Many of these pharmacologic treatments are off-label for pain or on-label for specific pain conditions, and these issues should be clearly conveyed and documented.

POINTS DE REPÈRE DU RÉDACTEUR

- Les gabapentinoïdes et les antidépresseurs tricycliques jouent un rôle important dans la prise en charge de la douleur neuropathique en soins primaires. Des données probantes publiées depuis la déclaration consensuelle de la Société canadienne de la douleur en 2007 sur le traitement de la douleur neuropathique démontrent que les inhibiteurs de la recapture de la sérotonine et de la noradrénaline devraient aussi compter parmi les agents de première intention.
- Le tramadol et les opioïdes sont considérés comme des traitements de deuxième intention en raison de la complexité du suivi et de la surveillance, sans compter leur potentiel d'effets secondaires indésirables, de complications médicales et d'usage abusif. Les cannabinoïdes sont présentement recommandés comme agents de troisième intention, étant donné l'absence actuelle d'études de qualité suffisante. Parmi les traitements de quatrième intention recommandés figurent la méthadone, les anticonvulsivants dont l'efficacité est corroborée par moins de données probantes (p. ex. lamotrigine, lacosamide), le tapentadol et la toxine botulique. Le recours à une combinaison d'analgésiques reçoit un certain appui dans des cas particuliers de douleur neuropathique.
- L'utilisation de bon nombre de ces pharmacothérapies est non indiquée pour la douleur ou encore est indiquée pour des problèmes de douleur spécifiques. Ces faits devraient être clairement communiqués et documentés.

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Prise en charge pharmacologique de la douleur neuropathique chronique

Revue de la déclaration consensuelle de la Société canadienne de la douleur

Résumé

Objectif Offrir aux médecins de famille un résumé clinique pratique de la déclaration consensuelle révisée de la Société canadienne

de la douleur (SCD) sur la prise en charge pharmacologique de la douleur neuropathique.

Qualité de l'information Un groupe d'intérêt multidisciplinaire au sein de la SCD a effectué une revue systématique des ouvrages scientifiques sur les traitements actuels de la douleur neuropathique dans le contexte de la rédaction d'une déclaration consensuelle révisée.

Message principal Les gabapentinoïdes, les antidépresseurs tricycliques, et les inhibiteurs de la recapture de la sérotonine et de la noradrénaline sont les agents de première intention pour traiter la douleur neuropathique. Le tramadol et les autres opioïdes sont recommandés comme agents de deuxième intention, tandis que les cannabinoïdes sont recommandés depuis peu comme agents de troisième intention. D'autres anticonvulsivants – la méthadone, le tapentadol, la lidocaïne topique et la toxine botulique – sont recommandés comme agents de quatrième intention.

Conclusion Il existe de nombreux analgésiques pharmacologiques pour le traitement de la douleur neuropathique. Par ses recommandations fondées sur des données probantes, la déclaration consensuelle révisée de la SCD aide à orienter les médecins de famille dans la prise en charge des patients souffrant de douleur neuropathique.

Neuropathic pain (NeP), caused by a lesion or disease of the somatosensory system, is a common condition seen in the primary care setting. Although the prevalence of NeP is estimated to be 2% to 3% in the developed world, population-based questionnaires estimate that the prevalence could actually be in the range of 4% to 8%.[1,2] The prevalence of NeP will increase over the next decades as our population ages and experiences more obesity. This has led to increased rates of postherpetic neuralgia and painful diabetic neuropathy.[3,4] Improved cancer screening and treatments are also leading to more cancer survivors experiencing NeP from various medical and surgical oncologic interventions.[5]

The goals of treatment of NeP, as with other pain conditions, include improvement in function and quality of life, along with the reduction of pain. The ideal treatment of NeP should entail a whole-person approach (biological, psychological, social, spiritual), be multidisciplinary in nature, include prevention or reversal of any underlying cause, and use appropriate pharmacologic and nonpharmacologic therapies. As first-line personnel in the treatment of NeP, primary care clinicians need to be aware of current Canadian guidance on the pharmacologic treatment of NeP so that an appropriate and rational stepwise approach is implemented. The primary aim of this article is to highlight the revised neuropathic pain medication algorithm that was created by a panel of experts within the Canadian Pain Society (CPS).

Consensus statement development

The Neuropathic Pain Special Interest Group of the CPS began meeting in 2012 to update the 2007 pharmacologic management guidelines for NeP.[6] This interest group is a multidisciplinary group of individuals with research and clinical expertise relevant to the pathophysiology and management of NeP. Randomized controlled trials (RCTs) and systematic reviews related to the pharmacologic management of NeP from 2007 up to September 2013 were reviewed to develop a revised evidence-based consensus statement.[7]

