**Chapter 125**

Management of Neurogenic Pain:
Indian Perspectives

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**INTRODUCTION**

Pain is an unpleasant sensation and emotion. Most of us have experienced pain, be it headache or abdominal colic. Pain can occur due to various causes. Neuropathic pain (NP) is a type of pain originating in the nervous system. In the classification of chronic pain, NP is defined as “pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system (CNS)”. International association for study of pain (IASP) has recently published a new definition of NP, which is defined as “pain caused by a lesion or disease of the somatosensory system”.

There are two important changes in the new definition:
1. The word “dysfunction” has been removed.
2. A lesion or disease affecting the nervous system has been specified to be a lesion or disease of the somatosensory system.¹

**PATHOPHYSIOLOGICAL MECHANISMS**

In the last decade, several mechanisms were attributed for precipitating NP such as sensitization of nociceptors, ectopic excitability of affected neurons, facilitation of nociception at spinal dorsal horn, disinhibition of spinal inhibitory network and central reorganization processes (Flow chart 1).²

**Sensitization of Nociceptors**

Nociceptors are receptors with stimulus specific modalities situated at free nerve endings of A delta (Aδ) and unmyelinated C fibers. As the peripheral nerves are damaged, Wallerian degeneration occurs with infiltration of immune cells. Released proinflammatory cytokines such as bradykinin, serotonin, noradrenaline, tumor necrosis factor (TNF), interleukins, etc. promote hyperalgesia and allodynia. Amongst others, more recent inclusion is family of nonspecific cation channels, transient receptor potential vanilloid 1 (TRPV1).

**Ectopic Excitability of Afferent Neurons**

Abnormal excitability of neurons results in positive symptoms like paresthesias and dysesthesias. They are caused by spontaneous discharge of myelinated A beta fibers. Altered excitability of unmyelinated C and Aδ fibers leads to lancinating or burning pain. Pathophysiologic basis of such increased excitability is increased expression of voltage-gated sodium channels.

**Facilitation at Spinal Dorsal Horn**

Central facilitation results in symptoms like pin prick hyperalgesia, dynamic alldynia and cold hyperalgesia. Afferent nociceptives terminate in spinal dorsal column neurons at two levels: interneurons and spinal projection neurons. Glutamate is the major excitatory transmitter in CNS including the pain system.

Various adaptive mechanisms result in increased excitability of nociceptive central neurons, which then become activated not only by stimulation of Aδ and C fibers but also by A beta fibers. Thus, the idea of blocking N-methyl-D-aspartate (NMDA) receptors in managing NP is appealing.

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**Flow chart 1: Pathophysiology**

1. Injury → Free nerve ending Aδ and C fiber → Wallerian degeneration with immune cells → Bradykinin, serotonin, NA → Hyperalgesia, allodynia
2. Increased expression of Na channel → Central facilitation at spinal dorsal horn → Increased excitability of central neurons → CRPS, phantom limb pain
3. Spontaneous nerve discharge → Cortical reorganization
4. Paresthesias

Abbreviations: NA, Noradrenaline; CRPS, Complex regional pain syndrome
Cortical Reorganization

Cortical reorganization processes were found in NP syndromes and in some experimental pain models. Examples are complex regional pain syndrome (CRPS) and phantom limb pain. These are presumably cortical reorganization processes resulting in a couple of phenomenon, not otherwise explainable. These reorganizations are correlated with motor dysfunction and increased activation of primary motor cortices both ipsilaterally and contralaterally.

DIAGNOSIS

In contrast to the motor disturbances, pain as a subjective sensory symptom is not visible, it is difficult to measure, and involves not only physical aspect, but also psychological and emotional components. The coexistence of signs of hyposensitivity and hypersensitivity is common in neurological disorders. Patients with NP almost always have areas of abnormal sensation in the affected area.

Bedside Assessment of Sensory Signs

A standardized examination of NP should include the following: pin prick, touch, pressure, cold, heat, vibration, and temporal summation. The responses should be graded as normal, increased or decreased. The stimulus evoked pain types are classified as hyperalgesic or allodynic.

- Touch can be assessed by gently applying cotton wool to the skin
- Pain assessed by the response to sharp pin prick stimuli
- Deep pain by gentle pressure on muscle and joints
- Temperature: Cold and heat sensation—by measuring response to thermal stimulus (metal objects at 20°C or 40°C)
- Vibration can be assessed by determining response to a tuning fork
- Abnormal temporal summation is the clinical equivalent of increasing neuronal activity after repetitive noxious C fiber stimulation of more than 0.3 Hz.

