Review Article

Pharmacological Management of Neuropathic Pain in India: A Consensus Statement from Indian Experts

Ashok Kumar Saxena, Parmanand Jain[1], Gur Prasad Dureja[2], Anil Venkitachalam[3], Subrata Goswami[4], Hammad Usmani[5], Shardul Kothari[6], Dipit Sahu[7], Baljit Singh[8], Vandana Trivedi[9], Gaurav Sharma[10], Sanjay Kamble[11], Amit Qamra[11], Salman Motlekar[11], Rishi Jain[11]

Department of Anesthesiology, Critical Care and Pain Medicine, University College of Medical Sciences and GTB Hospital, Delhi, [2]Department of Anesthesiology, Delhi Pain Management Centre, [8]Department of Anesthesiology, G.B. Pant Institute of Postgraduate Medical Education and Research, New Delhi, [1]Department of Anesthesiology, Critical Care and Pain, Tata Memorial Hospital, [3]Department of Neurology, LH Hiranandani Hospital, [6]Department of Diabetology, Shushrusha Hospital, [7]Department of Orthopaedics, Sir H N Reliance Hospital, [11]Department of Medical Affairs, Wockhardt Limited, Mumbai, Maharashtra, [4]Department of Anesthesiology, ESI Institute of Pain Management, Kolkata, West Bengal, [5]Department of Anesthesiology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, Uttar Pradesh, [9]Department of Anesthesiology, Shri M. P. Shah Government Medical College, Jamnagar, Gujarat, [10]Department of Anesthesiology, RUHS College of Medical Sciences, Jaipur, Rajasthan, India

Abstract

Neuropathic pain (NeP) constitutes a major pain-related disorder, which is often underdiagnosed and undertreated. Adverse physical, psychological, and economic consequences associated with NeP lead to poor quality of life. Burden of NeP in developing countries like India is colossal. Various international guidelines provide effective approaches to diagnose and manage NeP. However, differences in the genetic makeup of Indian population can result in subtle differences in clinical response, considering their low body weight, drug metabolism ability, and pain perception. Similarly, treatment-related adverse effects may also vary. Practice of Indian physicians may also differ for choice of drugs based on their availability and affordability. In the absence of country-specific guidelines, this document could serve as a guiding tool for health-care providers, ensuring uniformity in the treatment of NeP. Thus, applicability of all recommendations from any of these guidelines in Indian setting demands careful evaluation. Clinical experience of Indian physicians suggests that there are lot many challenges (e.g., busy outpatient departments, nonavailability of screening questionnaires in regional languages, and availability and affordability of medications) faced by them when managing NeP. In addition, in India, there are no country-specific guidelines that would help them to address these challenges. The objective for this consensus was to develop an expert opinion guideline to harmonize the management of NeP in India. The expert panel consisted of experts from various specialties such as pain medicine, anesthesiology, diabetology, neurology, and orthopedics. The panel critically reviewed the existing literature evidence and guideline recommendations to provide India-specific consensus on the management of NeP. The final consensus document was reviewed and approved by all the experts. This expert opinion consensus will help health-care professionals as a guiding tool for effective management of NeP in India. Use of Douleur Neuropathique 4 (DN4) questionnaire for NeP screening should be routine in day-to-day clinical practice. For effective utilization of DN4 questionnaire, it should be converted to regional language. If DN4 questionnaire screening fails to identify NeP, it should not be disregarded and should not replace the sound clinical judgment from the treating physician. Diagnostic tests may be considered as a supplement to clinical judgment. Cost-effective treatment should be the initial choice. Dosing should be individualized based on efficacy and tolerability. Tricyclic antidepressants (TCAs), gabapentinoids, and serotonin-norepinephrine reuptake inhibitors (SNRIs) can be considered among initial choices. Tramadol can be considered as a second-line add-on treatment for NeP if there is partial response to the first-line agent either alone or in combination. Fixed-dose combination (FDC) of gabapentinoids such as pregabalin (75 mg) with TCA such as nortriptyline (10 mg) is synergistic and improves treatment adherence. Among other treatments, Vitamin B12 (methylcobalamin) can be used either alone or in combination for the management of NeP. Use of Vitamin D and steroids should be limited to specific NeP in individual cases. Referral to pain specialists can be considered if two drugs fail to provide relief in NeP.

Keywords: Diagnosis, expert opinion, guidelines, Indian consensus, neuropathic pain, treatment

Introduction

Pain is referred to a mechanism pointing toward the tissue damage, either current or impending. Two types of

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Address for correspondence: Dr. Ashok Kumar Saxena, Department of Anesthesiology, Critical Care and Pain Medicine, University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi - 110 095, India.
E-mail: ashoksaxena504@gmail.com

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pain are essentially common, i.e., nociceptive pain and neuropathic pain (NeP), and their differentiation is essential as their etiologies, presentations, and management differ substantially.[1,2] The International Association for the Study of Pain (IASP) defines NeP as a "pain caused by a lesion or disease of the somatosensory nervous system."[3] The lesion or disease can be localized at the level of peripheral nervous system or central nervous system. Typical clinical manifestations of NeP are spontaneous burning pain, electrical and shooting pain, allodynia, and hyperalgesia. Besides the significant burden of NeP, the associated physical and emotional distress significantly impacts the quality of life (QoL).[4,5] NeP affects brain neurons in various regions associated with sensations, emotion, cognition, integrative processing, and pain modulation. Maladaptive changes in these regions lead to changes in behavior as suggested by frequent association of NeP with depression.[6,7]