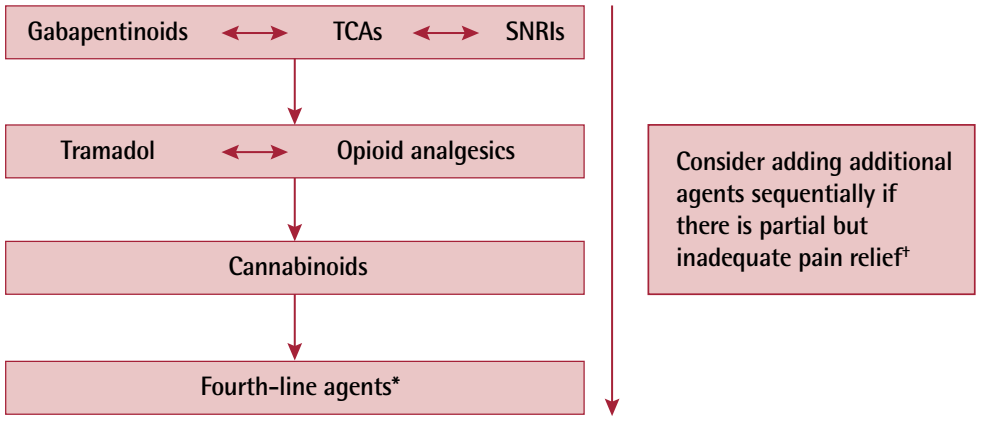
Quality of evidence

As per the published report,[7] MEDLINE and Cochrane databases were used to find systematic reviews, meta-analyses, treatment recommendations, guidelines, and consensus statements published since the first 2007 CPS consensus statement. Studies were excluded if they did not have a control group, had fewer than 10 patients, involved trigeminal or glossopharyngeal neuralgia, or involved cancer NeP, except for well-defined cancer-related postsurgical pain syndromes and chemotherapy-induced NeP. Medications were considered to be first-line if there was high-quality evidence of efficacy (at least 1 class I study or 2 consistent class II studies—level of recommendation grade B or better),[8] if there were positive results in at least 2 NeP models,[9] and if they were considered to be straightforward and of sufficient tolerability to prescribe and monitor. Second- or third-line medications require high-quality evidence of efficacy, but the medications also require more specialized follow-up and monitoring. Fourth-line treatments have at least 1 RCT with positive results, but require further study.

Main message

Neuropathic pain is a common condition seen in the family practice setting in Canada. **Figure 1** summarizes the revised 2014 CPS consensus statement for pharmacologic management of NeP.[7] Gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) are now recommended as first-line agents. Tramadol and opioids are considered second-line treatments owing to their increased complexity of follow-up and monitoring, plus their potential for adverse side effects, medical complications, and abuse. Cannabinoids are currently recommended as third-line agents, as sufficient-quality studies are currently lacking. Recommended fourth-line treatments include methadone, anticonvulsants with lesser evidence of efficacy (eg, lamotrigine, lacosamide), tapentadol, and botulinum toxin. There is some support for analgesic combinations in selected NeP conditions.

Figure 1. Algorithm for the pharmacologic management of neuropathic pain



SNRI—serotonin-norepinephrine reuptake inhibitor, TCA—tricyclic antidepressant.
*Fourth-line agents include topical lidocaine (second-line for postherpetic neuralgia), methadone, lamotrigine, lacosamide, tapentadol, and botulinum toxin.
†There is limited randomized controlled trial evidence to support add-on combination therapy.
Adapted from Moulin et al.[7]

Many of these pharmacologic treatments are off-label for pain or on-label for specific pain conditions, and these issues should be clearly conveyed and documented.

Assessment and diagnosis of NeP. Neuropathic pain can be mediated by central causes, such as stroke or multiple sclerosis, and by peripheral causes, such as diabetic neuropathy or surgical procedures. The patient's history and physical examination findings are essential to diagnosing NeP. Some diagnoses based on history are obvious, such as shingles and diabetes mellitus preceding postherpetic neuralgia and painful diabetic neuropathy, respectively. Questionnaires have been developed to help differentiate between nociceptive pain and NeP. True weakness (different from pain-related or antalgic weakness), reduced or absent reflexes, allodynia, and hyperalgesia all favour a diagnosis of NeP. Often patients describe neuropathic pain as accompanied by sensations of burning, tingling, and electric jolts. Screening tools, such as the Douleur Neuropathique 4, the self-report Leeds Assessment of Neuropathic Symptoms and Signs, and the ID Pain questionnaire (**Table 1**), have been shown to be valid and reliable discriminators of NeP.[10-12] Electromyography and nerve conduction studies can provide evidence of nerve injury but might not be sensitive for small-fibre neuropathies. Guidelines are available to determine the diagnostic certainty of NeP.[13,14]

CanMEDS–Family Medicine considerations. Chronic pain conditions, such as NeP, require management by physicians using more than pharmacologic expertise. The CanMEDS–Family Medicine roles described by the College of Family Physicians of Canada serve as a framework for improving patient care.[15] Specifically, as professionals, physicians must commit to regulated, ethical practice with high personal standards of behaviour. Being a scholar requires lifelong commitment to learning, creation, dissemination, and translation of medical pain knowledge. As family medicine experts, the knowledge is applied in a manner that places patients and families in the correct biopsychosocial-spiritual framework within their community. Patients with chronic pain experiencing NeP often describe this condition as severe and unrelenting, and it is often associated with comorbid anxiety and depression. As a communicator, the practitioner should facilitate the doctor-patient relationship through validation of the patient's pain and communicate the treatment goals, such as improvement of

Table 1. ID Pain questions and scoring: *If patients have >1 painful area, they are to consider the area that is most relevant when answering the ID Pain questions. Scores range from -1 to 5. Higher scores are more indicative of pain with a neuropathic component.*

QUESTION	SCORE	
	YES	NO
1. Did the pain feel like pins and needles?	1	0
2. Did the pain feel hot or burning?	1	0
3. Did the pain feel numb?	1	0
4. Did the pain feel like electrical shocks?	1	0
5. Is the pain made worse with the touch of clothing or bed sheets?	1	0
6. Is the pain limited to your joints?	-1	0

Adapted from Portenoy.[12]

sleep, physical functioning, and other elements of quality of life, and discuss pain reduction such that the pain might become "tolerable," rather than promise the elimination of the pain condition. Patients should be made aware that chronic pain might be a lifelong condition. As a collaborator and leader, treatment goals can be realized by involving multidisciplinary teams (psychologists, physiotherapists, etc) to maximize nonpharmacologic adjunctive treatments. Family physicians serve as their patients' main advocate within their communities, and help them to navigate the health care system.

