

# OPTIONS

Neuropathic Pain

Defining Neuropathic Pain and  
Optimizing Treatment Approaches  
*Reviews from published literature*

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## Mechanisms of Action Guide Rational Choice of Therapy in Neuropathic Pain

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## Optimal Therapeutic Choices in Neuropathic Pain Must Be Individualized

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## Neuropathic Pain Guidelines Are Becoming More Practical for a Logical Order of Therapy

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**Editorial Overview:**

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Neuropathic pain is caused by damage to the nervous system that produces abnormal firing of pain signals. This pain can be localized in the periphery or emanate from the central nervous system. While treatment of neuropathic pain was once dominated by empiric use of drugs employed off-label, guidelines are increasingly evidence-based. These have helped provide reasonable first-, second- and third-line options. The current guidelines now include therapies that have received regulatory approval specifically for the treatment of neuropathic pain. In the management of neuropathic pain, clinicians must remain sensitive to the heterogeneity of different etiologies and different underlying mechanisms of neuropathic pain as well as the interpatient variability of the therapeutic response. Due to this variability, failure of one agent within a drug class does not necessarily predict failure of an alternative. Most individuals can expect benefit from a treatment program that employs a rational, evidence-based approach.

Neuropathic pain, which stems from disturbances to the peripheral or central nervous system (CNS), is experienced by an estimated 2% to 3% of the Canadian population.<sup>1</sup> This already substantial incidence is likely to increase due to an aging population in whom many of the diseases that are predisposed to peripheral neuropathic pain such as diabetes, post-herpetic neuralgia and cancer are more common. Neuropathic pain can impose a considerable physical and psychological burden in its severe forms because of its chronicity and resistance to control. Unlike nociceptive pain, which resolves with healing or removal of the noxious stimulus, there is no dependable cure as yet for either peripheral or central neuropathic pain even though both can be controlled with appropriate treatments (Table 1).

The mechanisms of peripheral and central neuropathy are similar. In both, an injury to the nerve leads to abnormal conduction of sensory signals. Disturbances in nerve conduction may be experienced as one of a variety of abnormal sensations, including pain, tingling, burning or numbness. In the periphery, these sensations are due to a nerve injury that lowers the activation threshold for sensory conduction. This explains the frequent complaints of allodynia, which is when pain is experienced from non-painful stimuli. Once peripheral nerves are damaged, changes in molecular and cellular signalling may participate in a feedback of pain signals to sustain the condition.

In central neuropathy, the persistent and abnormal pain signalling is attributed to abnormal processing by dorsal horn neurons. The most common causes of central neuropathy include neurological degenerative diseases such as multiple sclerosis, stroke and spinal cord injury. As in peripheral neuropathy, there may be interpatient variability in the mechanisms that participate in sustaining central neuropathic pain. Two examples of pathways that participate in neuropathic pain include over-expression of voltage-gated N-calcium channels, which participate in the release of glutamate, and substance P,<sup>2</sup> and

**Table 1. Types of Pain**

Pain Type	Definition from International Association for the Study of Pain	Pain Control	Duration
Nociceptive	Pain generated by a noxious stimulus such as force or heat	Conventional analgesics or anti-inflammatory agents	Days to weeks
Peripheral neuropathic	Pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheral nervous system	First line: anticonvulsants or tricyclic antidepressants	Indefinitely
Central neuropathic	Pain initiated or caused by a primary lesion or dysfunction in the central nervous system	First line: anticonvulsants or tricyclic antidepressants	Indefinitely

Adapted from Dr. Ong-Lam.

irregularities in voltage-gated sodium channels, which have a direct effect on transfer of pain signals.<sup>3</sup> In any individual, differences in the relative role of these pathways may explain the differences in response to treatment targeted at one mechanism rather than the other.