Worldwide, NeP is underdiagnosed, and treatment is often inadequate.[8-11] Not only the individual, but the family and the society as a whole are affected from the direct and indirect consequences of NeP.[12,13] NeP severity is associated with loss of productivity and needs more visits to the physician and higher number of medications for treatment.[12] The economic burden of NeP is a significant concern in developing countries like India. Though reports are scant on the prevalence of NeP, the burden of NeP in India is enormous. In a recent evaluation from India, the reported prevalence of diabetic peripheral neuropathy (DPN) was 29.2% in patients with type 2 diabetes mellitus (T2DM).[14] A recent consensus document from India provides recommendations for pharmacological treatment of pain.[15] However, despite the knowledge of devastating complications of neuropathies, there are no specific guidelines or consensus recommendations on the diagnosis and treatment of NeP in Indian setting. In this document, we review the recommendations from current guidelines followed across the world for the treatment of NeP and provide India-specific consensus (opinions) to primary care physicians (PCPs) for effective screening, diagnosis, and treatment/referral of patients with NeP. Since pain is a multidisciplinary subject, a panel of senior specialists from various disciplines were included to formulate the current consensus on Indian NeP guidelines.

Need of the Expert Consensus Guidelines

In India, it is the PCP at large who encounters patients with NeP than the specialist. As such, there is a scarcity of doctors in India. At present, the doctor–patient ratio is 1:1700, and the Government of India is targeting to reduce it to 1:1000 in the next 10 years. There is hardly any structured pain medicine degree or diploma courses available in the country. Therefore, pain management is quite in a rudimentary state. Due to limited awareness and knowledge about pain, underdiagnosis and undertreatment are prevalent. Perceived pain of neuropathic origin is often treated as simple pain and hence gets neglected. Only at a specialist level, NeP is properly diagnosed and treated as per the existing international NeP guidelines. Late referral to pain specialist is also quite common which can be associated with disease progression and complications. Even if the disease is promptly diagnosed, factors that need to be strongly considered for effective management include presence of multiple etiologies, availability of drugs, choice of therapy, disparities in dose, and, most importantly, the affordability of treatment. In a recent survey, it was observed that low dosages of drugs such as amitriptyline, pregabalin, and gabapentin were preferred by majority of Indian health-care providers for the management of NeP.[16] Although it remained unclear whether the low doses were actually efficacious, these findings necessitated a need to relook at the available guidelines on NeP and formulate an India-specific consensus for the management of NeP. Hence, an expert panel consisting of caregivers from various specialties was invited on a common platform to share their expert opinion and formulate consensus guidelines for the whole of Indian population with a superlative objective of providing the practice recommendations to PCPs for the treatment of NeP.

Methodology Adopted to Formulate Guidelines

Expert consensus group

The expert panel for this consensus consisted of caregivers from various specialties such as pain specialists, anesthesiology, neurology, oncology, diabetes and endocrinology, and orthopedics involved in the management of NeP. The aim of the expert panel was to develop a clinical practice consensus document to help PCPs to better diagnose and manage NeP in Indian clinical setup.

Approach to consensus

The panel identified currently available international guidelines in the management of NeP. To adopt these guidelines in Indian setting, the panel felt the need of providing some India-specific recommendations. The recommendations from the Special Interest Group on Neuropathic Pain (NeuPSIG) of the IASP,[17] the second European Federation of Neurological Societies (EFNS) Task Force guidelines,[18] consensus statement from the Canadian Pain Society,[19] National Institute for Health and Care Excellence clinical guideline for NeP in adults,[20] the American Academy of Neurology guideline for treatment of painful diabetic neuropathy (DN),[21] trigeminal neuralgia (TN),[22] and postherpetic neuralgia (PHN), and NeP pathway for care from British Pain Society[23] were considered. Additionally, the expert panel also reviewed recommendations from the Middle East Region for peripheral NeP.[24]

The factors that were believed to be important to adopt these international recommendations in Indian setting were as follows:

- Geographic diversity
- Linguistic differences
- Patients' cultural preferences

- Availability of instruments for diagnosis
- Drugs' availability
- Cost and affordability of treatment
- Referral facilities.

Additionally, epidemiological data pertaining to India were also reviewed from the available randomized and/or observational studies. The felt need for improving diagnosis, treatment, and referral of NeP at PCP level was the main consideration for providing guidance in this document.

Developing a consensus document

All the discussion and consensus formulated at the meeting were recorded by a professional medical writer who prepared a final manuscript draft. The consensus document was then reviewed and edited by all panel members. After finalizing the manuscript with approval of all the panel members, it was submitted for publication.

