

# Challenges in Neuropathic Pain

In this issue of *Challenges in Neuropathic Pain*, the Multidisciplinary Panel on Neuropathic Pain present updated recommendations on several neuropathic pain conditions. We also present part 3 of the series on drugs for neuropathic pain, which discusses opioids, and an interesting case on a patient developing neuropathic pain following a traffic accident. Visit [www.neuropainhk.org](http://www.neuropainhk.org) to obtain back issues of *Challenges in Neuropathic Pain*, together with the Panel's recommendations on various neuropathic pain conditions and patient education materials.

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## Management of Diabetic Peripheral Neuropathy, Postherpetic Neuralgia and Trigeminal Neuralgia – Updated Recommendations

Since the Multidisciplinary Panel on Neuropathic Pain (MPNP) first developed recommendations for the management of painful diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN) and trigeminal neuralgia (TN), which were published in 2003,<sup>1-3</sup> new data for both pharmacological and nonpharmacological treatment approaches have emerged. Thus, the MPNP recently updated their recommendations – a summary of these updates is presented here. The full versions of these recommendations are available at the MPNP Web site – [www.neuropainhk.org](http://www.neuropainhk.org).

As a general rule, when there is no or poor response to initial pharmacotherapy for painful neuropathic conditions, a multidisciplinary approach may be required. This would include physical therapy, psychological treatment (eg, cognitive behavioural intervention), social readjustment and other complementary treatment strategies in addition to medical therapy for pain relief and management of comorbid conditions (eg, anxiety and depression).

### Recommendations for the management of painful DPN

Up to 50% of patients with long-standing diabetes develop some form of neuropathy and painful neuropathy may be present in as many as one third of all diabetic patients.<sup>4</sup> Distal symmetric polyneuropathy is the most common form of diabetic neuropathy – affecting about 40% of patients with diabetes of 25 years' or longer duration – and predominantly affects sensory functions.<sup>5</sup>

### Tricyclic antidepressants and anticonvulsants the mainstay therapies for DPN

Tricyclic antidepressants (TCAs) and anticonvulsants (gabapentin, pregabalin, lamotrigine, topiramate, phenytoin) remain the mainstay therapeutic agents for DPN. Newer classes of antidepressants have been recently investigated in painful DPN, including venlafaxine,<sup>6</sup> and the selective serotonin reuptake inhibitors citalopram, fluoxetine and paroxetine.<sup>7</sup>

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Anticonvulsants should be considered as an alternative first-line choice when TCAs are contraindicated. Gabapentin improves pain and sleep interference associated with DPN, and has positive effects on mood and quality of life.<sup>8</sup> The anticonvulsant pregabalin may also be given; pregabalin 300 to 600 mg/day effectively relieves pain, and improves sleep and overall well-being of patients with painful DPN.<sup>9–11</sup> These effects were observed within 1 week in many patients.

### Other agents

Other agents include intravenous lidocaine infusion<sup>12</sup> and 5% lidocaine patch.<sup>13</sup>

