Management of Neuropathic Pain

2nd Edition
Malaysian Guidelines

Management of Neuropathic Pain

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Editorial and Expert Panel:

Professor Ramani Vijayan
MBBS, DA (Lon), FFARCS (I), FFARCS, FRCA, FANZCA, FAMM
Department of Anaesthesiology
University of Malaya
Kuala Lumpur

Professor Goh Khean Jin
MBBS (S’pore), MRCP (UK), FRCP (Glasg)
Division of Neurology, Department of Medicine
University of Malaya
Kuala Lumpur

Dr Mary Suma Cardosa
MBBS, MMed (Anaes), FANZCA, FFPMANZCA
Department of Anaesthesiology
Hospital Selayang
Selangor

Professor Khoo Ee Ming
MBBS (UK), MRCGP (UK), M.D. (Mal), FAMM, FAFP (Mal)
Department of Primary Care Medicine
University of Malaya
Kuala Lumpur

Editorial Support: UBM Medica Sdn Bhd
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1.0 Objectives

The objectives of these guidelines are to assist medical practitioners from all disciplines to:

- Identify and assess patients with neuropathic pain;
- Improve patient management and drug selection;
- Improve patient’s overall quality of life.

2.0 Definition and Prevalence

2.1 Definition

Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as “pain caused by a lesion or disease of the somatosensory nervous system.” Neuropathic pain is a clinical description (and not a diagnosis) which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria.1

2.2 Prevalence

The prevalence of neuropathic pain is estimated to range from 1.5% of the general population, to 50% of patients attending pain clinics; about one-third of patients with cancer experience neuropathic pain.2–4 In Malaysia, the prevalence of chronic persistent pain was found to be 7.1% among 33,733 adults surveyed nationwide,5 while 54.8% of attendees at a primary care clinic at University Malaya Medical Center were found to have chronic pain.6 Census data from the Hospital Selayang pain clinic reported that 38.8% of patients had neuropathic pain.7
3.0 Pathophysiology

Figure 1 shows the normal pain signalling pathway. A patient suffers from neuropathic pain when there is a disease or lesion anywhere along this pathway, either at the peripheral or central level. The pathophysiology of neuropathic pain is complex and heterogeneous with multiple mechanisms involved. \(^{6,8,9}\)

![Diagram of pain signalling pathway](image)

**Figure 1. Pain Signalling Pathway – Somatosensory Nervous System**

**Peripheral mechanisms:**

- **Proliferation of sodium channels**
  Occurs at the neuroma site and along the length of the nerve after nerve injury.\(^{10}\) This can result in foci of ectopic activity leading to spontaneous pain that one sees in patients with neuropathic pain.

- **Sprouting of sympathetic axons**
  Induced around the dorsal root ganglion where the neuropathic pain is sympathetically mediated.\(^{11}\)

**Central mechanisms:**

- **Loss of inhibitory control**
  Nerve injury reduces the inhibitory control over dorsal horn neurons through various mechanisms.\(^{12}\)

- **Central sensitization of the dorsal horn neurons**
  This can manifest as a heightened response to noxious stimuli (hyperalgesia) as well as pain associated with stimuli in the non-noxious range (allodynia).\(^{13}\)
4.0 Assessment and Diagnosis

4.1 Types of Pain

In assessing patients, it is important to recognize the differences between acute and chronic pain, nociceptive and neuropathic pain, and stimulus-independent and stimulus-evoked pain.

**Acute pain** results from tissue injury but resolves with healing (e.g. posttraumatic pain from fractures and tissue injury), whereas **chronic pain** persists after the initial injury heals. Acute pain is usually nociceptive, but chronic pain may be nociceptive, neuropathic or both.

**Nociceptive pain** is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. **Neuropathic pain**, on the other hand, results from a primary lesion or disease of the somatosensory nervous system.

Both **stimulus-independent** and **stimulus-evoked pain** (positive sensory symptoms; *Table 1*) may be present in neuropathic pain. Stimulus-independent pain may be intermittent (shooting, lancinating or electric shock-like) or continuous (superficial burning or deep pressure). Stimulus-evoked pain results from chemical, thermal or mechanical stimuli and is characterized by **alldynia** and **hyperalgesia**.

In addition, most patients may experience co-existing negative sensory symptoms (*Table 1*).