India-Specific Consensus Guidelines

Epidemiology of neuropathic pain

True-prevalence estimates are difficult because of underreporting of NeP. The fact sheet of IASP for 2014–2015 reported 7%–8% prevalence of NeP in adults.[25] Estimates of NeP vary considerably by etiologies with 20% cancer-related NeP, 26% DN, 2.6%–10% of chronic PHN, up to 40% postsurgical NeP, 35% having HIV-related NeP, and 37% chronic low back pain (LBP) NeP.[25] A recent meta-analysis identifies the prevalence of pain with neuropathic features having best estimates between 6.9% and 10%.[26]

Unfortunately, no consolidated reports of NeP incidence or prevalence from India are available. Epidemiological evidence for NeP is based on observational studies and is summarized in Table 1. The prevalence estimates vary according to the type of methodology used in screening patients of NeP. Orthopedic neuropathies comprise a large group of etiologies resulting in NeP. A recent meta-analysis of epidemiological studies reported NeP in 55.8% of patients with LBP.[45]

Evaluation of neuropathic pain

Screening

In case of a high clinical suspicion of NeP, evaluation with different screening tools can be done. There are various screening tools devised to suit easy clinical applicability. Some

Table 1: Epidemiological estimates of neuropathic pain according to various etiologies in India

Author (years)	*n*	Patient population	Prevalence (%)
D'Souza *et al*. (2015)[27]	208	Diabetes	18.3-32.2
Bansal *et al*. (2014)[14]	2006	Diabetes	29.2
Gill *et al*. (2014)[28]	195	Diabetes	29.2
Kannan *et al*. (2014)[29]	88	Impaired glucose tolerance	32.8
Rani *et al*. (2010)[30]	1401	Diabetes	18.84
Dutta *et al*. (2005)[31]	100	Diabetes	29.0
Ashok *et al*. (2002)[32]	1000	Diabetes	19.1
Jain *et al*. (2014)[33]	300	Postcancer surgery	10.0
Bhatnagar *et al*. (2010)[34]	3238	Cancer	11.8
Jain *et al*. (2009)[35]	180	Cancer - Postsurgery	56.0
		Cancer - Postchemotherapy	44.4
		Cancer - Postradiation	51.1
IndiNep group (2008)[36]	446	Diabetes	72.2
		TN	5.16
		Postspinal cord injury	4.26
		Poststroke	4.04
		Carpal tunnel syndrome	3.60
		Postherpetic	3.14
		Cancer	0.90
		Other	4.48
Mazumder *et al*. (2016)[37]	149	Herpes zoster	98.0
Usha *et al*. (2015)[38]	100	Herpes zoster	15.0
Gupta *et al*. (2014)[39]	237	Herpes zoster	13.0
Kumar *et al*. (2016)[40]	319	Poststroke	20.7
Kalirathinam *et al*. (2015)[41]	100	Postspinal cord injury - Only NeP	36.0
		Postspinal cord injury - NeP positive Musculoskeletal pain	26.0
Dubey *et al*. (2013)[42]	75	HIV infection	40.0
Nair *et al*. (2009)[43]	140	HIV infection	32.0
Narayan R *et al*. (2017)[44]	161	Knee osteoarthritis	50.9 (overall) 45.6 (excluding diabetics)

NeP=Neuropathic pain, HIV=Human immunodeficiency virus, TN=Trigeminal neuralgia

tools incorporate clinical as well as instrumental variables, whereas others are purely clinical involving both the patient and the physician. Few of the tools are listed below:

- Douleur Neuropathique 4 (DN4)[46]
- ID Pain[47]
- Leeds Assessment of Neuropathic Symptoms and Signs[48]
- PainDETECT[49]
- Neuropathic Pain Questionnaire (NPQ)[50]
- The Neuropathic Pain Symptom Inventory[51]
- German Research Network on Neuropathic Pain testing[52]
- The Standardized Evaluation of Pain[53]
- The McGill Pain Questionnaire.[54,55]

The problem of busy outpatient departments

The panel identified that most of the PCPs and specialists have busy outpatient departments (OPDs) and patient load might not allow detailed evaluation of each patient. In such situation, NeP may be missed by both patients and physicians. We find the need of patient awareness to report NeP. Further, a self-administered questionnaire is required to assist physicians with easy and rapid identification of NeP in routine OPDs.

- Expert opinion: Use DN4 questionnaire for NeP assessment in day-to-day practice.

DN4 (or Neuropathic Pain 4 questions in French) was developed by French Neuropathic Pain Group.[46] It helps in the differentiation of NeP from non-NeP.

- The first question in the tool collects information about the description of pain such as burning, squeezing, painful cold, electric shock, and lancinating
- The second question screens the patient for paresthesia/dysesthesia by asking for symptoms such as pins and needles, tingling, numbness, and itching
- The third question evaluates the patient for sensory deficits through physical examination and reveals touch hypoesthesia (soft brush), pricking hypoesthesia (von Frey hair), heat hypoesthesia (40°C), and cold hypoesthesia (25°C) in the area of pain
- The fourth question in this tool assesses the patient for evoked pain that is caused or increased by brushing (three movements with soft brush), pressure (blunt pressure with a finger that would not usually provoke pain outside the pain area), and contact with cold or heat.

A cutoff score of 4 was reported to have a predictive value of 86%, a sensitivity of 82.9%, and a specificity of 89.9%.[56]

Though the pain assessment tools are widely used, there remains a doubt about the utility and applicability of one over the other. In a recent meta-analysis on 37 studies by Mathieson *et al*.[57] to assess measurement properties of various questionnaires, different questionnaires were found to have different properties. DN4 and NPQ were suggested as the most useful and suitable tools of clinical utility. The EFNS guidelines on NeP assessment provide Grade A recommendation for using these screening tools especially by nonspecialists for identifying patients with NeP, but their failure to identify NeP should not replace the clinical judgment.[58]

- Expert opinion: If DN4 questionnaire screening fails to identify NeP, it should not be disregarded and should not replace the sound clinical judgment from the treating physician.