First-line analgesics. The first-line medications are the gabapentinoid class of anticonvulsants, TCAs, and SNRIs. There are positive results showing efficacy in painful diabetic neuropathy for all first-line analgesics.[16-19] In the context of postherpetic neuralgia, there has been proof of efficacy for gabapentinoids and TCAs.[16,18] Pregabalin has additionally been shown to have analgesic benefit in patients with chronic central NeP after spinal cord injury[20,21] and secondary benefit (improved sleep and reduced anxiety) in central poststroke pain.[22] Tricyclic antidepressants have been shown to relieve pain in various NeP conditions.[23] Of the SNRIs, duloxetine has been found to have analgesic benefit in chemotherapy-induced painful neuropathy,[24] while gabapentin has been shown not to.[25] Additionally, high-dose venlafaxine has shown efficacy in mixed painful polyneuropathy.[26] In the context of idiopathic trigeminal neuralgia, an exception can be made for carbamazepine, which remains the first-choice analgesic.[27] Dosing guidelines for selected NeP analgesia agents can be found in **Table 2**.[7]

Tricyclic antidepressants are extensively studied, inexpensive, and administered daily. They inhibit the reuptake of serotonin and norepinephrine, block *N*-methyl-D-aspartate agonist–induced hyperalgesia, and block sodium channels.[28] When prescribing TCAs, secondary amines (nortriptyline, desipramine) are usually better tolerated in terms of sedation, postural hypotension, and anticholinergic effects when compared with tertiary amines (amitriptyline and imipramine) with comparable analgesic efficacy.[29] Side effects might also be reduced by starting at a lower dose, administration in the early evening, and titrating slowly. The analgesic effect of TCAs is independent of the antidepressant effect and the analgesic effect occurs at one-fifth to one-third of the dose required to treat depression.[30] In the geriatric population, TCAs might be deleterious, as they can impair cognition and increase the risk of falls.[31] The updated American Geriatrics Society Beers criteria and version 2 of the STOPP/START (Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment) criteria are useful references to minimize inappropriate prescribing in the elderly.[32,33] As TCAs have been associated with tachycardia and myocardial infarction (at doses above 100 mg daily), the Special Interest Group on Neuropathic Pain (NeuPSIG) recommends a baseline electrocardiogram in patients starting TCAs who are older than 40 years of age and are at risk of sudden cardiac death or who have a history of cardiovascular disease.[31]

Gabapentinoids lead to reduction of the influx of calcium in the terminals of primary afferent neurons entering the dorsal horn of the spinal cord.[28] Gabapentin and pregabalin are not hepatically metabolized, and they do not alter hepatic enzymes. As they are eliminated renally, dose adjustment is required in those with renal insufficiency or those who are undergoing dialysis.[34] Pregabalin can be taken twice a day and has more linear pharmacokinetics relative to gabapentin, which is taken 3 times a day. Somnolence, dizziness, edema, and weight gain are common side effects of gabapentinoids, and they might require low initial dosing and slow titration, especially in the elderly.[35]

Serotonin-norepinephrine reuptake inhibitors inhibit the reuptake of serotonin and norepinephrine at neuronal junctions. Duloxetine and venlafaxine are the 2 most studied drugs within this class. A typical side effect of duloxetine and venlafaxine is nausea; other side effects such as elevated heart rate and blood pressure are less common. Gastrointestinal side effects are most common with venlafaxine. Hepatotoxicity has been reported with duloxetine. Duloxetine directly relieves painful physical symptoms, in addition to the pain relief from improved depressive symptoms over time.[35,36] There is 1 phase III clinical trial of desvenlafaxine in the setting of NeP; at interim analysis, randomization to a 400-mg daily dose was discontinued owing to a clear increase in adverse events.[37] Duloxetine inhibits serotonin to norepinephrine reuptake at a ratio of 9:1 while venlafaxine has a ratio of 30:1.[38] At low doses (<200 mg daily), venlafaxine only inhibits serotonin.[39] There is evidence that combination pharmacotherapy with gabapentinoids and SNRIs can be helpful.[35] Duloxetine should be avoided in those with hepatic insufficiency and severe renal impairment; doses higher than 60 mg daily have not consistently shown benefit in clinical trials.[40] Tricyclic antidepressants, SNRIs, and selective serotonin reuptake inhibitors are all relatively contraindicated with concurrent use of monoamine oxidase inhibitors owing to the possibility of serotonin syndrome.[41]

If patients are appropriately identified as having NeP using standardized NeP tools, first-line medications are very effective early in the treatment process.[42] The quality of the evidence provided above is high for SNRIs and gabapentinoids in the treatment of NeP, but moderate for TCAs if started before opioids.[42] A reduction in pain of 20% to 30% should be considered a success. A change in a patient's function, sleep pattern, or their ability to be social are key matters of evaluation rather than a pain numeric rating scale score.

