



## CLINICAL PRACTICE GUIDELINES IN NEUROPATHIC PAIN MANAGEMENT

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### Abstract

Pain is a multifaceted experience involving physiological, cognitive and emotional aspects. Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms. The objective of this article was to merge current treatment guidelines and best practice recommendations for management of neuropathic pain into a comprehensive algorithm for physicians. The algorithm involves assessment, multidisciplinary conservative care, pharmacological management, interventional therapies, neurostimulation, low-dose opioid treatment, and targeted drug delivery therapy.

**Keywords:** Pain, neuropathic pain, pharmacological management

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## 1. Introduction

Pain is a multifaceted experience involving physiological, cognitive and emotional aspects. According to IASP (International Association of Pain), neuropathic pain is defined as “pain arising as a direct consequence of any lesion or disease affecting the somatosensory system,” which induces chronic pain that may originate from a peripheral nerve, a ganglion, the dorsal root, or from the central nervous system. Neuropathic pain is very challenging to manage because of the heterogeneity of its aetiologies, symptoms and underlying mechanisms.(1) This condition is the result of a series of different

pathological mechanisms and it is usually described based on the anatomic localization or etiology.(2) The most common clinical entities involved are metabolic disorders (e.g. peripheral diabetic neuropathy (PDN), burning mouth syndrome), neuropathies associated with viral infections (e.g. post-herpetic neuralgia, HIV, leprosy), autoimmune disorders affecting the central nervous system (e.g. multiple sclerosis and Guillain–Barre syndrome), chemotherapy-induced peripheral neuropathies, damage to the nervous system of traumatic origin (e.g. spinal cord injury (SCI) and amputation), inflammatory disorders, hereditary neuropathies, and channelopathies.(3)

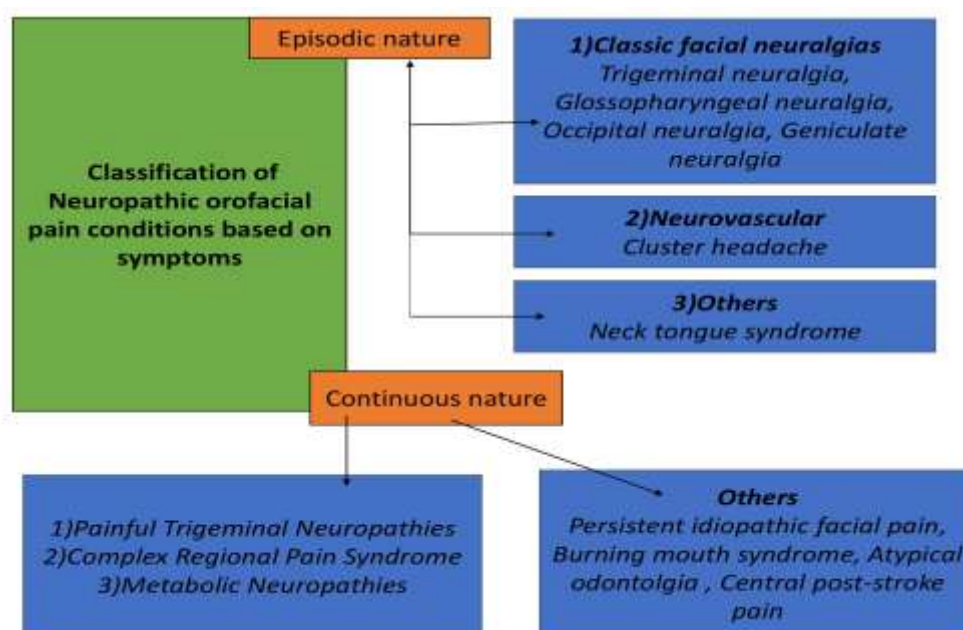


Figure 1:- Represents classification of neuropathic pain

Among the signs and the symptoms related to the presence of neuropathic pain are allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (an increase in the perception of pain generated by a stimulus that causes pain), and paresthesia (a condition that determines the perception of anomalous sensations comparable to needle bites, tingling, itching, reduced, or even loss of sensitivity).(4) In patients suffering from neuropathic pain, the perceived pain is usually spontaneous, manifesting itself without needing a stimulus. This pathological condition affects the quality of life of patients as well as compromising their psychological state.(5) Our research and knowledge have resulted in high-quality publications from Neuropathic pain management focuses on treating symptoms and only in some pathological conditions, the etiological causes can be treated to relieve pain.(4) Our team has extensive knowledge and research experience that has translate into high quality publications (6–15)