---

**Table 1. Positive and Negative Sensory Symptoms of Neuropathic Pain**

<table>
<thead>
<tr>
<th>Positive sensory symptoms</th>
<th>Negative sensory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Dysesthesias</td>
<td>● Loss or impairment of sensory quality</td>
</tr>
<tr>
<td>● Paresthesias</td>
<td>● Numbness and reduced sensation</td>
</tr>
<tr>
<td>● Stimulus-independent pain</td>
<td></td>
</tr>
<tr>
<td>− Intermittent lancinating pain</td>
<td></td>
</tr>
<tr>
<td>− Persistent burning sensation</td>
<td></td>
</tr>
<tr>
<td>● Stimulus-evoked pain</td>
<td></td>
</tr>
<tr>
<td>− Hyperalgesia</td>
<td></td>
</tr>
<tr>
<td>− Alldynia</td>
<td></td>
</tr>
<tr>
<td>Causes</td>
<td>Central</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td><strong>Trauma</strong></td>
<td>● Spinal cord injury</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td><strong>Peripheral nerve compression</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Infections</strong></td>
<td>● HIV myelopathy</td>
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<td></td>
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<td></td>
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<tr>
<td><strong>Metabolic diseases</strong></td>
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<tr>
<td><strong>Inflammation</strong></td>
<td>● Multiple sclerosis-related pain e.g. transverse myelitis</td>
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<td></td>
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<tr>
<td><strong>Neoplasms</strong></td>
<td>● Direct infiltration of spinal cord</td>
</tr>
<tr>
<td><strong>Drugs and toxins</strong></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Vascular</strong></td>
<td>● Central post-stroke pain</td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>
Conditions associated with neuropathic pain along with their underlying causes are listed in Table 2.\textsuperscript{19}

4.2 Patient Evaluation
Evaluation of a patient for neuropathic pain include\textsuperscript{4}:
- Screening
- Pain characteristics assessment
- Clinical history and physical examination, especially neurological assessment
- Ancillary diagnostic tests (if necessary)
- Assess the impact of pain on the patient’s function and quality of life.

4.2.1 Screening
These are questionnaires based on verbal description of pain with or without limited clinical examination and serve to identify possible neuropathic pain.\textsuperscript{20}

Examples include
- ID Pain (Table 3)\textsuperscript{21}
- \textit{Douleur neuropathique en 4 questions} (DN4) [Table 4]\textsuperscript{22}
- PainDETECT (available for download from www.northsomerset.nhs.uk/Services/Medicine_Management/Carehomes/PainDetect.pdf)\textsuperscript{23}
- Leeds assessment of neuropathic symptoms and signs (LANSS and S-LANSS)\textsuperscript{24,25}
- Neuropathic pain questionnaire (NPQ).\textsuperscript{26}
Table 3. ID Pain\textsuperscript{21}

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did the pain feel like pins and needles?</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Did the pain feel hot/burning?</td>
<td></td>
</tr>
<tr>
<td>3. Did the pain feel numb?</td>
<td></td>
</tr>
<tr>
<td>4. Did the pain feel like electrical shocks?</td>
<td></td>
</tr>
<tr>
<td>5. Is the pain made worse with the touch of clothing or bed sheets?</td>
<td></td>
</tr>
<tr>
<td>6. Is the pain limited to your joints?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Minimum total score = -1  Maximum total score = 5
-1  Neuropathic pain not likely
0 - 1  Neuropathic pain less likely
2 - 3  Consider neuropathic pain
4 - 5  Strongly consider neuropathic pain

Table 4. DN4 Neuropathic Pain Diagnostic Questionnaire\textsuperscript{22}

A “YES” score of ≥4 is diagnostic of neuropathic pain.

Interview of the patient

<table>
<thead>
<tr>
<th>Question 1</th>
<th>Does the pain have one or more of the following characteristics?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Burning</td>
<td>Yes  No</td>
</tr>
<tr>
<td>2. Painful cold</td>
<td>Yes  No</td>
</tr>
<tr>
<td>3. Electric shocks</td>
<td>Yes  No</td>
</tr>
</tbody>
</table>

Question 2

<table>
<thead>
<tr>
<th>Question 2</th>
<th>Is the pain associated with one or more of the following symptoms in the same area?</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Tingling</td>
<td>Yes  No</td>
</tr>
<tr>
<td>5. Pins and needles</td>
<td>Yes  No</td>
</tr>
<tr>
<td>6. Numbness</td>
<td>Yes  No</td>
</tr>
<tr>
<td>7. Itching</td>
<td>Yes  No</td>
</tr>
</tbody>
</table>

Examination of the patient

<table>
<thead>
<tr>
<th>Question 3</th>
<th>Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Hypoesthesia to touch</td>
<td>Yes  No</td>
</tr>
<tr>
<td>9. Hypoesthesia to prick</td>
<td>Yes  No</td>
</tr>
</tbody>
</table>

Question 4

<table>
<thead>
<tr>
<th>Question 4</th>
<th>In the painful area, can the pain be caused or increased by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Brushing</td>
<td>Yes  No</td>
</tr>
</tbody>
</table>

Patient Score: /10
4.2.2 Pain Assessment

Ask the patient direct questions about the characteristics of the pain to differentiate between neuropathic and nociceptive pain. The diagnosis of neuropathic pain relies almost entirely on a clinical diagnosis.

Patient is asked to indicate the number corresponding to her/his pain.

