

# Challenges in Neuropathic Pain

This 17<sup>th</sup> issue of *Challenges in Neuropathic Pain* provides a summary of the Multidisciplinary Panel on Neuropathic Pain's updated recommendations on the management of neuropathic pain associated with peripheral nerve entrapment. The series on drugs for neuropathic pain is continued, reviewing tramadol and the serotonin syndrome. The case in this issue is on persistent headache, and the Q&A investigates whether acute neuropathic pain is a distinct clinical entity. Visit [www.neuropainhk.org](http://www.neuropainhk.org) for back issues of *Challenges in Neuropathic Pain*, and other useful information on neuropathic pain.

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## Updated Recommendations for the Management of Neuropathic Pain Associated with Peripheral Nerve Entrapment

This article provides a summary of the updated recommendations from the Multidisciplinary Panel on Neuropathic Pain (MPNP) on the management of neuropathic pain associated with peripheral nerve entrapment. The full version of these recommendations is available at the MPNP Web site – [www.neuropainhk.org](http://www.neuropainhk.org).

Peripheral nerve entrapment can cause neuropathic pain symptoms, but its treatment differs from other neuropathic pain conditions (such as postherpetic neuralgia, painful diabetic neuropathy and trigeminal neuralgia) in that surgical decompression and nerve repair are often first-line treatment options, rather than pharmacological management. These recommendations describe some of the more common causes of neuropathic pain caused by peripheral nerve entrapment, and are structured by nerve level: root level and peripheral nerve level. The recommendations are summarized in the Table.

### Nerve Entrapment at the Root Level

#### Cervical radiculopathy

Cervical radiculopathy is a common symptom in patients with cervical spondylosis – a degenerative condition of the cervical vertebrae, intervertebral discs and surrounding ligaments. While cervical spondylosis may result from a previous neck injury, the main risk factor is ageing.

#### Diagnosis

Symptoms include progressive neck pain, limited head and neck movement, and pain or paraesthesia due to spinal cord or nerve root compression.

Cervical spine x-rays show narrowing of the disc space by osteophytes. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the spine confirm the location of the nerve root or spinal cord compression. Nerve conduction testing and electromyography (EMG) measure skeletal muscle activity. A myelogram can confirm the extent of nerve damage, but is not commonly used.

#### Treatment

Short-term use of a cervical collar, nonsteroidal anti-inflammatory drugs (NSAIDs), neck-care exercises, postural training and intermittent cervical traction may benefit some patients. Surgical decompression of the nerve root is indicated for severe cases or when other treatments have failed. In recent years, new surgical modalities have come into practice, including microsurgical cervical foraminotomy (posterior

**Table. Summary of updated recommendations on the management of neuropathic pain associated with peripheral nerve entrapment**

		Root level		Peripheral nerve level	
		Cervical radiculopathy	Lumbar radiculopathy	Carpal tunnel syndrome	Cubital tunnel syndrome
Diagnosis	Physical examination	✓	✓	✓	✓
	X-ray	✓		✓	✓
	CT scan	✓			
	MRI	✓	✓		
	Myelogram	(not commonly used)	(largely replaced by MRI)		
	EPS*	✓	✓	✓	✓
Treatment	Conservative	– Cervical collar – Physiotherapy/ neck care exercises	– Physiotherapy – PENS/TENS	– Physiotherapy – Wrist splinting	– Does not have a great role in treatment
	Medical	– NSAIDs – For neuropathic pain symptoms, anticonvul- sants or antidepressants may be effective	– NSAIDs – Gabapentin – Epidural corticosteroid injection – Chemonucleolysis	– Oral steroids and local steroid injections – Diuretics	– Does not have a great role in treatment
	Surgical	– Anterior discectomy with spinal fusion – Microforaminotomy – Spinal arthroplasty	– Discectomy – Microdiscectomy – Percutaneous discectomy	– Carpal tunnel release (open or endoscopic)	– Simple neurolysis (open or endoscopic) – Anterior transposition of the ulnar nerve – Medial epicondylectomy of the distal humerus – Cubital tunnel release