It is generally agreed that assessment should be carried out in the area of maximum pain with the contralateral area as a control.

Screening Tools

Pain is essentially a subjective experience described with patient-specific symptoms. Consequently, standardized screening tools such as the NP questionnaire, pain detect, the 6-item questionnaire (ID-pain) and Douleur Neuropathique 4 questions (DN4) have been developed to classify NP. The clinical strength of the screening tools is that they can be used to identify potential patients with NP, particularly by nonspecialist.

MANAGEMENT OF PAIN

The management of patients with chronic NP is challenging, despite several attempts to develop a more rational therapeutic approach. Nonpharmacological approaches also have been used in the treatment of intractable NP. Classical examples of chronic NP include diabetic polyneuropathies, postherpetic neuralgia (PHN), trigeminal neuralgia, central poststroke pain and spinal cord injury pain, although traumatic/postsurgical neuropathies and painful radiculopathies represent common conditions in the general population.

Most studies have been performed in PHN and diabetic peripheral neuropathy (DPN). These trials mainly studied the effects of monotherapy and were placebo-controlled. Outcome measures were generally restricted to a global assessment of pain by the patient and the quality of pain was seldom taken into account. However, newer studies have appeared that may allow us to revise this statement.

EVIDENCE-BASED RECOMMENDATIONS FOR PHARMACOLOGICAL MANAGEMENT OF PAIN

Pharmacological management of pain is shown in Flow chart 2.

First-line Medications

Antidepressant

Serotonin and norepinephrine reuptake inhibitions: A large number of placebo-controlled randomized controlled trials (RCTs) have found tricyclic antidepressants (TCAs) to be efficacious for NP. In addition, TCAs are also efficacious for the treatment of depression, a common comorbidity. Their analgesic efficacy in NP has been established independent of antidepressant effect. However, anticholinergic adverse effects are common that include dry mouth, constipation, orthostatic hypotension and urinary retention. These

Abbreviations: SNRIs, Serotonin and norepinephrine reuptake inhibitions; SSRIs, Selective serotonin reuptake inhibitors

Flow chart 2: Pharmacological management of pain
effects can be reduced by starting with low dosages and with slow titration, and also by using a secondary amine TCA, e.g. nortriptyline or desipramine.

Tricyclic antidepressants should be initiated at low dosages (10–25 mg in a single dose at bedtime) and then titrated as tolerated. Effective dosages vary (e.g. 25–150 mg amitriptyline or equivalent), the average dosage for amitriptyline being 75 mg/day.\(^5\)

**Selective serotonin reuptake inhibitors:** Venlafaxine and duloxetine are selective serotonin reuptake inhibitors (SSRIs) that have been found to be effective in peripheral NP. Venlafaxine has shown efficacy in painful polyneuropathies of different origins. Typically, 2–4 weeks are required to titrate to an efficacious dosage (i.e. 150–225 mg/day). Venlafaxine is available in short- and long-acting preparations. Cardiac conduction abnormalities have been reported in few studies and blood pressure increases can occur. It should be tapered slowly because a withdrawal syndrome has been observed.

Duloxetine does not produce significant electrocardiographic or blood pressure changes. The dose is 60 mg twice daily. The common adverse effect is nausea, which can be reduced by administering 30 mg once daily for 1 week, then increased to 60 mg once daily.\(^5,6\)

**Calciun Channel Alpha 2 Delta Ligands (Gabapentin and Pregabalin)**

Gabapentin and pregabalin bind to voltage-gated calcium (Ca) channels at alpha 2 delta (α2-δ) subunit and inhibit neurotransmitter release. They have shown efficacy in several painful neuropathies.\(^7\)

Gabapentin is started as 300 mg at night, and can be increased by 300 mg every other day to a maximum of 3,600 mg/day in three divided doses. Sedation and weight gain are the major side effects. Pregabalin is started as 75 mg/day, escalated by 75 mg every 3 days to a maximum of 600 mg/day in two divided doses.\(^8,9\)

**Topical Lidocaine**

The efficacy of topical lidocaine has been established mainly in PHN. However, the therapeutic gain is modest compared to placebo. Lidocaine patches are generally safe, because of low systemic absorption and only mild local adverse effects. Up to four patches per day for a maximum of 12 hours may be used.\(^5\)

**Second-line Medications**

**Tramadol**

Tramadol is a weak opioid µ-receptor agonist that also inhibits reuptake of serotonin and norepinephrine. It provides relatively rapid pain relief, although it may be somewhat less efficacious than strong µ-agonists (e.g. morphine and oxycodone). The risk of abuse with tramadol seems considerably less. The adverse effect profile of tramadol is similar to that of opioids, but tramadol also lowers the seizure threshold and can interact with certain medications [e.g. serotonin and norepinephrine reuptake inhibitions (SNRIs) and SSRIs] to cause serotonin syndrome, a potentially fatal reaction.