**Figure 2:** Pain Intensity Numerical Rating Scale (NRS).

Patient is asked to place a mark on the line corresponding to her/his pain intensity. Please note: The horizontal line should be exactly 100 mm long.

**Figure 3:** Visual Analogue Scale (VAS).

- **Pain Severity Scales**
  Pain severity can be assessed by using the Numerical Rating Scale (NRS) (Figure 2) and the Visual Analogue Scale (VAS) (Figure 3). These scales can also be used to gauge response to treatment.

- **Pain Characteristics**
  Ask the patient a series of direct questions to identify the following pain characteristics:

  **Quality**
  - Is the pain sharp, shooting, burning, throbbing or stabbing?
  - Are there abnormal, unpleasant sensations caused by normal stimuli (dysesthesia)?
  - Are there abnormal but non-painful sensations, e.g. tingling (paresthesia)?
  - Does the quality of the pain change over time?
  - Is the pain spontaneous or provoked?
  - Is the pain induced by non-noxious stimuli, e.g. light touch (allodynia)?
  - Is the pain out of proportion to the stimulus (hyperalgesia)?
Location
- Where is the pain?
- Where does it radiate to?

Duration
- How long have you had the pain (days, weeks, etc)?
- Is the pain episodic or continuous?
- If it is episodic, how often does it occur and how long does each episode last (frequency and duration of attacks)?

Aggravating and relieving factors
- What makes the pain worse?
- What makes the pain better?

4.2.3 Clinical History and Examination
Ask the patient about underlying causes for neuropathic pain e.g. diabetes mellitus, stroke, trauma etc (Table 2).19

Physical examination includes neurological evaluation of the motor, sensory and autonomic nervous systems. The aim is to localize the neurological lesion in the central or peripheral nervous systems. Figure 4 provides reference information.28

- Motor System Examination
  This would include inspecting for limb deformities, spontaneous movements e.g. spasms and fasciculations, muscle wasting, assessing the muscle tone and tenderness, tendon reflexes and muscle power.

- Somatosensory Assessment
  Determine the patient’s response to:
  Pain — prick with the sharp end of a wooden orange stick
  Touch — stroke with a cotton swab
  Position sense — test awareness of digit position with eyes closed
  Vibration — apply 128Hz tuning fork to a bony prominence
  Temperature — touch with a cold metal object (e.g. tuning fork)
Figure 4. Schematic Diagram Depicting Motor and Sensory Innervation and Root Values of Reflexes.\textsuperscript{28}

- **Autonomic Nervous System Evaluation\textsuperscript{16,29}**

  In patients with suspected complex regional pain syndrome (CRPS), look for changes in skin temperature, colour, if sweating is present, trophic changes in hair, nails or skin, and oedema in the affected limb.
4.2.4 Ancillary Laboratory Diagnostic Tests\textsuperscript{16,29}

Laboratory tests are generally not required to confirm the diagnosis of neuropathic pain, although ancillary diagnostic tests (e.g. motor, sensory, autonomic) may help define the pain syndrome in specific patients (Table 5). Some patients may have normal diagnostic test results. Overall, positive test results suggest abnormalities in the nervous system but negative test results do not rule out the diagnosis.

**Table 5. Ancillary Diagnostic Tests for the Patient with Neuropathic Pain\textsuperscript{16,29}**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Neuropathic pain condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electromyography and nerve conduction</td>
<td>Assesses the peripheral nervous system including the motor and sensory nerves. Nerve conduction studies primarily measure large myelinated fibres.</td>
</tr>
<tr>
<td>studies</td>
<td></td>
</tr>
<tr>
<td>Quantitative sensory testing</td>
<td>Assesses temperature and vibration thresholds. The former provides an assessment of small unmyelinated/thinly myelinated nerve fibres.</td>
</tr>
<tr>
<td>Skin punch biopsy</td>
<td>Assesses intra-epidermal nerve fibre density, an assessment of the small unmyelinated/thinly myelinated nerve fibres</td>
</tr>
<tr>
<td>Autonomic function tests</td>
<td>Electrocardiogram (to determine heart rate variability). Sudomotor axon reflex test (sympathetic skin response test) records response of sweat glands to stimulation.</td>
</tr>
<tr>
<td>Somatosensory and motor-evoked potentials</td>
<td>Assesses sensory and motor pathways.</td>
</tr>
<tr>
<td>Magnetic resonance imaging, computed</td>
<td>Image both the central and peripheral nervous systems.</td>
</tr>
<tr>
<td>tomography scanning</td>
<td></td>
</tr>
</tbody>
</table>

4.2.5 Assessment of the Impact of Pain on the Patient’s Function and Quality of Life

Neuropathic pain impairs physical and psychological functioning. Psychological factors such as anxiety and depression as well as sleep disturbances may exacerbate pain and increase its negative impact.\textsuperscript{30,31} Assessments for functional impairment, sleep disturbances, and anxiety or depression are essential to effective management of the neuropathic pain patient.\textsuperscript{29}