The problem of English language

We identified the need for transformation of pain scales into regional languages that can be understood by patients, relatives, and physicians easily. This will increase the effectiveness of screening NeP in OPDs. The indigenization of pain scales is a time-consuming task, and focused efforts are needed to provide validated pain scales. In one such effort, Gudala *et al*. translated DN4 questionnaire into Hindi and observed good internal consistency and test–retest reliability with the administration of Hindi questionnaire.[59]

- Expert opinion: PCPs should convert DN4 questionnaire into their regional vernacular language to screen NeP effectively.

Diagnosis

The characteristics of NeP can help ascertain the diagnosis of neuropathy. Symptom description by patients should not be ignored. Identifying the area of more severe pain or altered sensation may help to find the associated cause. Assessment of sensory abnormalities in the form of area distribution and local sensory changes needs more exploration. Simple measures that can be adopted to assess function include soft touch, pressure, and hot and cold sensations. Comparison of affected area with equilateral control area should be done. If the underlying pathology is diagnosed, specific treatment needs to be directed. A symptomatic treatment needs to be considered for no specific cause considering the QoL, physical functioning, and sleep quality of the patient.

The EFNS guidelines on NeP assessment recommend various other tests such as quantitative sensory testing, nerve conduction study, microneurography (single-axon recordings from peripheral nerves), laser-evoked potential, skin biopsy, functional magnetic resonance imaging, or positron emission technology scan.[58] Various bedside assessments that can be undertaken for specific symptoms have been reviewed in detail elsewhere.[60]

- Expert opinion: The tests described above may not be suitable for routine use in Indian OPDs. However, these should only be supplement for the diagnosis of NeP in individual cases. To establish the diagnosis of NeP, it is recommended to follow the following sequence:
  - Pain description
  - History of lesion or disease
  - Sensory test
  - Diagnostic test.

Management of neuropathic pain

Challenges while planning management strategies for NeP include different etiologies having differing pathophysiological mechanisms; dearth of head-to-head clinical trials comparing various therapies; and limitations of available treatments such

as unwanted side effects, multiple day-to-day dosing, modest efficacy of topical treatments, and their local side effects. Thus, there is a delicate balance of pain relief and adverse events which are directly linked to the treatment adherence.[61] Effective pain relief often requires combination treatment that acts by different mechanisms and is important in patients with partial relief to single agent or where increment in dose is not possible due to side effects.[62] Worldwide, various international guidelines provide treatment recommendations for NeP. The recommendations from recent NeupSIG guidelines of IASP are summarized in Table 2.[17]

After reviewing the available guideline recommendations, the expert panel identified key areas pertaining to India. The following are the guidance for the assessment and treatment of NeP in Indian setup. The panel also provided a basic algorithm to NeP management as discussed subsequently.

Issues of affordability and accessibility

Most patients find it difficult to bear the cost of therapy for longer duration. NeP treatments in patients having chronic neuropathies such as DN and poststroke pain (PSP) may face economic challenges. Certain treatments which are used outside India are not available in India (e.g., 8% Capsaicin cream). Strong opioids are controlled substances and are not available easily. Patients in need of such drugs may find it difficult to get access because of nonavailability or controlled access.

- Expert opinion: Using cost-effective treatment as an initial choice for NeP is strongly advised. Access to controlled treatments should not limit the therapy and specialist opinion should be undertaken in cases who need them the most.

Clinical evidence with first-line agents in Indian population

In a study from South India, cost-effectiveness analysis in diabetic painful neuropathy comparing pregabalin and duloxetine revealed equivalent efficacy in DN, but duloxetine was more cost-effective as it resulted in better improvement in QoL at a modest price increase than pregabalin.[63]

In another study from North India conducted on DN, pregabalin (75–300 mg twice a day) was as effective as amitriptyline (10–50 mg once a day), but pregabalin was associated with fewer side effects with significantly lower somnolence.[64]

In another randomized, double-blinded trial on PHN patients, gabapentin was found equally effective to nortriptyline. However, better tolerability with gabapentin was reported.[65]

A randomized, double-blinded, placebo-controlled trial from New Delhi compared pregabalin (150–600 mg/day), gabapentin (900–1800 mg/day), amitriptyline (50–100 mg/day), and placebo in patients with neuropathic cancer pain administered for 4-week duration. Pregabalin was the stand-out treatment in this trial as it was significantly effective in reducing cancer NeP, had significant improvements in Global Satisfaction Score and Eastern Co-operative Oncology Group scoring, and had significant morphine-sparing effect than other treatments. Adverse effects were numerically lower with pregabalin and were mild in severity.[66]

Guidance on treatment with medications

Choice of medications

As recommended by guidelines, the expert panel also suggests the following three classes of drugs as first-line agents [Table 3].

- Gabapentinoids (e.g., pregabalin, gabapentin)
- Tricyclic antidepressants (TCAs) (e.g., nortriptyline, amitriptyline)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine, venlafaxine).