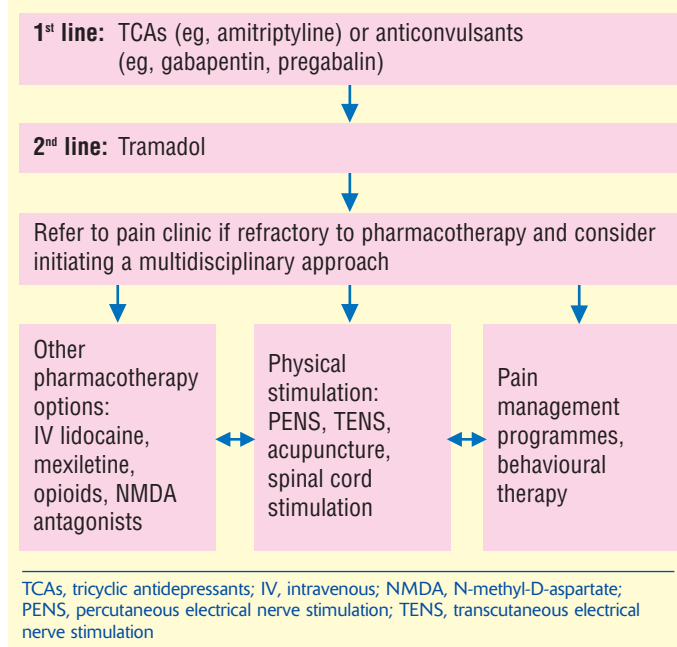
### Novel therapies

The antioxidant thiotic acid ( $\alpha$ -lipoic acid) may improve aspects of nerve conduction.<sup>14,15</sup> Benfotiamine, a lipid-soluble vitamin B<sub>1</sub> prodrug, may be beneficial in improving neuropathy, according to a randomized, double-blind, placebo-controlled pilot study.<sup>16</sup>

Physical stimulation, such as transcutaneous electrical nerve stimulation (TENS) and acupuncture, may counteract painful sensations. More invasive stimulatory interventions, eg, spinal cord stimulation (SCS), may be considered as a last option.

In summary, the proposed treatment algorithm for painful DPN is shown in Figure 1.

**Figure 1. Proposed treatment algorithm for painful DPN**



### Recommendations for the management of PHN

The reported incidence of PHN following acute herpes zoster infection varies from 9%–34%.<sup>17</sup> PHN is uncommon in patients younger than 40 years, but the risk increases sharply with age; up to 75% of patients older than 70 years experience pain 1 month after healing, while 50% continue to have pain at 1 year.<sup>17</sup>

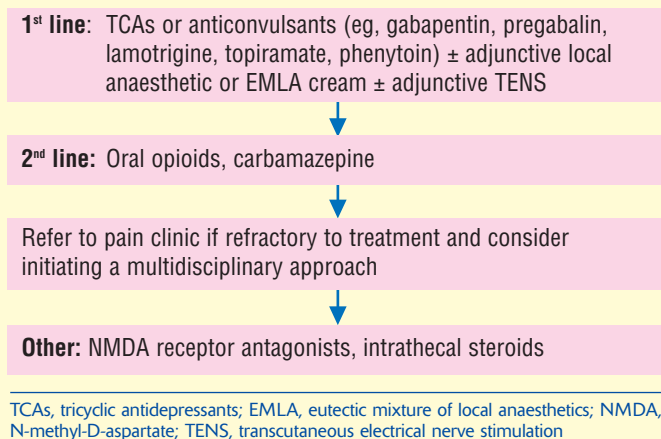
### TCAs and anticonvulsants the mainstay treatments for PHN

The mainstay treatments for PHN include TCAs and anticonvulsants (eg, gabapentin, pregabalin, oxcarbazepine). Early drug initiation can improve the success of TCA therapy – a retrospective study found that the time of TCA therapy initiation was the most predictive factor of treatment outcome.<sup>18</sup> In a randomized, double-blind, controlled clinical trial of patients with PHN and painful DPN, pregabalin regimens significantly reduced mean pain score and improved pain-related sleep interference compared with placebo.<sup>19</sup> Another randomized, double-blind, placebo-controlled trial of 173 PHN patients found that pregabalin 300 or 600 mg/day effectively

reduced pain.<sup>20</sup> Opioid analgesics and tramadol<sup>21</sup> also have a role in PHN treatment. For patients with shooting or lancinating pain, a trial of phenytoin, sodium valproate or carbamazepine may be beneficial.<sup>22</sup> For patients remaining unresponsive to conventional treatments after 8 weeks' trial, combination therapy<sup>23,24</sup> and/or adjunctive TENS may be considered.

In summary, the proposed treatment algorithm for PHN is shown in Figure 2.

**Figure 2. Proposed treatment algorithm for PHN**



### Recommendations for the management of idiopathic TN

TN is an extremely painful, easily diagnosed condition that can be managed medically in most cases. The prevalence of TN is around 0.1–0.2 per 1,000 population and the annual incidence is about 4–5 per 100,000 population.<sup>25,26</sup> TN occurs more frequently in older people, and is more likely to affect females than males. The pain is unilateral in most cases. Multiple sclerosis (MS) can be a cause of TN in about 2%–4% of TN patients,<sup>25,28</sup> and coexistent MS should be considered in younger TN patients.