\* Electrophysiological studies (EPS) are recommended in cases where clinical diagnosis is not certain.  
CT = computed tomography; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PENS = percutaneous electrical nerve stimulation; TENS = transcutaneous electrical nerve stimulation.

or anterior) and spinal arthroplasty, and have produced significant neurological and clinical improvements.<sup>1-5</sup>

### Lumbar radiculopathy

Lumbar radiculopathy is a common cause of low back pain, occurring when the sciatic nerve or lumbar root nerves are compressed. It is often accompanied by pain radiating from the back into the buttock and, sometimes, down the entire leg.

#### Diagnosis

Lumbar radiculopathy may cause muscle weakness, dermatomal sensory deficits, abnormal reflexes and a positive straight-leg-raising test. An MRI may be used to determine the location of disc herniation and has largely replaced the use of a myelogram.

#### Treatment

Bed rest is not recommended; mobility must be maintained.<sup>6</sup> Oral NSAIDs<sup>7</sup> and physiotherapy, including hot packs, manipulation and intermittent pelvic traction, may be beneficial. Percutaneous and transcutaneous electrical nerve stimulation (PENS/TENS) may provide short-term relief.<sup>8</sup>

In one study, gabapentin was shown to be effective in patients with chronic radiculopathy.<sup>9</sup> A recently published case report described two patients with lumbar radiculopathy being successfully treated with gabapentin.<sup>10</sup>

Epidural corticosteroid injections provide short-term relief from pain of disc herniation or radiculitis, but evidence of long-term relief is lacking.<sup>11-13</sup> Chemonucleolysis can potentially provide long-term relief.<sup>14</sup>

The standard surgical intervention for lumbar radiculopathy is discectomy, which has a high success rate (80%-96%).<sup>15</sup> Microdiscectomy gives broadly comparable results to standard lumbar discectomy.<sup>16</sup> Percutaneous discectomy is another treatment for disc herniation-associated radiculopathy; various techniques are available, including laser decompression<sup>17</sup> and mechanical aspiration.

## Nerve Entrapment at the Peripheral Level

### Median nerve: Carpal tunnel syndrome

Carpal tunnel syndrome, resulting from median nerve compression, causes paraesthesia, tingling, numbness, clumsiness and weakness of the affected hand.

The most common cause is repetitive stress injury or overuse

syndrome, usually from repetitive finger or wrist movements. Other causes include trauma, synovitis, arthritis, vascular injury, local tumours, endocrine or metabolic disorders, infection, collagen disease and chronic renal failure.

#### Diagnosis

Hand and wrist x-rays with a carpal tunnel view and electrophysiological studies assist in establishing the diagnosis. The presence of systemic disease must be ruled out. Clinical signs of carpal tunnel syndrome are:

- Wasting of the thenar muscles
- Weak thumb abduction and opposition
- Decreased pinprick sensation in the radial 3½ fingers (with intact palmar sensation)
- Positive Tinel's sign and Phalen's test

A newer test – the scratch collapse test – has significantly higher sensitivity than Tinel's test and the Phalen manoeuvre for detecting carpal tunnel syndrome and cubital tunnel syndrome.<sup>18</sup> In the scratch collapse test, patients resist bilateral shoulder external rotation with elbows flexed; the area of suspected nerve compression is lightly 'scratched', and then resisted shoulder external rotation is immediately repeated. Momentary loss of shoulder external rotation resistance on the affected side is considered a positive test.<sup>18</sup>

#### Treatment

Conservative management includes good ergonomics, splinting, rest at intervals, and reduction of tasks requiring hand or wrist movements. A review of the effectiveness of conservative treatment strategies concluded that significant short-term benefit may be derived from oral steroids, splinting, ultrasound, yoga and carpal bone mobilization.<sup>19</sup> Another review found evidence for the efficacy of local and oral steroids and splints, and limited or conflicting evidence for the efficacy of NSAIDs, diuretics, yoga, laser and ultrasound.<sup>20</sup>