Examples of questions to ask include:

- What can you not do because of the pain?
- How long can you sit/stand/walk before the pain gets worse?
- Does the pain affect your sleep?
- Do you still enjoy the things you used to enjoy?
- Do you feel tensed, frightened and restless?
5.0 Holistic, Multidisciplinary Management

The principal goals of treating neuropathic pain (Figure 5) are to:
- Reduce or eliminate pain
- Improve physical functioning
- Reduce psychological distress
- Improve the overall quality of life

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Treat underlying condition/symptomatic treatment</td>
</tr>
<tr>
<td></td>
<td>Reduce pain</td>
</tr>
<tr>
<td></td>
<td>Improve physical functioning</td>
</tr>
<tr>
<td></td>
<td>Reduce psychological distress</td>
</tr>
<tr>
<td></td>
<td>Improve overall quality of life</td>
</tr>
<tr>
<td>Step 3</td>
<td>Reassess</td>
</tr>
<tr>
<td></td>
<td>Continue/add/switch treatment</td>
</tr>
</tbody>
</table>

Stepwise Pharmacological Management of Neuropathic Pain (NP)

The best outcomes are achieved when a multidisciplinary team is used, which should include psychologists, physical and occupational therapists and social workers, in addition to doctors from different disciplines.

**Step 1**
- Assess pain and establish the diagnosis of NP; if uncertain about the diagnosis, refer to a pain specialist or neurologist.
- Establish and treat the cause of NP; if uncertain about availability of treatments for cause of NP, refer to appropriate specialist.
- Identify relevant comorbidities that may be affected by NP treatment and manage accordingly.
- Explain the diagnosis and treatment plan to the patient and establish realistic expectations.
Step 2  
- Initiate symptom treatment with one or more of the following:
  - A secondary-amine tricyclic antidepressant [TCA] (amitriptyline, nortriptyline, desipramine) or a serotonin–norepinephrine reuptake inhibitor [SNRI] (duloxetine, venlafaxine)
  - A calcium channel α2-δ ligand, either gabapentin or pregabalin
  - For patients with localized peripheral NP, topical lignocaine used alone or in combination with one of the other first-line therapies
  - For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies.

- Evaluate patients for nonpharmacological treatments and initiate if appropriate.

Step 3  
- Reassess pain and health-related quality of life frequently.
- If substantial pain relief (eg, average pain reduced to ≤3/10) and tolerable adverse effects, continue treatment.
- If partial pain relief (eg, average pain remains ≥4/10) after an adequate trial, add one of the other four first-line medications.
- If no or inadequate pain relief (eg, <30% reduction) at target dosage after an adequate trial, switch to an alternative first-line medication.

Step 4  
- If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a neurologist, pain specialist or multidisciplinary pain center.

A wide variety of treatment modalities are available (Figure 6) and are often used in combination.33-35
5.1 **Pharmacotherapy**

Pharmacotherapy is the most common first-line treatment option for neuropathic pain. The other treatment strategies described below should be used along with drug therapy in a multi-disciplinary treatment program. In some cases, a nonpharmacological treatment approach may be considered as a first-line treatment option (see sections 5.2 to 5.5).

Four drug classes have consistently demonstrated efficacy against various types of neuropathic pain in randomized, controlled clinical trials (*Table 6 and 7*). These are:

1. Anticonvulsants
2. Antidepressants
3. Opioids
4. Local anaesthetics.

- NSAIDs have not been found to be effective and should not be used for the treatment of neuropathic pain.
- Tricyclic antidepressants (TCAs) should be used with caution in the elderly and in patients with cardiac disease.\(^8\)
## Table 6: Drug Options and Dosages