Treatment with tramadol is typically started at 50 mg once or twice daily and then increased gradually as needed to a maximum of 400 mg/day. Older patients and those with renal or hepatic dysfunction are more prone to drug accumulation.

**Strong Opioid**

It is now established that strong opioids (oxycodone, methadone and morphine) have efficacy in peripheral NP.

The evidence is based on several positive RCTs in diabetic neuropathy and PHN using doses of oxycodone—the best-studied opioid drug in NP—ranging from 10–120 mg. The most common side effects are constipation, sedation, nausea, dizziness and vomiting.\(^5\)

**Third-line Medications**

Several additional medications have shown efficacy in either a single RCT or inconsistently across multiple RCTs. However, it is suggested that these medications should generally be reserved for patients who cannot tolerate or who do not respond adequately to first- and second-line medications. These medications include certain antidepressant medications (e.g. bupropion, citalopram and paroxetine), certain antiepileptic medications (e.g. carbamazepine, lamotrigine, oxcarbazepine, topiramate and valproic acid), topical low concentration capsaicin, dextromethorphan, memantine and mexiletine.\(^10\)

**Central Neuropathic Pain**

Only few controlled trials have been conducted in patients with NP caused by lesions in the CNS and such conditions may be relatively more refractory to treatment. Efficacy has been shown for TCAs in central poststroke NP, Ca channel α2-δ ligands in spinal cord injury and central poststroke NP, and tramadol in spinal cord injury NP. Cannabinoids appear to be efficacious in multiple sclerosis, but its use is limited by concerns regarding risks of abuse. Patients who do not respond adequately to these medications can be treated with the first- and second-line medications that have been indicated in peripheral NP.\(^11\)

**RECENT ADVANCES**

**Botulinum Toxin**

Several trials have suggested that botulinum toxin A (BTX-A), a potent neurotoxin used for the treatment of focal muscle hyperactivity, may have anecdotal effects possibly by acting on neurogenic inflammation. Recent studies reported long-term efficacy of a series of subcutaneous injections of BTX-A (from 100 units to 200 units) injected into the painful area in patients with mononeuropathies (mainly of traumatic origin) associated with mechanical allodynia, and in patients with diabetic painful polyneuropathies. The drug had an excellent safety profile with no systemic side effects.\(^8\)

**Lacosamide**

Lacosamide is an antiepileptic medication that acts at voltage-gated sodium channels. It has been studied extensively in painful DPN in addition to epilepsy. Evidence of the efficacy of lacosamide in patients with painful DPN has been provided in various controlled trials. So far Food and Drug Administration (FDA) has not approved this drug for treatment of painful DPN.

**Combination Therapies**

Most trials in NP have studied the effects of individual medications. However, no one medication is universally effective. Moreover, in most cases, the medications already mentioned provide only partial pain relief and adverse effects may limit dose. In clinical practice, two or more medications are often used in combination. Such a treatment strategy makes intuitive sense, particularly, if the medications act at different sites in pain signaling pathways or modulate different neurotransmitter systems.

The various combinations found to be effective in several controlled trials were extended release oxycodone and pregabalin, topical 5% lidocaine and pregabalin, sodium valproate and glyceryl nitrate therapy. Moreover, analgesics can be combined with any of the first-line medications.
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Nonpharmacological Treatment

Various nonpharmacological therapies have been in practice since several decades for treatment of intractable NP such as transcutaneous electrical nerve stimulation, spinal cord stimulation, frequency-specific microcurrent (FSM), aromatherapy, guided imagery, self-hypnosis, biofeedback and acupuncture. They have been found to be effective in decreasing the pain intensity along with the medications.

CONCLUSION

In India, painful diabetic neuropathy is the most common cause of NP (72%). Around 50% is reported substantial impact of pain-related interference in activities of daily living. Among those referred to specialists, 64% have moderate to severe pain who will need intensive therapy. The pharmacological treatment of chronic NP mainly depends on TCAs, SNRIs, antiepileptics (pregabalin and gabapentin) and topical lidocaine as the first-line medications. Recent advances include use of combination therapies, botulinum toxin, newer antiepileptics like lacosamide that have been found to be effective in intractable cases.

REFERENCES