Dosing of medications

Dosing preference from Indian physicians' survey (data on file) showed frequent use of lower dosages for major NeP treatments by majority of physicians as summarized below:[16]

- Amitriptyline: Initiate (71.01%) and maintain (78.3%) at 5–10 mg/day
- Pregabalin: Initiate (86.18%) and maintain (87.79%) at 50–75 mg/day
- Gabapentin: Initiate (81.76%) and maintain (80.16%) at 100–300 mg/day
    - Expert opinion: Dosing of individual drugs should be tailored based on efficacy and tolerability. The suggested dosing schedule is summarized in Table 3.

Table 2: Treatment recommendations for neuropathic pain from various international guidelines

Therapy choice	NeupSIG (2015)[17]	EFNS (2010)[18]	CPS (2014)[19]	NICE (2013)[20]
1st line	Gabapentinoids: Pregabalin, gabapentin, gabapentin XR TCAs; SNRIs: Duloxetine, venlafaxine	Gabapentinoids, SNRIs (DN); TCAs, topical lidocaine (PHN)	Gabapentinoids; TCAs; SNRIs	Gabapentinoids: Pregabalin, gabapentin; TCAs; SNRIs: Duloxetine, venlafaxine Tramadol*, capsaicin cream**
2nd line	Capsaicin 8% patch; tramadol; lidocaine patches	Tramadol, strong opioids (polyneuropathy); opioids, capsaicin (PHN)	Opioids; tramadol	
3rd line	Strong opioids Botulinum toxin A		Cannabinoids	

*Only if acute rescue therapy is necessary, **Localized neuropathic pain where oral therapy is avoided, or oral medications not tolerated. NeupSIG=The Neuropathic Pain Special Interest Group, EFNS=The European Federation of the Neurological Societies, CPS=Canadian Pain Society, NICE=National Institute of Health and Care Excellence, TCAs=Tricyclic antidepressants, SNRIs=Serotonin-noradrenaline reuptake inhibitors, DN=Diabetic neuropathy, PHN=Postherpetic neuralgia

Table 3: Medication guidelines (as per availability in India)

Drug	Dosing recommendation	Adverse effects	Contraindications/precautions/interactions	Additional benefits
Gabapentinoids				
Pregabalin	Initiate at 50 mg bedtime Increase to 75 mg in 48 h In case of <50% pain relief, increase the dose by 75 mg/day every 4-5 days Total titrated dose to be administered in two divided doses Maximum dose: 450 mg/day in 2 divided doses	Dizziness Vertigo Sedation Dryness of mouth Asthenia Peripheral edema	Nonsignificant drug interactions ↓Dose in renal insufficiency	Improves sleep abnormalities ↓Anxiety
Gabapentin	Initiate at 100 mg at bedtime (or 3 times daily) Carefully titrate to 100-300 mg 2-3 times daily week by week decided by efficacy and tolerability Maximum dose: 1800 mg/day in 3 divided doses	Same as pregabalin	Same as pregabalin	
SNRIs				
Duloxetine	Initiate at 20 mg once daily at bedtime Carefully titrate to 60 mg in two divided doses daily after a week 60 mg is optimal dose to provide efficacy with tolerability Higher dose to be used in individual cases after discussion with patient on potential benefits and risks	Gastro-intestinal: nausea with or without vomiting, constipation, ↓appetite, dry mouth	Contraindicated in severe hepatic and renal diseases, alcohol abuse, use of tramadol, and in concomitant use of MAO inhibitors Lower starting dose in mild-to-moderate hepatic and renal impairment Caution: History of mania, seizures, acute narrow-angle glaucoma, watch for worsening glycemic control, especially in patients with diabetes Inhibition of metabolism of drugs metabolized by CYP2D6 ↑Suicide risk	↓Depression ↓Anxiety
Venlafaxine	Initiate at 37.5 mg at bedtime Increase to 75 mg as per tolerability Maximum dose of 225 mg/day can be reached by titrating dose each week Do not discontinue abruptly Taper doses to avoid withdrawal syndrome Extended release formulation is better than immediate release for tolerability	Nausea	Caution in cardiac disease BP monitoring as risk of hypertension low ↓ dose in renal impairment and severe hepatic disease Caution: History of seizures and mania Interactions: Tramadol, TCAs, SSRIs, and SNRIs. Inhibit metabolism of drugs metabolized by CYP2D6 ↑Suicide risk	
TCAs				
Amitriptyline	Start with low dose (10 mg) Titrate upward slowly to maximum of 50-75 mg in two divided doses	Anti-cholinergic effects, sedation, dizziness	Concomitant use with tramadol: Risk of serotonin syndrome Drug interaction: Anti-arrhythmic; SSRI/SNRI or MAO inhibitors antidepressants, pimozide; ↑Suicidal risk Caution in elderly patients	↓Depression
Nortriptyline	Initiate with low dose (as like amitriptyline) Maximum dose 150 mg/day, single or divided doses	Same as amitriptyline	Same as amitriptyline	↓Depression
Opioid analgesics				
Tramadol	Initiate with 25 mg Titrate upward by 25 mg/day every 3-4 days to maximum of 100 mg thrice or four times daily judged by tolerability profile	Dizziness/ vertigo, constipation, sedation, nausea, vomiting	Concomitant use of alcohol and other CNS or respiration depressant, TCAs, SSRI/SNRIs Addiction risk	