Effective treatments of neuropathic pain have largely preceded an understanding of the pathophysiology, but there are signs that the targetable mechanisms of neuropathic pain are becoming better defined. While it has long been understood that analgesics are effective for control of nociceptive pain, which refers to the acute conventional pain associated with injury to tissues other than nerves, they are poorly effective in neuropathy. Controlled trials have demonstrated reproducible efficacy with other types of drugs, particularly anticonvulsants and antidepressants. The activity of agents within both of these classes is attributed to their ability to interrupt nerve signal conduction. However, most guidelines, including those from the Canadian Pain Society (CPS), list treatment strategies as first-, second- or third-line because of the variability in response that has established the need for alternatives when a first-choice therapy fails.<sup>4</sup>

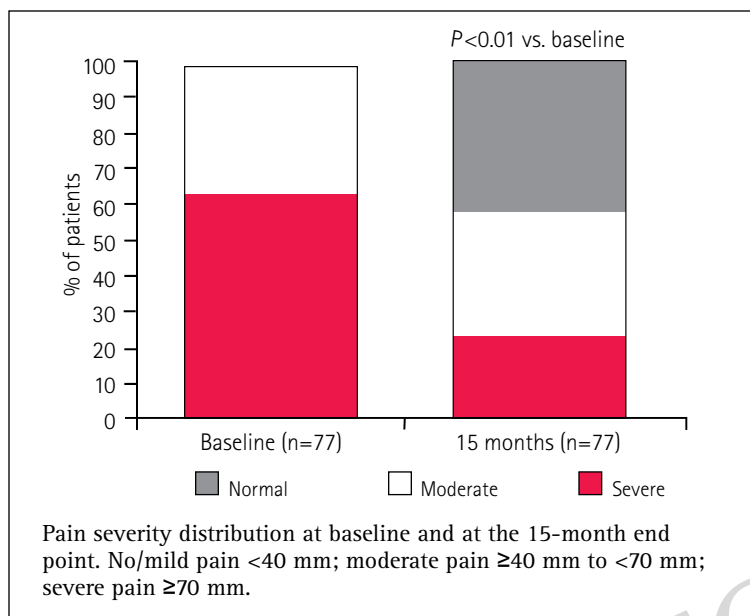
The failure of one first-line agent does not predict failure of another. Due to the variability in response, some patients respond well to one agent within a drug class but not to another. This has been vividly demonstrated with pregabalin and gabapentin,

both of which bind to voltage-gated calcium channels to inhibit release of the excitatory neurotransmitters glutamate and substance P that often drive neuropathic pain expression. The analgesic pregabalin is approved for control of neuropathic pain. In one study that evaluated patients with refractory neuropathic pain of which 60% classified their pain as severe, control was achieved in the majority of patients placed on pregabalin.<sup>5</sup> By the end of the 15-month period, approximately 40% were without pain, 40% had moderate pain, and only 20% still had severe pain (Figure 1).

While not approved for neuropathic pain, the anticonvulsant gabapentin may often be considered a first-line choice. In general, acceptable efficacy can be reached with a lower dose of pregabalin than gabapentin, reducing the risk of adverse events, making pregabalin a more attractive initial choice. However, if gabapentin is used first, it has been demonstrated repeatedly that failure of gabapentin does not predict failure of pregabalin. For example, pregabalin achieved high rates of sustained relief in a study of refractory neuropathic pain, which required failure on gabapentin for entry.<sup>5</sup> Despite being refractory to gabapentin and other treatments for neuropathic pain, 80% of the patients had improvement on pregabalin with follow-up out to 15 months.

Both pregabalin and gabapentin tend to be better tolerated than tricyclic antidepressants

Figure 1. Pain Severity



Adapted from Stacey et al. *Pain Medicine* 2008, p.4

(TCAs), which are also well established as first-line therapy for neuropathic pain, but the initial agent should be influenced by patient presentation. TCAs appear to provide control of neuropathic pain by one of several pathways, which not only includes inhibiting the reuptake of serotonin but also blockade of sodium channels and pain signalling mediated by N-methyl-D-aspartate.<sup>6</sup> These additional activities may explain why response rates have typically been greater with TCAs than agents from other antidepressant drug classes, such as selective serotonin reuptake inhibitors (SSRIs). While TCAs are often used after failure of an anticonvulsant, they should be considered as first-line therapy in patients with symptoms of mood disturbance whether or not the changes in mood are considered secondary to the persistent pain.

The differences in the mechanism of action of the analgesic pregabalin and the anticonvulsant gabapentin relative to TCAs raise the possibility that efficacy rates may differ by indication. For example, the activity of pregabalin and gabapentin in preventing release of substance P might suggest greater relative activity for control of burning pain, with which substance P has been associated,

than the dull pain more closely associated with upregulation of sodium channels. However, there are no compelling data to support these theories. Although there are data from large randomized and controlled trials to support the efficacy of pregabalin in the control of diabetic neuropathy and post-herpetic neuralgia,<sup>7,8</sup> the relative efficacy of TCAs is not well studied.