Table 2. Selected neuropathic analgesic dosing regimens

AGENT	INITIAL DOSE	TITRATION	DOSE RANGE	ADVERSE EFFECTS	ADDITIONAL INFORMATION
Anticonvulsants					
• Gabapentin	100-300 mg/d	Increase by 100-300 mg/d every wk	300-1200 mg 3 times/d	Drowsiness, dizziness, peripheral edema, visual blurring	Dosage adjustments required in renal failure and in elderly patients
• Pregabalin	25-150 mg/d	Increase by 25-150 mg/d every wk	150-300 mg twice daily	Drowsiness, dizziness, peripheral edema, visual blurring	Similar adjustments in renal failure
• Carbamazepine	100 mg/d	Increase by 100-200 mg/d every wk	200-400 mg 3 times/d	Drowsiness, dizziness, blurred vision, ataxia, headache, nausea, rash	Drug of first choice for idiopathic trigeminal neuralgia; as an enzyme inducer, it might interfere with activity of other drugs such as warfarin; monitoring of blood counts and liver function recommended
TCAs					
• Amitriptyline, nortriptyline, or desipramine	10–25 mg/d	Increase by 10 mg/d every wk	10-100 mg/d	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 substantial cardiovascular disease
SNRIs					
• Venlafaxine	37.5 mg/d	Increase by 37.5 mg/d every wk	150-225 mg/d	Nausea, dizziness, drowsiness, hyperhidrosis, hypertension	Dosage adjustments required in renal failure
• Duloxetine	30 mg/d	Increase by 30 mg/d every wk	60-120 mg/d	Sedation, nausea, constipation, ataxia, dry mouth	Contraindicated in patients with glaucoma
Controlled-release opioids*					
• Morphine	15 mg every 12 h	NA	NA	Nausea, vomiting, sedation, dizziness, urinary retention, constipation	Constipation requires concurrent bowel regimen; monitor for overdose, effectiveness, tolerance, dependence, and appropriateness
• Oxycodone	10 mg every 12 h	NA	NA		
• Fentanyl	12 µg/h (patch)	NA	NA		
• Hydromorphone	3 mg every 12 h	NA	NA		
Others					
• Tramadol	50 mg/d	Increase by 50 mg/d every wk	50-100 mg 4 times/d or 100-400 mg/d (controlled release)	Ataxia, sedation, constipation, seizures, orthostatic hypertension	Might lower seizure threshold; use with caution in patients with epilepsy
• Tapentadol (controlled release)	50 mg every 12 h	Increase by 50 mg/ dose every wk	Maximum dose 500 mg in 24 h	Nausea, constipation, somnolence, dizziness, vomiting, fatigue	Contraindicated in patients with creatinine clearance < 0.5 mL/s/m^2 and Child-Pugh class C. Caution in those at risk of seizure
• Lidocaine	NA	NA	5% patches or gel applied to painful areas for 12 h in a 24-h period	NA	Most useful for postherpetic neuralgia; has virtually no systemic side effects; lidocaine patches not available in Canada
• THC or nabiximols	1-2 sprays every 4 h, maximum 4 sprays on day 1	NA	2 sprays 4 times/d	Dizziness, fatigue, nausea, euphoria	Approved in Canada for neuropathic pain associated with multiple sclerosis; causes positive urine drug test results for cannabinoids; monitor application site (oral mucosa)
• Nabilone	0.25–0.5 mg at night (owing to side effects of drowsiness and fatigue)	Increase by 0.5 mg/d every wk	3 mg twice daily	Dizziness, drowsiness, dry mouth	Approved in Canada for nausea and vomiting associated with chemotherapy. Does not cause positive test results for cannabinoids on routine urine drug testing

NA—not available, SNRI—serotonin-norepinephrine reuptake inhibitor, TCA—tricyclic antidepressant, THC—tetrahydrocannabinol.
*Opioid initial dosing recommendations are for healthy opioid-naïve adults; opioid titration and dose range are not included owing to variability of patient and pain factors.
Adapted with permission from Moulin et al.[7]

However, once opioid medications are entrenched, the effect sizes of these first-line medications tend to be minimized.

Second-line analgesics. Tramadol is a second-line medication in the treatment of NeP and has been shown to be of benefit in RCTs for diabetic neuropathy and mixed NeP syndromes.[18] It is a weak μ-opioid receptor agonist and weak SNRI.[43] The NeuPSIG also recommends it as a second-line agent.[42] Tramadol might cause less constipation and nausea compared with other weak analgesics.[44] Along with common opioid side effects, tramadol can decrease seizure thresholds and can increase the risk of serotonin syndrome when combined with other serotonergic drugs.[31]

Opioids were found to be more effective than placebo for pain, with a moderate effect size, in a meta-analysis including 16 randomized trials for chronic NeP.[45] However, owing to their potential adverse effects, medical complications (endocrine dysfunction, sleep apnea, opioid-induced hyperalgesia), risks (overdose, diversion, addiction, withdrawal), and necessity of more specialized follow-up and monitoring, opioids are considered to be second-line agents for NeP (**Table 3**).[46] In the recent NeuPSIG systematic review and meta-analysis, opioids are recommended as third-line analgesics for the same reasons.[42]