## 2. Methods

All guidelines focused on the assessment of neuropathic pain highlight the use of a comprehensive history and clinical examination. The etiology of neuropathic pain can be broadly classified into two basic categories: peripheral and central etiologies.(4,16) The clinical presentation of neuropathic pain commonly includes descriptions of burning, pins and needles (paresthesia), tingling, numbness, electric shocks/shooting, crawling (formication), itching, and intolerance to temperature.(17)

Pain assessment:

The use of validated questionnaires is a simple means of identifying the presence of neuropathic pain and quantifying its impact on the patient.(5)

Commonly used Pain assessment scales and Questionnaires:-

- ❖ Visual Analog scale (VAS)

- ❖ Faces Pain Rating Scale
- ❖ Numerical Rating scale (NRS)
- ❖ Profile of Mood states
- ❖ McGill Pain Questionnaire (MPQ)
- ❖ Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
- ❖ Douleur Neuropathique en 4 Questions (DN4)
- ❖ Neuropathic Pain Scale (NPS)
- ❖ Brief Pain Inventory (BPI)
- ❖ Quantitative sensory testing (QST)

These questionnaires can be completed at an initial consultation to detect if such an impact is present, and thereafter, a more formal assessment can be done by the psychologist or allied health professional team.(18) A thorough examination is crucial to determine the actual presence of neuropathic pain. The overall purpose of the examination should be to rule out the relevant neural pathways related to the patient's history.(18,19) If a neural lesion is suspected, an electroneuromyography (EMG) and nerve stimulation study (NCS) can be performed to better define the region/area of defect and confirm the diagnosis.(20) If the examination fails to reveal a clear diagnosis but neuropathic pain is still suspected, referral to neurologist is needed. Lastly, magnetic resonance imaging (MRI) or skin biopsy can be used to identify central lesions or small fiber neuropathy, respectively.(21)