In patients who do not achieve adequate pain control on one of the first-line therapies alone, it is reasonable to consider a combination of a first-line anticonvulsant and a TCA in low doses before moving to a second-line agent. This provides a second mechanism of action and remains generally well tolerated. Another reasonable approach is the addition of topical lidocaine, which is listed as a second-line agent in the CPS guidelines. A potent sodium channel blocker, topical lidocaine poses a very low risk of systemic side effects and can be useful for adjunctive analgesia when peripheral neuropathy is localized (Figure 2).

Before moving to third-line agents, such as opioids, off-label use of antidepressants—including SSRIs or selective noradrenergic reuptake inhibitors such as venlafaxine, or anticonvulsants such as carbamazepine or lamotrigine—often prove efficacious in those unresponsive to the first-line agents. Although these agents are not as well studied or generally considered to be as effective as the first-line therapies for neuropathic pain, they appear to interfere with pain signal transduction by different mechanisms, thereby providing an opportunity to address the heterogeneity of patient response.

Opioid analgesics, such as morphine and oxycodone, have been shown to be effective in neuropathic pain, but these suppress CNS function, making them more difficult to employ in patients who are seeking to maintain normal activities. The same concern can be expressed about cannabinoids and methadone, which are listed as fourth-line choices in the CPS guidelines. Although moving to such therapies, or even invasive devices, such as epidural stimulators which use pacemaker technology to modulate pain dermatomes, is absolutely indicated when

**Figure 2. Canadian Pain Society (CPS) Guidelines**

First Line	Second Line
TCA or pregabalin, gabapentin, or carbamazepine	SSRI antidepressants or topical lidocaine
Third Line	Fourth Line
Tramadol or opioid analgesics	Cannabinoids or methadone or SSRI antidepressants or other anticonvulsants
<p><b>Modified CPS Guidelines</b></p> <ol style="list-style-type: none"> <li>1) In the absence of depression or anxiety, pregabalin or gabapentin</li> <li>2) In patients with mood disorder, consider TCAs first</li> <li>3) If localized pain is persistent, consider topical lidocaine</li> </ol> <p><b>If pain remains inadequately controlled:</b></p> <ol style="list-style-type: none"> <li>1) Try different first-line therapy, including pregabalin if patients started on gabapentin</li> <li>2) Try combination of first-line agents in low doses</li> <li>3) Consider second-, third-, and fourth-line agents as outlined in CPS guidelines</li> </ol>	

Adapted from Moulin et al. *Pain Res Manage* 2007;12:13-21.

these lead to an improved quality of life, it is important to consider the goal is not complete pain blockade but restoring patients to normal activities with the potential of diminished pain or diminished experience of pain over time.

## Summary

Control of neuropathic pain often requires empiric use of a broad array of therapies, some of which are prescribed off-label, but progress in understanding the pathways of pain and the mechanisms of pain control has provided a rational approach to treatment decisions. In published guidelines, including those from the CPS, pregabalin, gabapentin and TCAs are typically defined as first-line therapies based on support from multiple randomized trials. Inadequate response to one first-line therapy

does not predict inadequate response to another, including pregabalin after gabapentin or gabapentin after pregabalin. The need for multiple alternative therapies, including second-, third- and fourth-line agents, is based on the heterogeneity in patient response. This heterogeneity is such that patients who fail one agent may respond to another from the same therapeutic class. Current guidelines provide an organized approach to a challenging condition. ■

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**Editorial Overview:**

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In the management of neuropathic pain, the goal of analgesia should not be isolated from issues of relative tolerability, ability to perform normal functions and risk of drug interactions. Clinicians should be familiar with the array of current options so that adequate analgesia can be provided in the context of an acceptable quality of life. The influences on quality of life not only include the degree of therapeutic response in relationship to tolerability but the relative risk for drug interactions, the simplicity of dosing, and the potential for rare but serious adverse events. These issues are particularly important for treatment regimens, such as those employed to control neuropathic pain, that are likely to require prolonged or indefinite courses. Efficacy of treatment is essential but it cannot be divorced from the broader context of other variables likely to influence the adherence required for prolonged benefit. While there is no optimal therapy for neuropathic pain, there may be optimal regimens for individual patients.