MAO=Monoamine oxidase, SSRIs=Selective serotonin reuptake inhibitors, SNRIs=Serotonin-norepinephrine reuptake inhibitors, TCAs=Tricyclic antidepressants, CNS=Central nervous system, BP=Blood pressure, ↑=Increase, ↓=Decrease

Approach to treatment

Initial treatment with first-line agent should be continued for at least 12 weeks, and dose titration to lower strengths or tapering off can then be attempted. Evaluate treatment response at 2 and 4 weeks. In case of partial response, dose titration to higher strength can be attempted. For persistent poor response, a second class of drug can be tried in addition to the first treatment. In case of use of gabapentinoids as the first therapy, addition of TCAs such as nortriptyline or SNRIs can be considered and *vice versa*. TCAs should not be combined with SNRIs as their target mechanisms are essentially similar. Additionally, drugs from second- and third-line categories can be considered. The treatment flow is depicted in Figure 1.

Among second-line treatments, use of opioids and tramadol as additional agents for NeP management has been recommended. Use of strong opioids is restricted for being controlled substance. Thus, tramadol is available as an option for clinical use on an OPD basis.

In a randomized study from North India, tramadol (50–200 mg/day) was found to be effective and well tolerated with improvements in QoL in patients with PHN.[67] In a Cochrane meta-analysis of tramadol involving studies in cancer NeP, DN, PHN, polyneuropathies, and as add-on to conventional treatment, tramadol was effective in pain relief. NNT for 50% pain relief when compared to placebo was 3.8.[68]

- Expert opinion: Tramadol can be considered as second-line add-on treatment for NeP if there is partial response to first-line agent either alone or in combination. If the response to the treatment remains poor with two classes of medications, referral to specialist care is required for further diagnostic and therapeutic management [Figure 1].

Combination therapies

Recently, a Cochrane review was published on the role of combination treatment in NeP.[69] In this review of double-blinded, randomized studies, a total of 21 trials were included which used various combinations (opioid with gabapentin or pregabalin, opioid with TCAs, gabapentin with nortriptyline, tramadol with acetaminophen, and others). A meta-analysis reported opioid and gabapentin combination to be superior to gabapentin alone. However, the frequency of adverse effects was higher with combination. It was concluded that different good-quality studies have shown better efficacy with two-drug combinations.

Fixed-dose combinations

The availability of FDCs in India is looked upon by the expert panel. We find that FDCs of gabapentinoids such as pregabalin and gabapentin with TCAs, mainly nortriptyline, have certain advantages and disadvantages. Besides being additive in action, FDCs reduce polypharmacy and allow for lower dose use, thereby lowering the side effects of individual drugs. This can improve patient compliance. However, dosing flexibility may not be possible and may be difficult in comorbid conditions such as hepatic failure.

With positive treatment response while receiving FDC in stable doses, a FDC can be helpful in maintaining treatment adherence. As the evidence suggests, combinations of gabapentinoids with TCAs or opioids can be considered as per availability and affordability.

- Expert opinion: Rationality is an important factor for consideration of combination treatment including sustained release formulations along with the demonstration of sufficient efficacy and safety. Improvement in efficacy with no burden of additive or higher side effects should be the approach for providing combination treatment. FDCs especially of gabapentinoids like pregabalin (75 mg) with TCA like nortriptyline (10 mg) can be synergistic and improve treatment adherence, especially in Indian setting where compliance to therapy is generally poor.

When to refer to a specialist?

Immediate referral to a specialist care is suggested in the following situations:

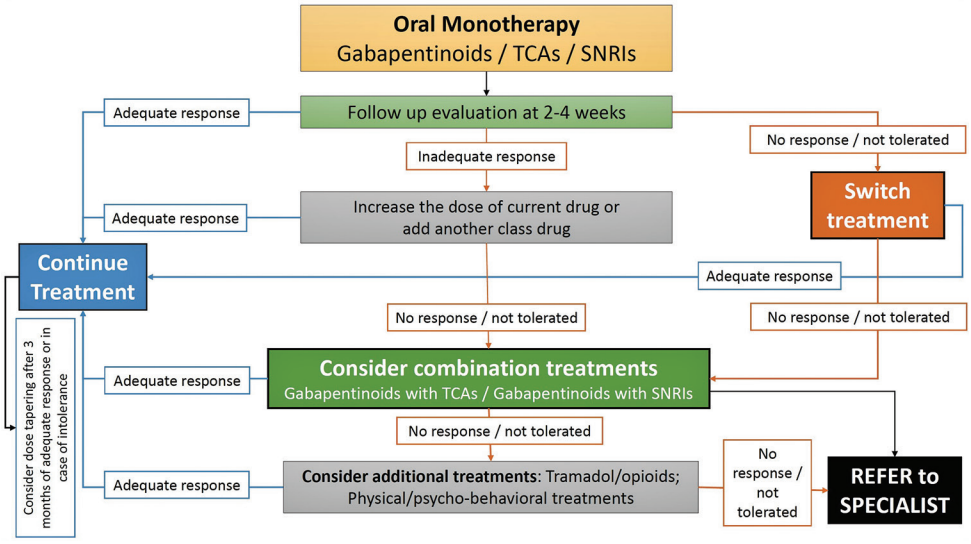

Figure 1: Treatment approach to neuropathic pain in Indian setup

- Failure to respond to two drugs from different classes at optimal doses
- Long-standing NeP
- Suspected polyneuropathy
- Significant sensory disturbance
- Any associated motor disturbances
- Contraindications to first-line medications.