A meta-analysis of 62 RCTs found that the most common opioid-related adverse effects were nausea (28%), constipation (25%), drowsiness (24%), dizziness (18%), and vomiting (15%).[45] Although some tolerance to side effects develops, there is little tolerance to constipation in prolonged use. Long-term opioid use complications include opioid-induced hyperalgesia[47] and multiple endocrine axis suppression such as adrenal and gonadal suppression.[48] The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain is strongly recommended as a resource for family physicians.[46] An online and mobile resource, My Opioid Manager, is recommended to help inform and engage patients to work with their health care providers in managing their pain with opioids.[49] Another mobile app, Manage My Pain, has more than 25 000 active users and is used in chronic pain to empower the physician-patient relationship.[50]

Third-line analgesics. Cannabinoids have been moved from a fourth-line to a third-line treatment option for chronic NeP in the 2014 CPS NeP guidelines.[7] The strongest evidence for cannabinoid use is for NeP from HIV, diabetic neuropathy, posttraumatic or postsurgical NeP, and mixed central and peripheral NeP states.[51-55] However, there is a paucity of high-quality studies with long trial duration, large sample size, and large effect size to better establish their efficacy and their potential for abuse. The NeuPSIG provides a weak recommendation against the use of cannabinoids in NeP owing to potential for misuse, diversion, and long-term risks in susceptible individuals.[42] Side effects of cannabinoids can vary but usually include somnolence, "getting high," confusion, dizziness, tachycardia, and hypotension.[56]

Cannabinoid formulations in Canada currently consist of nabilone, nabiximols, and dried cannabis.[57] Dosing for dried cannabis is highly individualized and relies greatly on titration owing to complex pharmacology, interindividual genetic differences in cannabinoid receptors, metabolism, and previous exposure. In clinical trials with positive results using dried cannabis for NeP conditions, the delta-9-tetrahydrocannabinol dose per day did not exceed 125 mg, and maximum tetrahydrocannabinol by weight was 9.4%. Although there is no established dosing guideline for dried cannabis, the Health Canada monograph on cannabis provides "rough" dosing guidelines.[56] Dried cannabis is not approved or regulated by Health Canada because it has not gone through the necessary rigorous scientific trials for efficacy or safety. Provincial guides and policies on medical marijuana can be found on the Canadian Medical Protective Association website.[58] For family physicians starting, maintaining, or terminating dried cannabis prescriptions, preliminary guidelines have been created by the College of Family Physicians of Canada.[57]

As per current guidelines, cannabis is not appropriate to start in those who are younger than 25 years of age, might be pregnant, have cardiovascular disease, have a respiratory disease, have a history of psychosis, or have a substance use disorder. In patients naïve to cannabis, a trial with a synthetic cannabinoid, usually nabilone, should be considered first. If dried cannabis is prescribed, physicians must continue to follow up and monitor patients to assess for potential misuse, abuse, and efficacy. Discontinuation of cannabis therapy is warranted when there is clearly no benefit or it is causing harm to the patient.[57] It is important also to be cognizant of cannabis hyperemesis syndrome as a differential diagnosis in young patients who present with cyclic vomiting and compulsive hot bathing.[59] There are several large-scale Canadian initiatives under way with the aim of creating evidence-based recommendations on the prescription of medical cannabis.

Fourth-line analgesics. Selective serotonin reuptake inhibitors are another class of antidepressants that have some analgesic efficacy, with the exception of fluoxetine, in painful diabetic neuropathy and painful polyneuropathy.[60-63] Similar to SNRIs, there is a risk of serotonin syndrome with medications that increase serotonin levels and they are also contraindicated in combination with monoamine oxidase inhibitors.[64]

Topical lidocaine is a local anesthetic useful in the management of peripheral NeP. It remains a second-line agent specifically for postherpetic neuralgia.[18]

Table 3. Selected opioid safety considerations

OPIOID	SAFETY CONSIDERATION
Codeine	• In breastfeeding women, there is risk of morphine toxicity in infants owing to rapid conversion of codeine to morphine
Tramadol	• Associated with seizures in patients at high seizure risk, or when combined with medications that increase serotonin level (eg, SSRIs)
Morphine	• In patients with renal dysfunction, morphine-6-glucuronide, an active metabolite of morphine, can accumulate to toxic levels
Oxycodone, hydromorphone, hydrocodone	• As with all opioids, use with caution in patients at risk of opioid misuse and addiction
Fentanyl	• Before starting fentanyl, ensure the patient has been fully opioid tolerant during the previous 2 wk (total dose of at least 60-90 mg/d morphine equivalence) on a scheduled dose (at least twice daily for CR or 4 times daily for IR) • Do not switch from codeine to fentanyl regardless of the codeine dose, as some patients taking codeine might have little or no opioid tolerance • Maintain the starting dose for at least 6 d and use extra caution with patients at higher risk of overdose (eg, the elderly, those taking benzodiazepines) • Advise the patient as follows: -Be alert for signs of overdose; if detected, remove the patch and seek medical attention -Apply the patches as prescribed; do not apply more than 1 patch at a time -Avoid heat sources such as heating pads -Enforce patch-for-patch exchange at pharmacy to reduce diversion
Methadone	• Use methadone to treat pain only if you hold a written Health Canada exemption • Titration is hazardous because of its very long half-life, which leads to bioaccumulation
Meperidine	• Not recommended for use in CNCP owing to poor bioavailability and inferior effectiveness to codeine • Normeperidine, a metabolite of meperidine, can accumulate with frequent use causing seizures and delirium
Acetaminophen-opioid combinations	• Use with caution to not exceed maximum dose of 3.2 g/d of acetaminophen for adults (10 tablets/d of opioid-acetaminophen combinations) • No more than 8 tablets/d for tramadol-acetaminophen combinations • Warn alcohol drinkers to not mix alcohol with acetaminophen
CR formulations	• Each CR tablet can contain a higher opioid dose than IR formulations do and can be converted to IR by biting or crushing the tablet
Tapentadol	• Contraindicated in those with severe hepatic or renal dysfunction, or taking monoamine oxidase inhibitors • Small risk of seizure seen in postmarketing reports
Parenteral opioids	• Parenteral opioids are not recommended for treatment of CNCP owing to increased risk of overdose, abuse, addiction, and infection