The multiple pathways of neuropathic pain may explain the variability in response to currently available therapies. In treatment algorithms proposed by the CPS and others,<sup>1,2</sup> first-line treatments typically include anticonvulsants and TCAs but invite clinicians to move promptly to combination therapies or alternative agents in the event of inadequate pain control, unacceptable side effects or other issues that diminish the advantages of the first-line agents. In these algorithms, the order of treatments has been suggested by the quality of evidence demonstrating an acceptable balance of efficacy and safety, but individualization of therapy is important due not only to the variability in response but also to specific patient characteristics that may make one choice more appropriate than an alternative.

The concept of balancing pain control against a more global satisfaction with treatment explains why the most potent analgesics, such as opioids, are not first-line in the management of neuropathic pain despite their potent analgesic effect.<sup>1</sup> According to Boulanger et al.<sup>3,4</sup> in Quebec, opioids can be used in first, or second or third-line, depending on the urgency of pain requiring treatment. In general, treatments considered first-line have been selected for their efficacy in relationship to their tolerability; however, first-line treatments should not be considered interchangeable. They differ in mechanism of action, relative risk of specific side effects, risk of drug interactions and inconvenience of dosing. These considerations should influence the order in which the first-line agents are employed (Table 1).

With a specific indication for the treatment of diabetic neuropathy and postherpetic neuralgia, pregabalin is increasingly among the most widely used of the first-line choices because of both efficacy and an acceptable tolerability profile. The advantage of pregabalin over many other well tolerated treatments is that it does not require off-label use and its efficacy has been demonstrated in well controlled trials.<sup>5,6</sup> It inhibits release of excitatory neurotransmitters associated with pain conduction, such as glutamate and substance P, by preventing

**Table 1. Managing Neuropathic Pain**

Drug	Strategy	Side Effects	Drug Interactions
Pregabalin	First line	Mild sedation, dizziness	None
Gabapentin	First line	Mild sedation, dizziness	None
TCA's	First line	Substantial sedation, dizziness, anticholinergic effects	Competition with agents also using P450 liver enzymes for metabolism
Venlafaxine <sup>a</sup> and duloxetine <sup>b</sup>	Second line	Headaches, nausea, sedation, sexual dysfunction, somnolence	Class effect: triptans <sup>a</sup> , fluconazole <sup>a</sup> phenothiazines <sup>b</sup>
Opioids	Third line	Class effect: Nausea, vomiting, sedation, dizziness, constipation	Codeine and oxycodone partially metabolized by CYP405 2D6 Fentanyl metabolized by CYP405 3A4
Carbamazepine	Fourth line	Mild sedation, moderate dizziness, anticholinergic side effects	Competition with agents also using P450 liver enzymes for metabolism

calcium from entering the presynaptic terminals. Despite its generic name, pregabalin does not appear to exert analgesic activity by interacting with GABA receptors.

The most common adverse events associated with this agent are dizziness and somnolence, but these can be modified in those who experience them by several approaches. The first is to employ the lowest dose that provides adequate pain relief. Starting doses as low as 50 mg/day are reasonable in patients for whom sedation is a concern, although much higher doses can be employed in many patients with no sedative effects. The maximum recommended dose is 600 mg/day. Another approach to reducing the risk of sedation is to prescribe a higher evening dose relative to the daytime dose. It is also important to recognize that both dizziness and sedation may abate in some individuals with continued use. Relative to other agents effective in neuropathic pain, pregabalin poses a low risk of drug interactions, making this agent favourable in patients with concomitant medical problems.

The mechanism of action of gabapentin is less well understood, though considered comparable to that of pregabalin, but it similarly does not appear to provide analgesia by interacting with GABA receptors. Although

its half-life of approximately six hours is similar to that of pregabalin, this agent is typically administered three to four times per day while pregabalin is more typically administered two to three times daily. Both share dizziness and somnolence as their most common adverse events, but each is dose-related and occurs in a minority of patients even at the highest doses.

However, these agents do not have an entirely overlapping therapeutic activity. This latter characteristic is important because of an expectation that patients who do not respond to one will not respond to the other. Clinical studies have demonstrated that these medications are not interchangeable. Inadequate response to one agent does not preclude good pain control with the other, which has been especially well demonstrated when pregabalin is taken after gabapentin. Due to the relative safety and efficacy of these agents in first-line care of neuropathic pain, it may be appropriate to test both agents before moving to less well tolerated therapies.