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended for</th>
<th>Starting dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>PHN (1st line) DPN (1st line) TN (2nd line)</td>
<td>150 mg/day as 75 mg bid</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PHN (1st line) DPN (1st line) TN (2nd line)</td>
<td>Day 1, 300 mg at bedtime; Day 2, 300 mg bid; Day 3, 300 mg tid</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>TN (1st line) PHN (2nd line)</td>
<td>100 mg bid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>TN (2nd line)</td>
<td>25 mg/day for 2 weeks</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>PHN (1st line) DPN (1st line) TN (2nd line)</td>
<td>10–25 mg daily at bedtime</td>
</tr>
<tr>
<td>Nortriptyline, desipramine</td>
<td>PHN (1st line) DPN (1st line) TN (2nd line)</td>
<td>10–25 mg at bedtime</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>DPN (1st line)</td>
<td>30 mg/day</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone, methadone</td>
<td>Conditions with mixed nociceptive/neuropathic pain</td>
<td>10–15 mg morphine q4h or as needed (equianalgesic dosages should be used for other opioid analgesics)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>PHN (2nd line) DPN (2nd line)</td>
<td>50 mg qd or bid</td>
</tr>
<tr>
<td><strong>Local anaesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV lignocaine</td>
<td>Used by pain specialists only</td>
<td>5 mg/kg over 30–60 min</td>
</tr>
<tr>
<td><strong>Topical agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>PHN (1st line)</td>
<td>0.075% applied tds-qds</td>
</tr>
<tr>
<td>5% lignocaine patch</td>
<td>PHN (1st line)</td>
<td>Apply patch for a maximum of 12 h per day</td>
</tr>
<tr>
<td>EMLA*</td>
<td>PHN (1st line)</td>
<td>tid, under occlusive dressing if possible</td>
</tr>
<tr>
<td>Drug</td>
<td>Recommended for</td>
<td>Starting dosage</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------</td>
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</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>PHN (1st line), DPN (1st line), TN (2nd line)</td>
<td>150 mg/day as 75 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PHN (1st line), DPN (1st line), TN (2nd line)</td>
<td>Day 1, 300 mg at bedtime; Day 2, 300 mg bid; Day 3, 300 mg tid</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>TN (1st line), PHN (2nd line)</td>
<td>100 mg bid</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>TN (2nd line)</td>
<td>25 mg/day for 2 weeks</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>PHN (1st line), DPN (1st line), TN (2nd line)</td>
<td>10–25 mg daily at bedtime</td>
</tr>
<tr>
<td>Nortriptyline, desipramine</td>
<td>PHN (1st line), DPN (1st line), TN (2nd line)</td>
<td>10–25 mg at bedtime</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>DPN (1st line)</td>
<td>30 mg daily</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone, methadone</td>
<td>Conditions with mixed nociceptive/neuropathic pain</td>
<td>10–15 mg morphine q4h or as needed (equianalgesic dosages should be used for other opioid analgesics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local anaesthetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV lignocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>PHN (1st line)</td>
<td>0.075% applied tds-qds</td>
</tr>
<tr>
<td>5% lignocaine patch</td>
<td>PHN (1st line)</td>
<td>Apply patch for a maximum of 12 h per day</td>
</tr>
<tr>
<td>EMLA®</td>
<td>PHN (1st line)</td>
<td>tid, under occlusive dressing if possible</td>
</tr>
</tbody>
</table>
Table 7: Side Effect Profiles and Management Tips

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Dizziness, somnolence, weight gain, blurred vision, dry mouth, constipation, peripheral oedema, euphoric mood, disturbed attention, increased appetite, unsteady gait</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Sedation, dizziness, gait abnormalities, nausea &amp; vomiting.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Serious AEs: hyponatraemia, agranulocytosis, aplastic anaemia, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Skin rash (potentially severe), irritability, headache, drowsiness, insomnia, dizziness, tremor, nystagmus, ataxia, diplopia, blurred vision, nausea, vomiting, diarrhoea, constipation, tiredness, arthralgia, painful menses, back pain</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Dry mouth, sweating, sedation, disturbed vision, cardiotoxicity, palpitations, postural hypotension, urinary retention, constipation, drowsiness</td>
</tr>
<tr>
<td>Nortriptyline, desipramine</td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Nausea/vomiting, dry mouth, constipation, GI distress, decreased appetite, insomnia, dizziness, somnolence, blurred vision, increased sweating, fatigue</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone, methadone</td>
<td>Constipation, sedation, nausea, dizziness, vomiting, respiratory depression</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Dizziness, dry mouth, nausea, constipation, somnolence; risk of seizures/epilepsy; risk of serotonergic syndrome if combined with SSRIs</td>
</tr>
<tr>
<td><strong>Local anaesthetics</strong></td>
<td></td>
</tr>
<tr>
<td>IV lignocaine</td>
<td>Nausea, hypotension, bradycardia, hypertension, paraesthesia, dizziness, vomiting</td>
</tr>
<tr>
<td><strong>Topical agents</strong></td>
<td></td>
</tr>
<tr>
<td>5% lignocaine patch</td>
<td>Mild localized skin reactions around application site</td>
</tr>
<tr>
<td>EMLA®</td>
<td>Pale skin, redness or swelling at the application site, burning, change in hot or cold sensation</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Local, transient pain and erythema</td>
</tr>
<tr>
<td>Drug</td>
<td>Potential adverse effects</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Dizziness, somnolence, weight gain, blurred vision, dry mouth, constipation, peripheral oedema, euphoric mood, disturbed attention, increased appetite, unsteady gait</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Sedation, dizziness, gait abnormalities, nausea &amp; vomiting.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Skin rash (potentially severe), irritability, headache, drowsiness, insomnia, dizziness, tremor, nystagmus, ataxia, diplopia, blurred vision, nausea, vomiting, diarrhoea, constipation, tiredness, arthralgia, painful menses, back pain</td>
</tr>
<tr>
<td>Antidepressants</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Dry mouth, sweating, sedation, disturbed vision, cardiotoxicity, palpitations, postural hypotension, urinary retention, constipation, drowsiness</td>
</tr>
<tr>
<td>Nortriptyline, desipramine</td>
<td>Nortriptyline causes less sedation and anticholinergic effects than amitriptyline; CI in patients with glaucoma and those taking MAO inhibitors.</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Nausea/vomiting, dry mouth, constipation, GI distress, decreased appetite, insomnia, dizziness, somnolence, blurred vision, increased sweating, fatigue</td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Dizziness, dry mouth, nausea, constipation, somnolence; risk of seizures/epilepsy; risk of serotonergic syndrome if combined with SSRIs</td>
</tr>
<tr>
<td>Local anaesthetics</td>
<td></td>
</tr>
<tr>
<td>IV lignocaine</td>
<td>Nausea, hypotension, bradycardia, hypertension, paraesthesia, dizziness, vomiting</td>
</tr>
</tbody>
</table>
5.2 Physical and Occupational Therapy