CNCP—chronic noncancer pain, CR—controlled release, IR—immediate release, SSRI—selective serotonin reuptake inhibitor.
Adapted with permission from the Michael G. DeGroote National Pain Centre.[46]

However, there was no benefit shown in postsurgical nerve injury or in mixed NeP.[65,66] Topical lidocaine is safe, as only negligible levels are detected in blood and there are rarely any systemic side effects with topical use.[67]

Capsaicin is another topical agent with evidence for effectiveness at high concentrations (8%) in postherpetic neuralgia and in painful HIV neuropathy for up to 12 weeks after a single application.[68] As initial application of capsaicin causes sensitivity of nociceptors leading to an intense burning sensation, local anesthetic before application might be required. In Canada, the high-potency capsaicin patch may be obtained through compassionate release.

Methadone is a synthetic opioid with unique *N*-methyl-D-aspartate and SNRI properties.[69] Only small RCTs and surveys have suggested efficacy in mixed NeP conditions.[70-72] In Canada, a specialized methadone exemption is required for prescribing and guidelines are available for its management in chronic pain.[73]

Tapentadol is a newer opioid available in Canada with analgesic effect through μ-receptors and monoamine reuptake inhibition, but minimal effect on serotonin reuptake. This dual analgesic effect might contribute to its efficacy in treating painful diabetic neuropathy.[74] Like other opioids, common side effects include nausea and vomiting, somnolence, and dizziness but with lower incidence

compared with oxycodone. Another advantage is the lower potential for metabolic variation due to enzyme polymorphism. Similar to tramadol, serotonin syndrome can occur when combined with other serotonergic drugs but at a reduced rate.[75] As the efficacy of tapentadol has only been studied in a single NeP pain model, it is considered a fourth-line agent and is not included as a second-line treatment with tramadol and other opioids.

Other anticonvulsants studied in NeP management include lamotrigine, lacosamide, topiramate, and valproic acid. Lamotrigine provided negative results in studies of diabetic neuropathy, mixed NeP, chemotherapy-induced NeP, and spinal cord injury pain. Results of small studies investigating lamotrigine's effect in HIV neuropathy, trigeminal neuralgia, and central poststroke pain were positive.[76] Lacosamide has been mostly studied in the context of painful diabetic neuropathy with modest benefit.[77] Topiramate and valproic acid have had mixed results in NeP trials.[18]

Botulinum toxin injections represent a novel treatment in NeP with positive results in diabetic neuropathy and focal painful neuropathy. However, these studies are underpowered, with small sample sizes.[78,79] Therefore, the evidence for botulinum toxin remains preliminary and further evidence is needed.

Combination pharmacotherapy. Recent review of combination pharmacotherapy in the treatment of NeP has involved variations of an opioid with gabapentin, pregabalin, or a TCA, the combination of gabapentin and nortriptyline, and various topical medications.[80] A meta-analysis of the combination of gabapentin with an opioid showed superiority in terms of analgesia when compared with gabapentin alone, but the combination also led to more discontinuations owing to side effects.[80] An RCT comparing duloxetine (60 mg daily) and pregabalin (300 mg daily) to high-dose duloxetine or pregabalin monotherapy did not yield any difference in 24-hour pain; however, all secondary outcome measures favoured combination therapy.[81] Current evidence does not support a recommendation of any one specific drug combination for NeP, but it remains an important and understudied strategy.

Conclusion

Based on the 2014 CPS NeP consensus statement,[7] gabapentinoids and TCAs continue to play an important role for first-line management of NeP. As a result of evidence published since the 2007 CPS NeP consensus statement, SNRIs are now also among the first-line agents. Topical lidocaine, a previous second-line agent, remains in the same tier of treatment only for postherpetic neuralgia, but is otherwise now a fourth-line analgesic. Opioids including tramadol have been moved from third-line to second-line treatment. Cannabinoids (including dried cannabis) have been elevated from fourth-line agents to a third-line treatment option for chronic NeP. The fourth-line analgesic medications are understudied but can still be of therapeutic value when other options have failed or are intolerable.