The mechanism of action of TCAs in control of neuropathic pain is also poorly understood, although there is some evidence that their influence on the noradrenergic and serotonergic systems produces an interaction

with endogenous opioids in the CNS. TCAs are considered more effective than the SSRIs, despite the fact that this class of antidepressants exerts a cleaner effect on serotonergic activity. TCAs can be as effective as pregabalin on a number-needed-to-treat basis but they are usually less well tolerated. However, TCAs are reasonable first-line choices, particularly in patients with significant depression or anxiety associated with their neuropathic pain.

The relatively burdensome side effect of TCAs is attributed to its broad effects on multiple neurotransmitter systems, particularly acetylcholine. In addition to sedation, common adverse events include blurred vision, constipation, dry mouth, cognitive changes and tachycardia, but these are dose-related so up-titration should be slow. Patients should be maintained on the lowest dose that provides adequate pain relief. Employing larger doses at bedtime relative to daytime doses may also help improve tolerability. This strategy is particularly useful for patients who complain of insomnia, whether or not they relate it to their neuropathic pain. As with many medications, the risk of adverse events may diminish with continued use, although TCAs are increasingly being reserved for patients who are not controlled on better tolerated anticonvulsants. In addition, TCAs are metabolized by the hepatic P450 cytochrome system, making it a problematic choice in patients taking other drugs that are metabolized by the same pathway.

As a member of the serotonin-norepinephrine reuptake inhibitor class of antidepressants, both venlafaxine and duloxetine have demonstrated efficacy for neuropathic pain in controlled trials.<sup>7,8</sup> The mechanism of action for analgesia is not yet well established, although the pathway may be related to that of the TCAs. Venlafaxine and duloxetine are not generally considered to be first-line agents for neuropathic pain because there is more evidence of benefit from other options. These are also associated with adverse events, although the specific side effects differ. Venlafaxine is associated with substantial rates of somnolence and gastrointestinal

complaints. Duloxetine is also associated with nausea and somnolence but may also cause constipation and sexual dysfunction. Both are relatively weak inhibitors of the P450 cytochrome system and therefore pose a lower risk of drug interactions than compounds in the TCA class.

Although oral medications are typically required for control of chronic neuropathic pain, it is important to note that topical lidocaine should also be considered a first-line treatment, particularly for highly localized complaints. In those for whom lidocaine provides adequate relief, the risk of unwanted systemic adverse events can be avoided entirely. However, due to CNS conduction of neuropathic pain, topical therapies, including lidocaine, are often best combined with oral agents in order to achieve adequate pain control (Table 2).

Similarly, due to differences in their mechanisms of action, it is reasonable to consider oral first-line agents in combination when single-agent regimens prove to be inadequate. Although a combination may mean added side effects, patients who respond to two drugs administered in low doses may experience fewer adverse events than a single agent administered at maximal doses.

Alternative agents are not ranked second- or third-line due to a reduced likelihood of efficacy. In the case of alternative anticonvulsants such as carbamazepine, lamotrigine, topiramate or levetiracetam, or alternative antidepressants such as bupropion or paroxetine, the supportive data are less compelling but these agents may be effective in individual patients due to the interpatient variability of response. They may also improve pain control when combined with a first-line agent. Potent analgesics, such as oxycodone or another opioid, are good choices when the improvement of quality of life from pain relief provides an acceptable benefit:risk ratio. According to Moulin et al.,<sup>1</sup> the use of cannabinoids is considered fourth-line treatment; however, others<sup>3,4</sup> consider this class of agents as second-line in the treatment of neuropathic pain.

**Table 2. Pharmacologic Treatment of Diabetic Peripheral Neuropathic Pain**

Drug Class	Action	Individual Agents
Tricyclic antidepressants	Inhibits reuptake of serotonin and norepinephrine	<input type="checkbox"/> Tertiary: amitriptyline <input type="checkbox"/> Secondary: desipramine HCl
$\alpha_2\delta$ ligands	Modulate voltage-gated calcium channels	<input type="checkbox"/> Pregabalin <sup>1</sup> <input type="checkbox"/> Gabapentin <sup>1</sup>
Selective serotonin and norepinephrine reuptake inhibitors	Highly specific inhibition of serotonin and norepinephrine reuptake	<input type="checkbox"/> Duloxetine HCl <input type="checkbox"/> Venlafaxine
Opioids	$\mu$ -opioid receptors agonists	<input type="checkbox"/> Codeine <input type="checkbox"/> Tramadol <sup>2</sup> <input type="checkbox"/> Oxycodone HCl controlled-release <input type="checkbox"/> Morphine sulfate <input type="checkbox"/> Methadone HCl <input type="checkbox"/> Fentanyl transdermal <input type="checkbox"/> Hydromorphone HCl
Cannabinoids	CB1/CB2 receptors agonists	<input type="checkbox"/> Nabilone <input type="checkbox"/> THC/CBD <input type="checkbox"/> Dronabinol

<sup>1</sup> Pregabalin and gabapentin do not overlap in efficacy so that one can be used in those who fail the other.