5.2.1 Physical Therapy
- Recommend exercises for muscle strengthening, flexibility and endurance.\textsuperscript{29,36}
- Transcutaneous Electrical Nerve Stimulation (TENS) is a well-tolerated and useful adjunctive treatment that is relatively free of adverse effects. It has been used in PHN and phantom limb pain.\textsuperscript{2,37}

5.2.2 Occupational Therapy
Focus on rehabilitation and improving function.

5.3 Psychological Therapy
This may be done as individual or group therapy. It includes patient education, cognitive behavioural therapy, relaxation and teaching of pain management strategies like distraction, planning and pacing.

5.4 Intervenational Therapy

5.4.1 Surgical Procedures
Decompressive laminectomy (e.g. spinal stenosis), microvascular decompression (e.g. TGN), spinal cord stimulation (e.g. CRPS).

5.4.2 Sympathetic Block
Stellate ganglion block, lumbar sympathetic block for CRPS.

5.4.3 Epidural Steroid Injections
May be used for symptomatic relief of lumbar or cervical radiculopathy.

5.4.4 Intrathecal Therapy
May be considered in severe and difficult to control pain from post-spinal cord injury pain and CRPS.

5.4.5 Spinal Cord Stimulation
May be considered in severe pain in CRPS which is not responding to sympathetic blocks or pharmacological therapy.
5.5 **Complementary Therapies**
In Malaysia, as in other countries, complementary or alternative therapies, such as massage, hypnosis, acupuncture and herbal medicine are also used to treat neuropathic pain. However, acupuncture or any other complementary therapies have not been shown to provide long-term benefit in neuropathic pain in randomized, controlled trials.²

### 6.0 Algorithms for Management of Specific conditions
Management should follow the principles outlined previously on page 11.

#### 6.1 Postherpetic neuralgia³⁸
Postherpetic neuralgia is a neuropathic pain syndrome characterized by severe pain (burning, throbbing, sharp, or shooting) and paraesthesia in dermatome areas involved in the original infection.

1. **1st line**
   - Pregabalin, gabapentin
   - Amitriptyline
   - EMLA cream/ Capsaicin/ 5% lignocaine patch

2. **2nd line**
   - Tramadol

Refer to pain clinic if refractory to pharmacotherapy

**Other drug options:**
- IV lignocaine
- Opioids
- Ketamine

**Physical:**
- TENS
- Acupuncture
- Physiotherapy

**Psychological:**
- Pain management programmes
- Cognitive behaviour therapy
- Relaxation therapy
6.2 Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) refers to a group of progressive, degenerative conditions involving autonomic, motor, or sensory peripheral nerves, thought to result from poor glycaemic control and long-term hyperglycaemia.

1st line
- Pregabalin, gabapentin
- Amitriptyline
- Duloxetine, Venlafaxine

2nd line
- Tramadol

Refer to pain clinic if refractory to pharmacotherapy

Other drug options:
- IV lignocaine
- Opioids
- Ketamine

Physical:
- TENS
- Acupuncture
- Physiotherapy

Psychological:
- Pain management programmes
- Cognitive behaviour therapy
- Relaxation therapy
6.3 **Trigeminal neuralgia**\(^{40,41}\)

Also called tic douloureux, trigeminal neuralgia (TGN) usually occurs in elderly individuals, is generally unilateral, is more common on the right than left side, and is twice as common in women than in men. Typical features consist of paroxysms of electric shock-like pain that last from a few seconds up to 2 minutes. Attacks and spasms of the facial muscles can be caused by common daily activities such as eating, face washing, shaving, and teeth cleaning. Need to exclude symptomatic TGN by MR imaging and treat underlying cause e.g. tumour, multiple sclerosis.