Guidelines on individual neuropathies

A brief guidance on specific neuropathies is provided in the following sections, and the first-choice treatments are summarized in Table 4. We identify diagnosis of NeP as more of clinical entity. Using sophisticated tests may put an extra economic burden to the patients and hence are not considered for routine evaluation. Further, any chronic pain over 3-month duration may have neuropathic component.[70] Addition of NeP treatments may help achieve pain relief in such cases.

Diabetic peripheral neuropathy

- In every diabetic patient, tuning fork examination being a basic screening tool should ideally be considered for screening of NeP on an annual basis
- Differentiation of DN from lumbar radiculopathy is essential. Clinically, DN is more symmetric as against lumbar radiculopathy
- Low-dose TCAs can be considered as first-choice treatment if there are no contraindications
- Gabapentinoids should be the first choice whenever available or in cases of intolerance to TCAs
- Side effects of duloxetine may limit the patient compliance
- Venlafaxine can be considered if available and in affordable patients. Slow titration is advised
- Optimal treatment duration is for 12 weeks or more for satisfactory pain relief
- Consequent prevention and treatment of hyperglycemia and management of cardiovascular risk factors that exacerbate the neuropathy are needed.[72]

Postherpetic neuralgia

- We advise the start of treatment during prodromal phase, even before the appearance of rashes since neuralgia may well begin in prodromal phase itself. However, there is a need to study this hypothesis further
- Famciclovir is a choice over acyclovir if available, which might improve patient compliance
- Pregabalin can be started from day 0 of herpes
- Low-dose amitriptyline can be utilized as an add-on therapy
- Utility of other agents such as methylcobalamin and magnesium sulfate remains unclear and are not advised
- Interventions such as nerve blocks, epidural steroid injections, and pulsed radiofrequency lesioning (if available and affordable) may be useful in intractable cases. It should be restricted to the dermatomes involved[73,74]
- Recent investigation from India shows that a multimodal intervention with pulsed radiofrequency and pregabalin is associated with early pain relief and greater rise in brain-derived neurotrophic factor levels than pregabalin alone.[75]

Table 4: Etiology-specific treatment of neuropathic pain in Indian setting

Etiology	First Choice
DN[18]	TCAs (low dose)/gabapentinoids
PHN[21]	Gabapentinoids/TCAs
TN[22]	Carbamazepine/baclofen TCAs if neuropathic component present
CP[71]	Gabapentinoids/TCAs

DN=Diabetic peripheral neuropathy, PHN=Postherpetic neuralgia, TN=Trigeminal neuralgia, CP=Central pain, TCAs=Tricyclic antidepressants

Cancer neuropathic pain

- Expert clinical assessment to identify NeP in cancer is needed
- The prevalence of chemotherapy-induced NeP is unknown. Future studies need to be directed in this area
- Among the various chemotherapeutic agents in cancer, paclitaxel and docetaxel are common associations for NeP.[76] Severe NeP may affect compliance to chemo regimens
- There are no head-to-head clinical trials comparing various agents
- In case of uncontrolled pain, drugs such as capsaicin, strong opioids, transdermal fentanyl, and buprenorphine may be tried. However, due to unavailability of capsaicin in the country and strong opioids being controlled substances and not easily accessible, transdermal fentanyl and buprenorphine patches may be tried as tolerated
- No data on the prevention of cancer NeP are available in Indian setup.

Trigeminal neuralgia

- Medical management is the first-line treatment
- In carbamazepine unresponsive patients, baclofen may be tried.[77] If neuropathy is present (not just neuralgia), TCAs can be added. Tramadol is not useful
- Failure of pain relief with three medications in optimal doses qualifies for surgery or interventional treatment
- Peripheral nerve block may be tried as the second-line option
- Gasserian ganglion radiofrequency ablation is performed if available and affordable
- Surgical treatment is costly and not readily available.

Central pain

- Need for more epidemiological data on central pain including PSP
- Neuropathy is more common in ischemic than hemorrhagic stroke.[78] PSP is usually seen within 6 months after stroke, whereas complex regional pain syndrome occurs in few days and poststroke headache occurs immediately during poststroke period

- Early identification of PSP is necessary to improve adherence to physiotherapy
- Assessment and diagnosis of central pain, especially PSP, is ascertained by the clinical history and examination
- In clinical management of central NeP, preference is given to pregabalin or TCA like amitriptyline depending on benefits and risks in individual patient.

Chronic persistent postsurgical pain

- Chronic persistent postsurgical pain (CPPP), a form of peripheral NeP, is usually seen after thoracotomy, amputation, breast surgery, and back surgery
- A recent study from India reported CPPP incidence of 38.1% after laparotomy for ovarian carcinoma[79]
- A preventive rather than curative approach is necessary to avoid CPPP
- Postoperative administration of gabapentinoids such as pregabalin and gabapentin is associated with lower incidence of CPPP.[80]

Other treatments

Among the treatments discussed above, there are various other treatments that have been tried with varying success rates in NeP. Corticosteroids,[74] electroacupuncture,[73,81] Vitamins especially B12[82] and D,[83] smoked cannabis,[84] and intravenous immunoglobulin in vasculitic neuropathy[85] are studied in NeP. Few of them need a mention here.