<sup>2</sup> Weak inhibition of reuptake of serotonin and norepinephrine.

Adapted from Galluzzi et al. *JAOA* 2007;107(Supp 6):E539-E48.

## Summary

The most important goal of treatment in neuropathic pain is to improve quality of life. This requires an appropriate balance of adequate analgesia with a low burden of adverse events. The currently available agents are not interchangeable by mechanism of action, relative efficacy in an unselected population or tolerability. Due to an important variability in response to any single compound, it is reasonable to employ treatment algorithms that identify a rational order of first-, second- and third-line agents. In the absence of curative agents, regimens must be selected for their ability to be employed over sustained periods. ■

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Patients with neuropathic pain should not be promised a cure, but should be reassured that substantial pain control is a reasonable expectation. In the past, treatment guidelines have typically identified tricyclic antidepressants (TCAs) and anticonvulsants as having similar value as initial therapy, but pregabalin is the only therapy currently available with regulatory approval for the treatment of neuropathic pain. Although first-line therapies are not interchangeable in a practical sense, this does not diminish the importance of multiple options in the treatment of neuropathic pain. There is considerable variability in treatment response so individualization of care is needed. While cost is another variable that may affect treatment choice, it is important to recognize that the most effective therapy for pain control will often be the most cost-effective by reducing utilization of health services. Due to the wide variability in how any individual with neuropathic pain will respond to available treatments, clinicians should remain prepared to use second-, third- and fourth-line therapies when required.

The International Association for the Study of Pain defines neuropathic pain as a disturbance of nerve function.<sup>1</sup> Such disturbances, which have a broad spectrum of etiologies and generate a diverse array of specific symptoms, occur in the absence of a visible lesion. Without conducting sophisticated tests of nerve transduction, clinicians face the challenge of diagnosing a problem they cannot see and then evaluating treatment on the patient's subjective evaluation of benefit. Moreover, benefit is not necessarily measured as symptom eradication but on the basis of improvements in function and well-being. Yet clinicians can anticipate an accurate diagnosis and effective treatment program in the vast majority of patients by adhering to established protocols.

In guidelines recently developed by the Quebec Forum on Neuropathic Pain and posted on the Web site of *Les Cahiers de MedActuel*,<sup>2</sup> a clinical approach to the diagnosis of neuropathy was characterized as appropriate and sufficient in the majority of patients. With a careful history and physical examination, a non-neurological source of symptoms can usually be ruled out satisfactorily. The Quebec guidelines also advocate the DN4 questionnaire, which serves as a checklist of symptoms expressed by the patient or evaluated on a physical examination that guide the clinician to a diagnosis of neuropathic pain. A history of localized symptoms typical of neuropathy, such as burning, tickling or numbness, in the absence of stimuli or in the presence of non-painful stimuli, can provide good sensitivity and specificity for the diagnosis. An empiric course of therapy is reasonable when there is no alternative explanation for the patient's complaints.

In previous guidelines, TCAs and anticonvulsants have been given equal consideration as first-line choices. While pregabalin is approved as an analgesic for the treatment of peripheral and central neuropathic pain, guidelines issued by experts in Quebec listed it as an anticonvulsant along with gabapentin. They share first-line status with TCAs, but the TCAs are listed below the

**Table 1. Pharmacokinetic profile of pregabalin and gabapentin**

	<b>Pregabalin</b>	<b>Gabapentin</b>
Oral bioavailability	90% Independent of dose	57% after 300 mg 42% after 600 mg Dependent of dose
Absorption	Linear Independent of food intake	Non-linear Reduced bioavailability (of 20-30%) by oral antacids
Regimen	Simple b.i.d. dosing Fast dose escalation	Multiple t.i.d.-q.i.d. dosing Slow dose titration
Compliance	High	Low

Adapted from Gilron I. *Curr Opin Anaesthesiol* 2007;5:456-72.

anticonvulsants. This order of treatments, more defined than an indiscriminate listing of anticonvulsants or TCAs, may still be misleading in practical terms. Pregabalin or gabapentin have a favourable efficacy-to-safety ratio relative to TCAs, but these drugs are not interchangeable, and TCAs may still be a superior first choice in patients who have both neuropathic pain and mood disturbance.