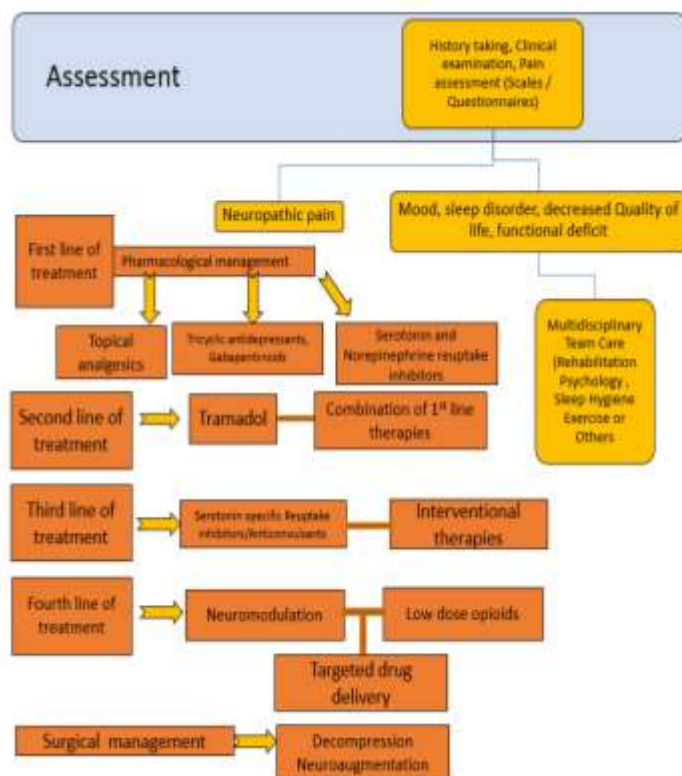
### Management:-

#### Firstline Treatment

Pain is an unpleasant sensation that can affect the emotional and social behaviour of the patient. Although all management strategies should strive for improvements in pain reduction; the functional, sleep, mood, social, and spiritual consequences of pain must also be treated.(22) These factors affect patient's quality of life. First line of treatment includes pharmacological management such as topical analgesics, tricyclic antidepressants, gabapentinoids, serotonin & norepinephrine reuptake inhibitors, non-pharmacological management and non-interventional therapies such as psychology, physiotherapy, exercise, and massage should be initiated early to address issues such as depression, anxiety, pain, sleep disturbance, etc. If tried alone without pharmacological or interventional strategies, it is recommended that these are limited to a duration of six to eight weeks. If adequate pain relief is not achieved within this time, first line medications should be initiated.(23)

#### *Pharmacological Management*

Medications form the basis of first- and second-line therapy for neuropathic pain. Tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, tramadol, lidocaine, and capsaicin are the most effective options. Medication should be recommended for 3-8 weeks and then review to assess the effectiveness of the treatment.(16)



**Flowchart:-** Algorithm for the management of neuropathic pain

**Tricyclic antidepressants:-**

TCAs as a firstline therapy is supported across multiple guidelines.They act by blocking the reuptake of serotonin and norepinephrine in presynaptic terminals, which leads to increased concentration of these neurotransmitters in the synaptic cleft. TCAs should be used with caution in elderly patients to avoid adverse effects such as cardiac arrhythmias, orthostasis, urinary retention and dry mouth.(5)

**Serotonin and Norepinephrine Reuptake Inhibitors.:-**

Most commonly included SNRIs are duloxetine and venlafaxine. They facilitate descending inhibition by blocking serotonin and noradrenaline reuptake. Beyond neuropathic pain, SNRIs have been shown to be effective in osteoarthritis, chronic low back pain, fibromyalgia, and depression.If pain reduction is not achieved, dosage adjustment or change to other first line medications, or combination therapy is required.(22)

**Gabapentinoids.:-** Gabapentinoids include gabapentin and pregabalin. They are anticonvulsant

medications that act by blocking presynaptic alpha-2-delta calcium channels in the dorsal horn, inhibiting neurotransmitter release.The most common adverse effects include fatigue, dizziness, and lower extremity edema.(22).

**Topical:-** As an alternative to TCAs, SNRIs, and gabapentinoids, topical medications such as Lidocaine, Capsaicin, and Transdermal Substances are supported by multiple guidelines.

- 1) *Lidocaine* - Topical lidocaine works by decreasing ectopic firing of peripheral nerves.It is difficult to apply topical lidocaine to the distal extremity neuropathies.
- 2) *Capsaicin* - Capsaicin has its action through binding to the TRPV1 receptor located on the A-delta and C-nerve fibers. This results in release of substance P and depolarization of the nerve. Long-term exposure causes overstimulation, depletion of substance P, desensitization of the nerve, and reversible nerve degeneration (1).
- 3) *Transdermal Substances* - transdermal approach is an alternative approach for some patients.Commonly used are topical applications of ketamine, amitriptyline, diclofenac and clonidine.(1)

S. No	Drug class	Drug	Recommendation
1)	Topical analgesics	5% lidocaine	Apply 3-4 times on pain site
		8% capsaicin	Apply for 60 minutes under supervision of a physician
2)	Tricyclic antidepressants	Nortriptyline	10–25 mg (Max - daily dose ¼ 150 mg)
		Amitriptyline.	10–25 mg (Max - daily dose ¼ 150 mg)
3)	Anticonvulsants	Gabapentin	300 mg (Max- 900-2400mg)
		Pregabalin	150mg (Max-300-600 mg)
		Carbamazepine	100-200 mg (Max. of 1200 mg)
		Oxycarbazepine	300mg (Max- 1200-2400mg)
		Lamotrigine	25mg (Max- 400-600mg)
4)	Skeletal muscle relaxant	Baclofen	5-15mg(Max.-30-60mg)