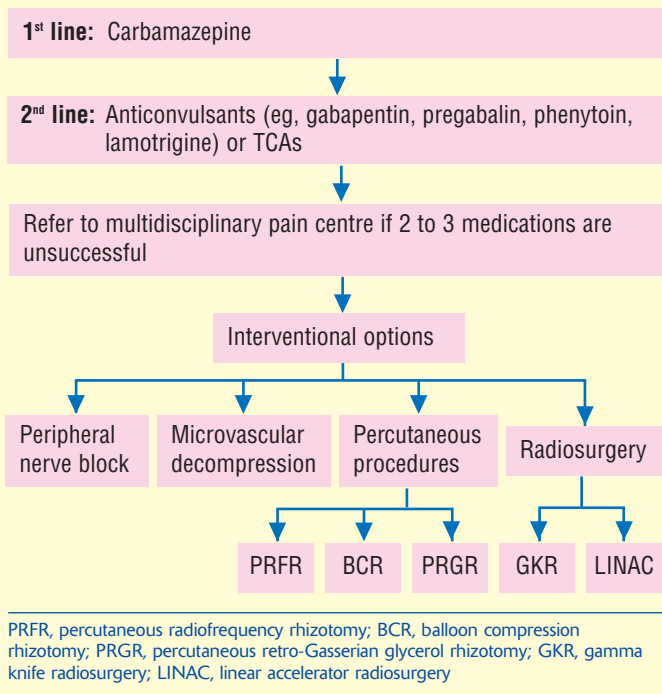
### First- and second-line treatments for TN

The anticonvulsant carbamazepine is the recommended first-line treatment for TN. There are several second-line alternatives to carbamazepine when this agent is contraindicated, including other anticonvulsant agents (eg, gabapentin, pregabalin, lamotrigine, valproic acid) and lidocaine. Gabapentin should be commenced as a single 300 mg dose on day 1, 600 mg/day on day 2 (divided bid) and 900 mg/day on day 3 (divided tid). The dose can subsequently be titrated up as needed for pain relief, to a daily dose of 1,800 mg/day (divided tid) with a daily maximum of 3,600 mg, if necessary.<sup>29</sup> Care should be taken in dose selection and the dose should be adjusted for elderly patients or those with impaired renal function, based on their creatinine clearance values.<sup>29</sup> Pregabalin, a new anticonvulsant, is also emerging as an effective treatment for various neuropathic pain syndromes,<sup>9,19,21</sup> and may have a role in TN, although it has not been evaluated in this condition. Pregabalin is initiated at 150 mg/day in two divided doses and increased to 300 mg/day after 3–7 days. Pregabalin may be up-titrated to a maximum dose of 600 mg/day, depending on patient response.

### Nonpharmacological approaches

Nonpharmacological approaches include peripheral trigeminal nerve block and surgical interventions on the trigeminal nerve (microvascular decompression; percutaneous procedures; and radiosurgery, eg, gamma knife radiosurgery [GKR] and linear accelerator [LINAC] radiosurgery). The major side effect of peripheral trigeminal nerve block is reduced facial sensation, which may last for several weeks.<sup>30</sup> GKR is a relatively new intervention for TN. A review of 151 TN cases treated with GKR showed that 47% of patients were pain-free without medication after 1 year of follow-up, and 34% of patients after 3 years of follow-up.<sup>31</sup> However, 27% of patients with

**Figure 3. Proposed treatment algorithm for TN**



initial improvement subsequently experienced pain recurrence after 12 months (median) post-surgery. Retrospective studies with varying durations of follow-up have analysed the efficacy of LINAC radiosurgery to provide pain relief in TN.<sup>32,34</sup> In the largest of these studies,<sup>33</sup> 56.1% of patients from a single centre who had received dedicated LINAC radiosurgery for the treatment of TN remained pain-free at a mean follow-up of 23 months; however, 32% of patients experienced facial numbness. Longer-term follow-up and reports from other centres are awaited before any recommendations on the efficacy of dedicated LINAC radiosurgery can be made.

In summary, treatment recommendations for TN are shown in Figure 3.