Surgery is indicated when conservative treatment has failed or there is motor involvement or severe numbness. The endoscopic carpal tunnel release (ECTR) technique is now more popular than the standard open carpal tunnel release (OCTR). However, comparative efficacy studies show no strong evidence supporting the replacement of OCTR with alternative surgical procedures.<sup>21</sup>

## Ulnar nerve: Cubital tunnel syndrome

Cubital tunnel syndrome arises mainly from ulnar nerve entrapment. Other causes include tardive ulnar palsy due to an old fracture, deformity of the elbow, rheumatoid arthritis, osteoarthritis, a ganglion or lipoma, a subluxing ulnar nerve or a supracondylar spur. The patient experiences pain, paraesthesia, numbness and progressive weakness along the ulnar aspect of the hand.

### Diagnosis

An elbow x-ray with a cubital tunnel view and electrophysiological studies confirm the diagnosis of cubital tunnel syndrome. Clinical signs of cubital tunnel syndrome are:

- Claw hand deformity
- Weak flexor carpi ulnaris and flexor digitorum profundus to the ring finger and little finger
- Atrophy of intrinsic muscles, except for the thenar muscles and two radial lumbrical muscles
- Weak finger abduction
- Positive Froment sign
- Reduced pinprick sensation in the ulnar 1½ fingers and corresponding area of the palm and dorsum
- Positive Tinel sign at the level of the median epicondyle

### Treatment

Treatment of cubital tunnel syndrome frequently requires a release operation, commonly through simple neurolysis, anterior transposition

of the ulnar nerve, medial epicondylectomy of the distal humerus or endoscopic cubital tunnel release. As with carpal tunnel syndrome, the endoscopic approach is now being utilized for cubital tunnel syndrome and is associated with encouraging results.<sup>22,23</sup>

### Other sites

Tarsal tunnel syndrome results from compression of the posterior tibial nerve or plantar nerves in the tarsal tunnel. Ill-fitting footwear, posttraumatic fibrosis, tendon sheath cysts or tenosynovitis, ganglia, rheumatoid arthritis, hypothyroidism, acromegaly or a thickening of the flexor retinaculum can cause tarsal tunnel syndrome.

Nerve conduction tests are more difficult in the lower limb. Treatment of tarsal tunnel syndrome with no associated motor deficit or mild symptoms includes drugs, such as NSAIDs and anticonvulsants (eg, gabapentin). If symptoms persist, surgical intervention to release the nerve is required.

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## DRUGS FOR THE TREATMENT OF NEUROPATHIC PAIN

*In this issue, we continue our series on drugs for the treatment of neuropathic pain. Part 8 discusses an uncommon, but potentially serious, complication associated with the use of tramadol.*

### Part 8 – Tramadol and the serotonin syndrome

Tramadol, a weak  $\mu$ -opioid agonist and inhibitor of norepinephrine and serotonin uptake, is an effective treatment for neuropathic pain.<sup>1,2</sup> Tramadol is usually recommended for second-line use, but can be considered a first-line agent in certain clinical circumstances (such as when prompt pain relief is required during titration of a first-line medication, for acute neuropathic pain or exacerbations of severe pain, and neuropathic cancer pain).<sup>2</sup> However, its use in conjunction with other serotonergic medications (eg, selective serotonin reuptake inhibitors [SSRIs] and selective serotonin and norepinephrine reuptake inhibitors [SSNRIs]) may increase the risk of serotonin syndrome; caution must be exercised if prescribing combination therapy with these medications.<sup>2</sup> Furthermore, the increased prevalence of the CYP2D6\*10 allele – a genetic polymorphism of cytochrome P450 – in Asian populations has an impact on drugs metabolized by CYP2D6, such as tramadol.<sup>3,4</sup> As enzyme activity is reduced in those with this genotype, circulating drug levels may be increased, potentially increasing the risk of drug interactions.<sup>3</sup>