---

**1st line**
Carbamazepine
Oxcarbazepine

**2nd line**
Baclofen, Lamotrigine
Gabapentin, Pregabalin, Amitriptyline, Duloxetine

Refer to pain clinic if refractory to pharmacotherapy

**Interventional options**

- Microvascular decompression
- Percutaneous procedures
- Radiosurgery

**PRFR = Percutaneous radiofrequency rhizotomy**
**BCR = Balloon compression rhizotomy**
**PRGR = Percutaneous retro-Gasserian glycerol rhizotomy**
6.4 Radiculopathies

<table>
<thead>
<tr>
<th></th>
<th>Cervical radiculopathy</th>
<th>Lumbar radiculopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pharmacological</td>
<td>Cervical collar</td>
<td>Percutaneous electrical nerve stimulation / TENS</td>
</tr>
<tr>
<td></td>
<td>Physiotherapy</td>
<td>Physiotherapy</td>
</tr>
<tr>
<td></td>
<td>Neck care</td>
<td>Back care</td>
</tr>
<tr>
<td></td>
<td>Postural training</td>
<td></td>
</tr>
<tr>
<td>Pharmacological</td>
<td>*NSAIDs[^42,43] Gabapentin/Pregabalin</td>
<td>*NSAIDs[^42,43] Gabapentin/Pregabalin Epidural steroid</td>
</tr>
<tr>
<td>Surgery</td>
<td>Decompression/discectomy</td>
<td>Decompression/discectomy</td>
</tr>
</tbody>
</table>

**Carpal tunnel syndrome**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Same as for mild above and/or Local steroid injection[^44]</td>
</tr>
<tr>
<td>Severe</td>
<td>Decompression</td>
</tr>
</tbody>
</table>

[^42,43]: Use of NSAIDs is only appropriate when there is mixed nociceptive/neuropathic pain, and only for short periods of time (not for prolonged use).
6.5 **Central pain**\(^{45}\)

The most frequent central neuropathic pain states are caused by stroke, spinal cord injury or multiple sclerosis.

**Central post-stroke pain (CPSP)** — previously known as ‘thalamic syndrome’. This condition is characterized by allodynia, a burning or freezing pain, and a partial or complete lack of sensation to thermal and/or sharp stimuli. Patients with CPSP, who are generally younger stroke patients, may have concurrent nociceptive pain such as frozen shoulder. CPSP may be one-sided and may involve only small areas. The intensity of such pain may vary within the affected area, and symptoms may be intensified by stress or reduced by relaxation.

---

**Diagram:**

1. **Treat underlying cause**
2. **1st line**
   - Pregabalin, gabapentin
   - Amitriptyline
   - Carbamazepine
   (for paroxysmal tonic spasms in multiple sclerosis)
3. **2nd line**
   - Opioids
4. **Refer to pain clinic if refractory to pharmacotherapy**

**Other drug options:**
- IV lignocaine
- Opioids
- Ketamine

**Physical:**
- TENS
- Acupuncture
- Physiotherapy

**Psychological:**
- Pain management programmes
- Cognitive behaviour therapy
- Relaxation therapy

**Interventional:**
- Intrathecal tx for spinal cord injuries
6.6 Complex regional pain syndrome\textsuperscript{46}

Complex regional pain syndrome (CRPS) type I (reflex sympathetic dystrophy syndrome) — a chronic disorder characterized by severe burning pain in an extremity accompanied by sudomotor, vasomotor changes in the skin and trophic changes in bone and nails without an associated specific nerve injury. This condition is most often precipitated by trauma to soft tissue. The skin over the affected region may be erythematous and demonstrates hypersensitivity to tactile stimuli.

Complex regional pain syndrome (CRPS) type II (causalgia) — a neuropathic pain condition caused by nerve injury in which pain may be associated with autonomic alterations (e.g. sweating or vasomotor dysfunction) and/or trophic changes (e.g. hair loss). Characteristic features are burning pain, allodynia, and hyperpathia in the affected limb. Pain is usually experienced within the distribution of the damaged nerve, but often involves adjacent dermatomes.
Early referral to multidisciplinary pain centre

Psychological and cognitive behavioural management
- Pain management programmes
- Cognitive behaviour therapy
- Relaxation therapy

Pharmacological pain management
- 1st line
  - Antidepressant
  - Anticonvulsant or both

  2nd line
  - Opioids

  3rd line
  - Lignocaine
  - Ketamine

Occupational therapy and physiotherapy
- Active mobilization
- TENS

Interventional pain management
- Sympathetic blockade
- Spinal cord stimulation
- Peripheral nerve stimulation
- Intrathecal therapy
6.7 Persistent post-surgical pain

Persistent post-surgical pain is a common but under-recognized problem. It is chronic pain that persists after surgery beyond the normal period of healing. The incidence varies between 10 – 50%, with 2-10% having disabling pain.47-49

Inguinal hernia repair, breast surgery, lower limb amputation, total knee replacement, thoracotomy, coronary artery bypass graft and caesarean section are recognized procedures that can lead to post-surgical pain.49 Risk factors that predispose to its development include the severity of pre- and post-operative pain and intraoperative nerve injury.48,50

Post-surgical pain is the consequence of either ongoing inflammation or, more commonly, a manifestation of neuropathic pain resulting from surgical injury to peripheral nerves.