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**CASE PRESENTATION**

*A case of a young man who develops radiculopathy following a traffic accident is presented.*

**Radiculopathy**

**Presenting symptoms and objective findings**

A 29-year-old man sustained multiple fractures in a road traffic accident in July 2005. He had fractures of the right humerus, right radius, right ulnar shaft and right clavicle, which were treated with open reduction and internal fixation. He also sustained fractures of the right pelvis and spinous process of the T12 vertebra. The pelvic fracture was of the lateral compression type with associated fracture of the right superior pubic ramus. The pelvic fracture was treated with internal fixation.

**Management**

After the pelvic fracture fixation, the patient complained of right leg cramps with numbness of the left leg. It was likely due to right L5 radiculopathy. He was seen by the pain team for pain management, and was treated with amitriptyline, DF118 (dihydrocodeine), diclofenac SR, pregabalin, baclofen and syrup morphine. The medical treatment successfully relieved his neuropathic pain. The medication was reduced to pregabalin 75 mg bid, amitriptyline 25 mg nocte and DF118 prn 6 weeks postoperatively. He was rehabilitated with progressive weight-bearing exercise. The pain and numbness associated with radiculopathy gradually subsided and medications were stopped 10 weeks after the operation.

**Discussion**

During the internal fixation of a fractured pelvis, drilling and local swelling can cause nerve irritation. Subsequent adhesion or the actual implant may cause nerve impingement. The nerve is hypersensitive, which may result in neuropathic pain and numbness. Motor symptoms occur when there is definite damage to the nerve. The pain and numbness can be very severe, and strong intravenous analgesics may be required for pain control. For neurapraxia-type nerve injury, the nerve irritation usually subsides within 4–10 weeks. However, the pain may become chronic if hypersensitivity of the nervous system persists. Neuropathic pain can be successfully treated with medications like amitriptyline, gabapentin or pregabalin.

**Q & A**

*Forward your questions on diagnosis, treatment or management of neuropathic pain to the Multidisciplinary Panel on Neuropathic Pain at [mpnp@asia.cmpmedica.com](mailto:mpnp@asia.cmpmedica.com).*

**Are there benefits to a multi-disciplinary approach for neuropathic pain treatment?**

A multidisciplinary approach to neuropathic pain treatment allows for treatment of the whole patient. It places equal emphasis on understanding the cellular and molecular mechanisms underlying pain, as well as the multidimensional interactions of cognitive, behavioural and environmental influences. It offers an opportunity to achieve both adequate pain relief and improve physical, behavioural and psychological function. There is evidence to support the efficacy of a multidisciplinary approach for treating neuropathic pain. A meta-analysis of 10 trials involving 1,964 patients with chronic low back pain showed that intensive multidisciplinary biopsychosocial rehabilitation with a functional approach reduced pain and improved function.<sup>1</sup> A small study of patients with spinal cord injury and neuropathic pain also showed that educational, cognitive and behavioural interventions, as part of a comprehensive pain management programme, can be valuable complements to pharmacotherapy.<sup>2</sup>

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# DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

We continue our series on drugs for the treatment of neuropathic pain. Part 3 of the series examines evidence on opioids in neuropathic pain.

## Part 3 – Opioids

Historically, opioids were largely considered as ineffective in the treatment of neuropathic pain. However, in recent years, clinical trials have demonstrated that oxycodone, morphine, tramadol, methadone and levorphanol have efficacy in the treatment of neuropathic pain.<sup>1-11</sup> Opioids used for neuropathic pain are selective for  $\mu$ -opioid receptors; opioids that are selective for  $\kappa$ -opioid receptors (eg, butorphanol, nalbuphine) are not generally useful in this setting.<sup>2</sup>

Two recent meta-analyses assessed the efficacy and safety of opioids for the treatment of (a) nonmalignant neuropathic pain and (b) evoked neuropathic pain, based on published randomized controlled trials.<sup>12,13</sup> In the treatment of nonmalignant neuropathic pain, short-term studies (<24 hours) provided only equivocal evidence for efficacy.<sup>12</sup> However, in intermediate-term studies (median, 28 days; range, 8–56 days) opioids demonstrated significant benefit over placebo.<sup>12</sup> In the treatment of evoked neuropathic pain, short-term studies showed that opioids reduced the intensity of dynamic mechanical allodynia and perhaps cold allodynia.<sup>13</sup> Intermediate-term studies demonstrated the efficacy of opioids over placebo for evoked neuropathic pain.<sup>13</sup>