Serotonin syndrome results from excessive activation of serotonin, or 5-hydroxytryptamine (5-HT), receptors in the central nervous system (CNS), on the surface of platelets and on the vascular endothelium.<sup>5</sup>

This results in a cluster of symptoms, including altered cognition and behaviour (eg, confusion, elevated mood, coma), autonomic dysfunction (eg, fever, hyperhidrosis, tachycardia) and neuromuscular changes (eg, rigidity, myoclonus, tremors).<sup>5,6</sup> The major differential diagnoses include neuroleptic malignant syndrome, sepsis and malignant hyperthermia; as treatment of these conditions differs from serotonin syndrome, an accurate diagnosis is important.<sup>5</sup>

Management of serotonin syndrome requires discontinuation of the serotonergic agent(s).<sup>5,6</sup> Mild cases may not require hospitalization, but the majority of patients will require symptomatic and supportive care, with severe cases needing intensive care and mechanical ventilation. Cyproheptadine, a 5-HT antagonist that is administered orally or via nasogastric tube, rapidly resolves symptoms, particularly CNS effects.<sup>5</sup> While serotonin syndrome can be fatal, there is a good prognosis for most cases following discontinuation of medication.<sup>6</sup>

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## Q & A

Forward any questions on neuropathic pain to the MPNP at [mpnp@asia.cmpmedica.com](mailto:mpnp@asia.cmpmedica.com).

### Is acute neuropathic pain a distinct clinical entity?

Neuropathic pain is often considered a type of chronic pain!<sup>1</sup> However, while nociceptive pain is more common in the acute pain setting, neuropathic pain may also be present.<sup>2</sup> Acute neuropathic pain can arise from surgery, trauma and acute medical conditions, such as acute herpes zoster (shingles), transverse myelitis, stroke and intervertebral disc herniation. Acute neuropathic pain is often under-recognized, may be difficult to treat, and can progress to a chronic pain state.<sup>1</sup>

Most research and reviews focus on the management of chronic neuropathic pain. Hence, there are limited data available on acute neuropathic pain conditions. A guideline on acute pain from the Australian and New Zealand College of Anaesthetists states that based on experience in chronic neuropathic pain, it would be reasonable to use drugs such as tricyclic antidepressants, anticonvulsants and membrane stabilizers (eg, lignocaine) to manage acute neuropathic

pain.<sup>2</sup> Furthermore, a 2007 review by Dworkin et al recommends that tramadol or opioid analgesics may be used alone or in combination with other pain medications for acute neuropathic pain.<sup>3</sup> In a recent case series, patients hospitalized with burn injury and suffering from dysesthesia at either the injury or graft donor site were prescribed gabapentin in addition to standard analgesia.<sup>4</sup> Gabapentin use resulted in a rapid reduction in the severity of the neuropathic component of the pain.

Acute neuropathic pain can be considered a distinct clinical

entity and clinicians should be alert to recognize typical neuropathic pain symptoms, such as sharp or burning pain, altered sensation, numbness, pain out of proportion to the injury, and allodynia. While there are limited data available in acute neuropathic pain conditions, pharmacological agents proven effective in the management of chronic neuropathic pain may be of use.

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## CASE PRESENTATION

*In this issue, a case of chronic intractable headache is discussed.*

## Intractable migraine?

### History

The patient is a 30-year-old female clerk with a 10-year history of migraine headache. Her migraine attacks usually begin in the right parietal area and extend to involve the right side of her head, and are associated with nausea. She does not complain of aura or photophobia. The headache is pulsating, severe, and lasts for 2 to 3 days.