It is appropriate to single out pregabalin and gabapentin as first-line therapies for neuropathic pain on the basis of efficacy and tolerability as demonstrated in controlled trials.<sup>3,4</sup> However, pregabalin and gabapentin are often misrepresented as interchangeable. There are numerous reasons to challenge this characterization. Foremost, the efficacy or lack of efficacy of one does not predict the clinical response of the other. In a referral setting in which patients have been started on gabapentin previously and are not achieving adequate pain control, pregabalin remains a viable option, despite the similarity in the chemical structure of the two compounds.<sup>6</sup> Secondly, pregabalin is generally easier to administer than gabapentin because it is more effective at lower doses due to greater oral bioavailability and absorption (Table 1). With gabapentin, a substantial proportion of patients will require a daily dose of  $\geq 1800$  mg, at which point the tolerability diminishes as dosing frequency must be increased, both of which reduce compliance.

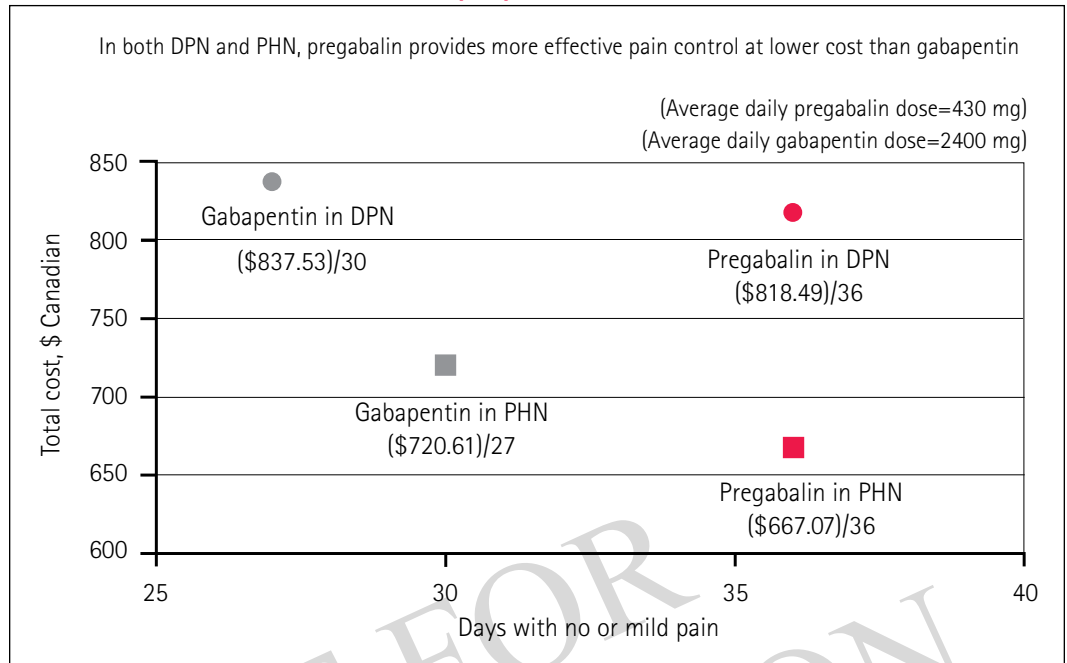
From a practical standpoint, these data are a basis for considering pregabalin as a first-line therapy among first-line choices. This advantage may not only mean more efficient pain control and a shorter interval to an improvement in quality of life, but there are also data to suggest greater cost efficacy for pregabalin relative to gabapentin. In a 12-week Canadian study that compared resource utilization in 126 patients with either diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN), pregabalin reduced direct medical costs for both conditions relative to gabapentin due to a greater number of pain-free days (Figure 1).<sup>5</sup>

In patients who have been started on gabapentin but whose pain is not adequately controlled, pregabalin can be initiated before weaning patients from this initial therapy. In patients who are not adequately controlled on pregabalin, the efficacy of gabapentin has not been studied. Switching to a TCA or adding a low dose of a TCA may be more beneficial, particularly in patients with psychological symptoms such as depression or anxiety accompanying their neuropathy.