### Factors to consider when prescribing an opioid for neuropathic pain

Factors to consider when prescribing opioids or tramadol are shown in the Table.<sup>1</sup> One other consideration is that opioid analgesic use is often limited by high rates of adverse events, which include nausea and vomiting, constipation, drowsiness and somnolence, dizziness and altered cognition.<sup>12</sup> It may be necessary to initiate an opioid contract with patients prior to starting opioid therapy, to ensure they understand the benefits and risks of opioids, including the potential for abuse.<sup>14</sup>

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**Table. Factors to consider when prescribing opioids or tramadol for neuropathic pain<sup>1</sup>**

Opioids	Tramadol
<b>Ability to sleep</b>	<b>Drug–drug interactions</b> <ul style="list-style-type: none"> <li>• Selective serotonin reuptake inhibitors (SSRIs)</li> <li>• Monoamine oxidase inhibitors (MAOIs)</li> </ul>
<b>Cognitive impairment</b>	<b>History of seizures</b> <ul style="list-style-type: none"> <li>• Increased risk in patients with history of seizures or those receiving concurrent drugs that reduce the seizure threshold (eg, opioids, tricyclic antidepressants, neuroleptics)</li> </ul>
<b>Elderly</b> <ul style="list-style-type: none"> <li>• Risk of cognitive impairment and mobility problems</li> </ul>	<b>Cognitive impairment</b>
<b>History of substance abuse</b> <ul style="list-style-type: none"> <li>• Use with extreme caution in these patients</li> </ul>	<b>Elderly</b> <ul style="list-style-type: none"> <li>• Risk of cognitive impairment</li> </ul>
<b>Depression</b> <ul style="list-style-type: none"> <li>• Use with extreme caution in these patients</li> </ul>	<b>Renal or hepatic disease</b> <ul style="list-style-type: none"> <li>• Dose adjustment required</li> </ul>
<b>Suicidal tendencies</b> <ul style="list-style-type: none"> <li>• Use with extreme caution in these patients</li> </ul>	<b>Need for titration, in general</b> <ul style="list-style-type: none"> <li>• May require 2–7 weeks</li> </ul>
<b>Physical dependence</b>	

Part 1 and 2 of this series can be found at <http://www.neuropainhk.org/newsletter.asp> – Issues 10 and 11.

## LITERATURE REVIEW

McCarberg B, Billington R. *Consequences of neuropathic pain: Quality-of-life issues and associated costs.* *Am J Manag Care* 2006;12(9 suppl):S263-S268.

Chronic pain, including neuropathic pain, has a high prevalence and places a significant burden on society and the patient. Indeed, in the United States chronic pain is the most common cause of disability.

Various studies have estimated the direct and indirect costs of chronic pain. Patients with neuropathic pain are more likely than a control population without neuropathic pain to have other pain-related conditions and comorbidities. The presence of neuropathic pain is associated with around a three-fold increase in direct healthcare costs compared with the control population. Factors that contribute to indirect costs associated with chronic pain include absenteeism from work and reduced productivity while at work. Studies have shown that patients with neuropathic pain report greater losses in productivity and negative effect on employment status than patients without neuropathic pain.

Neuropathic pain adversely affects patients' quality of life and is associated with comorbidities such as depression, increased anxiety and pain-associated sleep interference. Thus, effective management of chronic pain, including neuropathic pain, requires evaluation of not just pain but associated conditions. The authors state that to achieve optimal functionality, the triad of chronic pain, sleep disturbances and depression or anxiety must be addressed. Pharmacological treatments

of pain and pain-associated comorbidities have an impact. For instance, studies have shown that duloxetine, lidocaine patch 5%, tramadol, gabapentin and pregabalin improve quality of life in neuropathic pain; gabapentin and pregabalin also improve sleep in such patients.

To improve outcomes for patients with chronic pain, effective assessment and management strategies are required to address pain and associated comorbidities.

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