Chronic pain, once established, is difficult to treat. There is evidence that the incidence of post-surgical pain can be reduced by changing surgical techniques to include minimally invasive surgery.48 Aggressive control of acute post-operative pain using multimodal analgesic techniques have also been found to reduce post-surgical pain. They include the concomitant use of opioids, NSAIDs, regional analgesia and gabapentinoids.51,52
Prevention by good post-operative analgesia with multimodal techniques

1st line
- Pregabalin, gabapentin
- Amitriptyline
- Duloxetine

2nd line
- Tramadol

Refer to pain clinic if refractory to pharmacotherapy

Other drug options:
- IV lignocaine
- Opioids
- Ketamine

Physical:
- TENS
- Acupuncture
- Physiotherapy

Psychological:
- Pain management programmes
- Cognitive behaviour therapy
- Relaxation therapy
References


43. O’Connor D, Marshall SC, Massy-Westropp N. Non-surgical treatment (other than steroid injection) for carpal tunnel syndrome. Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD000219. DOI: 10.1002/14651858.CD000219


47. Macrae WA. Chronic postsurgical pain-10 years on. Br J Anaesth 2008;101:77-86


29
Glossary

**Acute pain** — results from tissue injury but resolves with healing (e.g. posttraumatic pain like fractures and tissue injuries). Acute pain is usually nociceptive. See chronic pain.

**After sensation** — the abnormal persistence of a sensory perception provoked by a stimulus even though the stimulus has stopped.

**Alloodynia** — a painful response to a stimulus that normally does not provoke pain. See hyperalgesia and stimulus-evoked pain.

**Apraxia** — loss of the ability to carry out familiar, purposeful movements in the absence of paralysis or other motor or sensory impairment.

**Chronic pain** — persists after the initial injury heals. Chronic pain may be nociceptive (e.g. osteoarthritis), neuropathic, or both. See acute pain.

**Dysoesthesia** — abnormal, unpleasant, but not necessarily painful, sensation caused by normal stimuli. May be spontaneous or provoked by external stimuli. See paraesthesia.

**Hyperalgesia** — a magnified response to painful stimuli. See allodynia and stimulus-evoked pain.

**Hyperpathia** — a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. See complex regional pain syndrome type II.

**McGill Pain Questionnaire (MPQ)** — a widely used means of determining the quality of spontaneous neuropathic pain. It includes a list of words that serve as affective, evaluative, and sensory pain descriptors. It is used to indicate pain location and intensity and to quantify changes in pain quality and pattern (i.e. intermittent or continuous) over time.

**Neuropathic Pain Scale (NPS)** — an accurate, validated tool for the assessment of neuropathic pain that is based on a series of numerical rating scales. See Appendix.

**Nociceptive pain** — a normal physiological response resulting from exposure of nociceptors to noxious stimuli. It has a protective function in acute conditions, since it indicates the likelihood of tissue damage and alerts an individual to the need to prevent additional injury.

**Numerical rating scale (NRS)** — an 11-point pain-intensity scale. The NRS can be used to identify clinically important reduction in an individual’s pain. See Figure 1.

**Paraesthesia** — abnormal but non-painful sensations, which can be spontaneous or evoked, e.g. tingling. See dysoesthesia.

**Stimulus-evoked pain** — results from chemical, thermal, or mechanical injury and is characterized by allodynia and hyperalgesia. Also called stimulus-dependent pain. See stimulus-independent pain.

**Stimulus-independent pain** — or spontaneous pain may be intermittent or continuous. Spontaneous continuous pain, often felt as superficial burning or deep pressure, is present all or almost all the time, although it can vary in intensity. Spontaneous intermittent pain is episodic and typically of relatively short duration. Often paroxysmal, it is described by patients as shooting, lancinating, or like an electric shock.

**Trophic changes** — tissue alterations due to interruption of nerve or blood supply; may include changes in hair growth and texture of skin.

**Vasomotor changes** — alteration in regulation of dilation or constriction of blood vessels.

**Visual analogue scale (VAS)** — this pain scale evaluates pain intensity and pain relief with treatment. Lines on the VAS are exactly 100 mm long, and patients are asked to mark on the line their degree of pain (see Figure 3). The scale score is the distance in millimetres from the left end of the scale to a patient’s mark.
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Tel: 03-5666 6600  Fax: 03-5666 6600  http://www.pfizer.com.my

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