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Contributors
All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

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References

1. Foley KM. Opioids and chronic neuropathic pain. *N Engl J Med* 2003;348(13):1279-81.
2. Gilron I, Watson CP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. *CMAJ* 2006;175(3):265-75.
3. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain* 2008;136(3):380-7. Epub 2007 Sep 20.
4. Torrance N, Smith BH, Watson MC, Bennett MI. Medication and treatment use in primary care patients with chronic pain of predominantly neuropathic origin. *Fam Pract* 2007;24(5):481-5. Epub 2007 Aug 1.
5. Kautio AL, Haanpää M, Kautiainen H, Kalso E, Saarto T. Burden of chemotherapy-induced neuropathy—a cross-sectional study. *Support Care Cancer* 2011;19(12):1991-6. Epub 2010 Nov 16.
6. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP, Sessle BJ, et al. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007;12(1):13-21.
7. Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Res Manag* 2014;19(6):328-35.
8. Ashman EJ, Gronseth GS. Level of evidence reviews: three years of progress. *Neurology* 2012;79(1):13-4. Epub 2012 Jun 20.
9. Dworkin RH, Turk DC, Basch E, Berger A, Cleeland C, Farrar JT, et al. Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy. *Pain* 2011;152(8):1705-8. Epub 2011 Mar 10.
10. Bennett MI, Smith BH, Torrance N, Potter J. The S-LANSS score for identifying pain of predominantly neuropathic origin: validation for use in clinical and postal research. *J Pain* 2005;6(3):149-58.
11. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005;114(1-2):29-36. Epub 2005 Jan 26.
12. Portenoy R. Development and testing of a neuropathic pain screening questionnaire: ID Pain. *Curr Med Res Opin* 2006;22(8):1555-65.
13. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011;152(1):14-27. Epub 2010 Sep 19.
14. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;70(18):1630-5. Epub 2007 Nov 14.
15. Working Group on Curriculum Review. *CanMEDS—Family Medicine.* Mississauga, ON: College of Family Physicians of Canada; 2009. Available from: **www.cfpc.ca/uploadedFiles/Education/CanMeds%20FM%20Eng.pdf**. Accessed 2017 Sep 6.
16. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17(9):1113-e88. Epub 2010 Apr 9.
17. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *PM R* 2011;3(4):345-52, 352.e1-21.
18. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150(3):573-81.
19. Rowbotham MC, Goli V, Kunz NR, Lei D. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004;110(3): 697-706. Erratum in: *Pain* 2005;113(1-2):248.
20. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006;67(10):1792-800.
21. Vranken JH, Dijkgraaf MG, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008;136(1-2):150-7. Epub 2007 Aug 20.
22. Kim JS, Bashford G, Murphy TK, Martin A, Dror V, Cheung R. Safety and efficacy of pregabalin in patients with central post-stroke pain. *Pain* 2011;152(5):1018-23. Epub 2011 Feb 12.
23. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;118(3):289-305. Epub 2005 Oct 6.
24. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013;309(13):1359-67.
25. Rao RD, Michalak JC, Sloan JA, Loprinzi CL, Soori GS, Nikcevich DA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 2007;110(9):2110-8.

26. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial. *Neurology* 2003;60(8):1284-9.
27. Zakrzewska JM. Medical management of trigeminal neuropathic pains. *Expert Opin Pharmacother* 2010;11(8):1239-54.
28. Jensen TS, Madsen CS, Finnerup NB. Pharmacology and treatment of neuropathic pains. *Curr Opin Neurol* 2009;22(5):467-74.
29. McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68(2-3):217-27.
30. Sullivan MJ, Reesor K, Mikail S, Fisher R. The treatment of depression in chronic low back pain: review and recommendations. *Pain* 1992;50(1):5-13.
31. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132(3):237-51. Epub 2007 Oct 24.
32. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44(2):213-8. Epub 2014 Oct 16.
33. American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015;63(11):2227-46. Epub 2015 Oct 8.
34. *Neurontin* [product monograph]. Kirkland, QC: Pfizer Canada Inc; 2014. Available from: **www.pfizer.ca/sites/g/files/g10023216/f/201505/NEURONTIN_PM_175273_EN_12September2014.pdf**. Accessed 2017 Sep 6.
35. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med* 2009;122(10 Suppl):S22-32.
36. Harada E, Tokuoka H, Fujikoshi S, Funai J, Wohlreich MM, Ossipov MH, et al. Is duloxetine's effect on painful physical symptoms in depression an indirect result of improvement of depressive symptoms? Pooled analyses of three randomized controlled trials. *Pain* 2016;157(3):577-84.
37. Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. *J Pain Res* 2014;7:339-51.
38. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 2001;25(6):871-80.
39. Richelson E. Pharmacology of antidepressants. *Mayo Clin Proc* 2001;76(5):511-27.
40. Wright A, Luedtke KE, Vandenberg C. Duloxetine in the treatment of chronic pain due to fibromyalgia and diabetic neuropathy. *J Pain Res* 2010;4:1-10.
41. Barowsky J, Schwartz TL. An evidence-based approach to augmentation and combination strategies for: treatment-resistant depression. *Psychiatry* (Edgmont) 2006;3(7):42-61.
42. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14(2):162-73. Epub 2015 Jan 7.
43. Tramadol—a new oral analgesic. *Med Lett Drugs Ther* 1995;37(952):59-62.
44. Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N, et al. Combination tramadol plus acetaminophen for postsurgical pain. *Am J Surg* 2004;187(4):521-7.
45. Furlan A, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and non-enriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Res Manag* 2011;16(5):337-51.
46. Michael G. DeGroote National Pain Centre. *2017 Canadian guideline for opioids for chronic non-cancer pain*. Hamilton, ON: McMaster University; 2017. Available from: **http://nationalpaincentre.mcmaster.ca/documents/Opioid%20GL%20for%20CMAJ_01may2017.pdf**. Accessed 2017 Oct 16.
47. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. *Pain* 2002;100(3):213-7.
48. Demarest SP, Gill RS, Adler RA. Opioid endocrinopathy. *Endocr Pract* 2015;21(2):190-8. Erratum in: *Endocr Pract* 2015;21(5):559.
49. Furlan A, Robidas A. *My opioid manager*. Toronto, ON: Toronto Rehabilitation Institute, University Health Network; 2015. Available from: **www.opioidmanager.com**. Accessed 2017 Sep 6.
50. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, Ladak SS, et al. The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. *J Pain Res* 2015;8:695-702.
51. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol* 2015;10(2):293-301. Epub 2015 Mar 22.
52. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65(6):812-9.
53. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004;329(7460):253. Epub 2004 Jul 16.
54. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 2012;153(10):2073-82. Epub 2012 Aug 23.
55. Meng H, Hanlon JG, Katznelson R, Ghanekar A, McGilvray I, Clarke H. The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report. *Can J Anaesth* 2016;63(3):307-10. Epub 2015 Oct 27.
56. Health Canada. *Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids*. Ottawa, ON: Health Canada; 2013. Available from: **https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf**. Accessed 2017 Sep 6..
57. College of Family Physicians of Canada. *Authorizing dried cannabis for chronic pain or anxiety. Preliminary guidance*. Mississauga, ON: College of Family Physicians of Canada; 2014.
58. Canadian Medical Protective Association. *Medical marijuana: considerations for Canadian doctors*. Ottawa, ON: Canadian Medical Protective Association; 2016. Available from: **www.cmpa-acpm.ca/en/advice-publications/browse-articles/2014/medical-marijuana-new-regulations-new-college-guidance-for-canadian-doctors**. Accessed 2017 Sep 6.
59. Ruffle JK, Bajgoric S, Samra K, Chandrapalan S, Aziz Q, Farmer AD. Cannabinoid hyperemesis syndrome: an important differential diagnosis of persistent unexplained vomiting. *Eur J Gastroenterol Hepatol* 2015;27(12):1403-8.
60. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326(19):1250-6.
61. Otto M, Bach FW, Jensen TS, Brøsen K, Sindrup SH. Escitalopram in painful polyneuropathy: a randomized, placebo-controlled, cross-over trial. *Pain* 2008;139(2):275-83. Epub 2008 Jun 10.
62. Sindrup SH, Bjerre U, Dejgaard A, Brøsen K, Aaes-Jørgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992;52(5):547-52.
63. Sindrup SH, Gram LF, Brøsen K, Eshøj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42(2):135-44.
64. Sproule BA, Naranjo CA, Brenmer KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions. A critical review of the evidence. *Clin Pharmacokinet* 1997;33(6):454-71.
65. Cheville AL, Sloan JA, Northfelt DW, Jillella AP, Wong GY, Bearden JD 3rd, et al. Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). *Support Care Cancer* 2009;17(4):451-60. Epub 2009 Jan 13.
66. Ho KY, Huh BK, White WD, Yeh CC, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. *Clin J Pain* 2008;24(1):51-5.
67. Gammaitoni AR, Davis MW. Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Ann Pharmacother* 2002;36(2):236-40.
68. Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2013;(2):CD007393.
69. Peng PW, Tumber PS, Gourlay D. Perioperative pain management of patients on methadone therapy. *Can J Anaesth* 2005;52(5):513-23.
70. Gagnon B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. *Pain Res Manag* 2003;8(3):149-54.
71. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliat Med* 2003;17(7):576-87.
72. Moulin DE, Palma D, Watling C, Schulz V. Methadone in the management of intractable neuropathic noncancer pain. *Can J Neurol Sci* 2005;32(3):340-3.
73. Lynch ME. A review of the use of methadone for the treatment of chronic noncancer pain. *Pain Res Manag* 2005;10(3):133-44.
74. Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011;27(1):151-62.
75. Vadivelu N, Timchenko A, Huang Y, Sinatra R. Tapentadol extended-release for treatment of chronic pain: a review. *J Pain Res* 2011;4:211-8. Epub 2011 Aug 1.
76. Wiffen PJ, Derry S, Moore RA. Lamotrigine for acute and chronic pain. *Cochrane Database Syst Rev* 2011;(2):CD006044.
77. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;(2):CD009318.
78. Lakhan SE, Velasco DN, Tepper D. Botulinum toxin-A for painful diabetic neuropathy: a meta-analysis. *Pain Med* 2015;16(9):1773-80. Epub 2015 Mar 20.
79. Ranoux D, Attal N, Morain F, Bouhassira D. Botulinum toxin type A induces direct analgesic effects in chronic neuropathic pain. *Ann Neurol* 2008;64(3):274-83. Erratum in: *Ann Neurol* 2009;65(3):359.
80. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev* 2012;(7):CD008943.
81. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013;154(12):2616-25. Epub 2013 May 31.