5)	Tricyclic antidepressants	Nortriptyline	10–25 mg( Max - daily dose ¼ 150 mg)
		Amitriptyline	10–25 mg(Max daily dose ¼ 150 mg)
6)	Serotonin and norepinephrine reuptake inhibitors	Duloxetine	30 mg (Max daily dose ¼ 60 mg)
		Venlafaxine	37.5 mg(Max daily dose ¼ 225 mg)
7)	Opioids	Tramadol	50 mg (Max daily dose ¼ 400 mg)

Table 1:- The above table represents drugs commonly used for the management of neuropathic pain

### Second-Line Treatment

#### *Combination Therapy*

90% of patients having neuropathic pain require multiple medications for their pain reduction. Combination therapy plays a vital role in the management of neuropathic pain by most guidelines; however, there is limited evidence on effective strategies.

#### *Tramadol and Tapentadol*

Tramadol has multiple mechanisms of action but primarily acts as a weak opioid agonist and inhibitor of serotonin and norepinephrine reuptake. Tapentadol is a newer weak receptor agonist and norepinephrine reuptake inhibitor. It is considered third or fourth-line treatment by some guidelines due to its increased potency over tramadol.(24)

### Third-Line Treatment

#### *Serotonin-Specific Reuptake Inhibitors/Anticonvulsants/NMDA Antagonists*

For the patient who does not tolerate or fails to have pain relief from first- or second-line therapy, a referral to a neurologist is recommended. The specialists may consider use of serotonin-specific reuptake inhibitors (SSRIs); anticonvulsants such as lamotrigine, carbamazepine, topiramate, and sodium valproate; and NMDA antagonists.(18)

#### *Interventional Therapies*

**Epidural Injection.** Many authors have suggested that epidural injection should be considered in patients who have failed to respond to other therapies and in whom more invasive techniques are being considered. With regards to technique of epidural injection, the transforaminal approach is more likely to provide a positive outcome. (25)

#### *Pulsed Radiofrequency.*

Pulsed radiofrequency (PRF) is a non-destructive radiofrequency technique that passes an electrical field across the nerve resulting in changes in synaptic transmission in a neuromodulatory-type

effect[90]. From a practical perspective, epidural injection is likely to provide short-term benefit and PRF provides moderate relief for six months.(26)

#### *Adhesiolysis.*

Adhesiolysis for FBSS and radicular pain is performed by injecting hyaluronidase, normal or hypertonic saline, and steroids through a catheter in the epidural space to break down adhesions to relieve pain.(1)

#### *Sympathetic Blockade.*

Sympathetic block with local anaesthetic can be used for treatment of complex regional pain syndrome.

#### *Radiofrequency Denervation.*

Radiofrequency (RF) denervation is a destructive technique where the nerve is ablated using heat. (27)

### Fourth-Line Treatment

#### *Neurostimulation*

Considering the limited efficacy of opioids in neuropathic pain, the authors have recommended a trial of neurostimulation before commencing low-dose opioids, placing it as fourth-line treatment after appropriate conservative, pharmacological, and interventional management has failed to achieve an acceptable quality of life for the patient.(28)

### Fifth-Line Treatment

#### *Low-Dose Opioid*

Authors have recommended opioids should be considered after a trial of neurostimulation has been attempted, as per the NICE guidelines. Opioids such as oxycodone, morphine, methadone, and levorphanol have demonstrated efficacy in neuropathic pain patients.(27)

### Sixth-Line Treatment

### Targeted Drug Delivery

Targeted drug delivery is used to deliver medications directly to their site of action at the dorsal horn of the spinal cord, bypassing the first pass effect and the blood-brain barrier. This significantly increases the potency of the medication, allowing much smaller doses to be used. If patient still persists to have pain, patient is advised for surgical management such as neuroaugmentation or nerve decompression.(29)

### 3. Conclusion

Neuropathic pain is highly debilitating, difficult to diagnose, and does not respond to a single drug. A multidisciplinary, structured stepwise approach is needed to decrease pain and attain an acceptable quality of life for patients.

### Acknowledgement

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### Conflict Of Interest

Nil

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