In the use of these first-line therapies, trials of two to three months with escalating doses should be employed before characterizing a therapy as ineffective. Measuring benefit with a standardized approach should be part of the management protocol. While patients should not expect complete pain relief, they should

## NEUROPATHIC PAIN GUIDELINES ARE BECOMING MORE PRACTICAL FOR A LOGICAL ORDER OF THERAPY

**Figure 1. Cost-effectiveness of pregabalin for the management of neuropathic pain associated with DPN and PHN: a canadian perspective**



Anh Nguyen, 2008 Adapted from Tarride et al. *Clinical Therapeutics* 2006; 28 (11): 1922-34

be given a goal by which to judge efficacy; a 30% reduction in symptoms from a baseline pain rating is a reasonable initial target and clinically important, regardless of disease type, age, sex or baseline pain.<sup>7</sup> Managing expectations and avoiding disappointment often plays an important role in restoring a patient to an acceptable level of function.

In patients with specific areas of localized allodynic pain, topical lidocaine can be a useful adjunct to pregabalin, gabapentin or TCAs for pain control. Patients with a partial response on first-line therapies may further boost pain control without escalating pharmacologic therapy through pain management techniques such as biofeedback, coping skills counselling, exercise and other strategies. However, moving to second-line or higher therapeutic strategies is important when patients have poor or no response to first-line agents. Second-line agents are not necessarily more potent, but they do introduce different mechanisms of action that may explain efficacy in an individual who is not responsive to initial options.

In the guidelines published by the Quebec Forum consensus group, second-line agents

are the selective serotonin and norepinephrine reuptake inhibitors venlafaxine and duloxetine, and the cannabinoids, which include dronabinol, nabilone, oral extract of delta-9-tetrahydrocannabinol and cannabimol. Both come before selective serotonin reuptake inhibitors (SSRIs), the anticonvulsants other than gabapentin, such as carbamazepine, topiramate and lamotrigine, or other antidepressants, such as bupropion, all of which are listed as third-line agents. The fourth-line agents include methadone, ketamine and baclofen. In patients who are not responsive to pharmacologic therapies, a referral for an invasive procedure that involves neurostimulation may be appropriate, but these cases are relatively rare.

In patients with severe initial pain, tramadol and opioids must be rapidly introduced as first-line therapy while any other first-line agent is being titrated to an effective dose. Moreover, these analgesics should also be maintained during the trial of second, third and fourth-line therapies.

These recommendations differ from those issued by the Canadian Pain Society (CPS),

which provide a more general recommendation for TCAs or anticonvulsants as first-line therapies.<sup>8</sup> Although the CPS recommendations are appropriately based on published studies, they do not appear to be sensitive to the practical issues of efficacy in relation to tolerability. Although the efficacy of TCAs for neuropathic pain is well supported in controlled trials, they are not as easy to administer as pregabalin or gabapentin due to the adverse events, making them less suitable for first-line therapy, except for individuals with depression related or not to neuropathic pain.

When patients with neuropathy are stabilized on a pain control medication, follow-up visits can be scheduled at three- to six-month intervals depending on the degree of residual symptoms. At each visit, pain scores should be recorded using standardized methodology for rating symptoms. It is important to monitor pain levels in different settings, such as at work, at night or during daily activities. Patients should be focused on the goal of improving their ability to achieve normal function, but elimination of pain should not be promised. Although many patients who reach a pain-free state can be weaned from medication to achieve what might reasonably be characterized as a cure, the vast majority will continue to experience some degree of symptoms. A recurrence of neuropathic pain to pre-treatment levels is not common, but helping patients to cope with pain may be as important as providing adequate analgesia.

## Summary

Given the broad array of therapies currently available for the treatment of neuropathic pain, numerous guidelines have been developed to provide a rational approach to treatment. Even though many guidelines advocate therapies that must be employed off-label, there is a strong basis for considering pregabalin, the only treatment indicated for central and peripheral neuropathic pain, as a first choice in the majority of patients due to a favourable balance of efficacy and safety. Relative to gabapentin, pregabalin is more

effective at lower doses. It also demonstrates efficacy in patients not adequately controlled on gabapentin. However, clinicians must be prepared to move to second-, third- or fourth-line agents as required in patients who do not achieve adequate pain control on initial options. Although none of the current therapies offers a cure, an appropriate regimen will permit a large proportion of patients to resume many normal activities. ■

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