### Management and progress

Previous neurological evaluation and investigations including MRI have been unremarkable. Over the past 3 years, the headache has been difficult to control (4 to 5 attacks each month) and she has tried many different medications both for prophylaxis and treatment, including paracetamol, different nonsteroidal anti-inflammatory drugs (NSAIDs), codeine phosphate, carbamazepine, atenolol, propranolol, pizotifen, Cafergot, tricyclic antidepressants, topiramate, valproate, gabapentin, pregabalin and sumatriptan. Many of the medications were stopped either because they became ineffective or were poorly tolerated because of side effects. She has also tried transcutaneous electrical nerve stimulation (TENS), trigger point injections and relaxation therapy. The patient has consulted different GPs, neurologists and pain specialists over the years.

Her current medications are atenolol and pizotifen for prophylaxis, and paracetamol, diclofenac and sumatriptan for acute attacks. Over the last 5 months the patient has been taking the "attack" treatment medications 4 to 5 days a week in order to prevent a severe episode.

The headache occurs when she wakes up in the morning. She is also depressed and complains of insomnia.

### What is your working diagnosis?

The patient is likely to have medication overuse headache (MOH). Chronic headache affects 3% to 4% of the general population, with 30% to 50% of such headaches attributed to medication overuse. The diagnostic criteria for MOH from the International Classification of Headache Disorders (ICHD) include:

1. Headache present  $\geq 15$  days per month
2. Regular overuse of one or more acute/symptomatic treatment drugs for  $\geq 3$  months
3. Development or marked worsening of headache during medication overuse

### What is your management plan?

Management of MOH must include a thorough neurological evaluation to exclude recent neurological disease that may have resulted in the change in headache pattern. An important component of the withdrawal treatment strategy is to commence preventive treatment for primary headache before withdrawing the suspected overused medication. Behavioural therapy (eg, biofeedback, relaxation, cognitive behavioural therapy) is effective in primary headache and helpful in MOH.

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Source: MPNP members

## LITERATURE REVIEW

*Sumpton JE, Moulin DE. Fibromyalgia: Presentation and management with a focus on pharmacological treatment. Pain Res Manage 2008;13:477-483.*

This article provides an overview of the pathophysiology and clinical presentation of fibromyalgia, and current approaches to management. Fibromyalgia is characterized by widespread musculoskeletal pain and is often accompanied by a number of other symptoms, including extreme fatigue, sleep dysfunction and cognitive impairment. The prevalence of fibromyalgia in developed countries is 2% to 7%, with the condition being most common in women aged 30 to 55 years at symptom onset. The cause of fibromyalgia is currently unknown, and there are no objective laboratory tests or imaging studies readily available that can produce positive results for fibromyalgia.

Although a large number of symptoms are attributed to fibromyalgia, almost all patients will experience pain, fatigue and sleep disturbance. Chronic pain is the key symptom, with patients describing their pain as widespread and exhausting, tingling, deep aching, throbbing, shooting, stabbing, sharp or burning; allodynia and hyperalgesia are commonly experienced. Up to 90% of patients do not get any restorative sleep, and cognitive impairment may worsen during symptom flare-up.

A multidisciplinary approach to treatment is necessary – aiming to decrease pain, improve sleep and establish a regular exercise programme – with treatment tailored to the patient's symptoms. Non-pharmacological interventions, including exercise and cognitive behavioural therapy, should complement pharmacological management.

As many fibromyalgia patients are unusually sensitive to adverse effects of medication, treatment should start at a low dose and be titrated slowly to minimize potential side effects. Antidepressants, such as amitriptyline and duloxetine, gabapentin, pregabalin\*, tramadol, zopiclone and sodium oxybate have demonstrated effectiveness in treating fibromyalgia. The authors conclude that effective management of fibromyalgia is complex, but recent advances in understanding the pathophysiology of fibromyalgia and the emergence of novel agents provide new opportunities for treating this disabling condition.

\* Pregabalin is currently the only drug in Hong Kong indicated for fibromyalgia monotherapy

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