Vitamin B12

Among various analogs of Vitamin B12, methylcobalamin is an active form which is a coenzyme associated with methionine synthase involved in the methylation of nucleic acids. Methylcobalamin has been shown to be effective in experimental and clinical conditions associated with NeP. Its efficacy has been reported in diabetic peripheral NeP and LBP, glossopharyngeal neuralgia, TN, and subacute herpetic neuralgia.[82] However, the studies assessing the last three conditions were too old with limited patient pool and involved different dosages, routes of administration such as intrathecal route, and concomitant medications. Therefore, the effectiveness of methylcobalamin in pain associated with PHN, glossopharyngeal neuralgia, and TN needs to be evaluated further. A randomized, comparative evaluation of Vitamin B12 and nortriptyline in painful DN reported significantly better improvements in pain, paresthesia, and tingling sensation with Vitamin B12. However, the possibility of introduction of bias in this single-blinded study cannot be ruled out.[86] Another randomized study identified the effectiveness of Vitamin B12 in subclinical carpal tunnel syndrome (CTS) in nonparetic side after stroke. However, the study reported that only 31% and 30% patients of treated and untreated patients, respectively, met the electrophysiologic criteria for CTS.[87]

Two small trials from India have assessed the efficacy of methylcobalamin in combination with pregabalin. In MAINTAIN pilot study, the combination of methylcobalamin (750 μg), alpha-lipoic acid (100 mg), and pregabalin (75 mg) was associated with significant improvements in pain, sleep disturbance, and nerve function. However, it is not clear whether the benefits observed are derived from vitamin B12, lipoic acid or both in addition to the effect of pregabalin.[88] Another observational study reported significant pain relief with FDC of sustained release pregabalin and methylcobalamin over 14 days.[89] These results warrant a need for a long-term study to confirm the benefits in Indian population. A systematic review of clinical trials conducted in 2005 reported better symptomatic relief with Vitamin B12 administration than the changes observed in electrophysiological results in patients with DPN. However, of the five included trials in this review, only two trials were of fairly good quality.[90] A Cochrane review in 2008 reported that the evidence from randomized studies is insufficient to state whether Vitamin B12 is effective or not in peripheral NeP.[91] A brief review of clinical studies on Vitamin B12/methylcobalamin in NeP is presented in Table 5.

Though some small studies suggested the efficacy of methylcobalamin, the evidence is not convincing to accept or refute the role of Vitamin B12 in NeP. The panel therefore suggested that there is a need to generate further evidence from large-scale randomized controlled trials in Indian setting for confirming the effectiveness of methylcobalamin in NeP.

- Expert opinion: Current evidence is not convincing to accept or refute the use of methylcobalamin in NeP. There is a need to further generate evidence from randomized trials, especially in Indian patients.

Corticosteroids

Steroids are found useful in NeP associated with cancer,[100] acute persistent postoperative NeP,[101] and lumbar radiculopathy.[102] A Cochrane meta-analysis for the utility of corticosteroids in PHN found them ineffective in preventing neuralgia.[103] The panel identified need of further evidence to support or refute the use of steroids in other types of NeP.

- Expert opinion: There is a need to generate further evidence to support the utility of corticosteroids in the management of NeP.

Nonpharmacological treatments

The panel did not discuss any nonpharmacological treatments and interventions and surgeries for NeP management. No expert opinions are made for these treatments.

Future Directions and Research

There is an immense need to generate epidemiological data in different neuropathies. We urge physicians across India to publish their observations on the incidence and prevalence of NeP which will help understand the true burden of NeP. Genetic tests to identify single-nucleotide polymorphisms and thereby response to the treatment need further evaluation in multicentric studies. Their routine use is not indicated. However, in the recent proceedings of 16th World Congress on Pain, Bouhassira and Attal suggested that, rather than using simple algorithms, it could become possible to use more elaborate therapeutic algorithms based on patients' clinical phenotypes to reduce therapeutic failure in NeP.[104] Evidence on rational combination

Table 5: Vitamin B12/methylcobalamin in neuropathic pain

Author (years)	Study details	Interventions	Major findings
In DPN			
Yaqub, *et al*. (1992)[92]	RCT 16 weeks *n*=43	Methylcobalamin 250 mg, 2 capsule TDS versus placebo	Improvement with methylcobalamin in Somatic symptoms (*P*=0.003) Autonomic symptoms (*P*=0.01)
Stracke, *et al*. (1996)[93]	RCT 12 weeks *n*=24	Combination of benfotiamine plus Vitamin B6/B12	Significant improvement in nerve conduction velocity (*P*=0.006) Improvement in vibration perception threshold
Simeonov, *et al*. (1997)[94]	RCT 12 weeks *n*=45	50 mg benfothiamine and 0.25 mg cyancobalamin (Milgamma tablets - 2 tablets QID for 3 weeks followed by 1 tablet TDS for 9 weeks) versus conventional Vitamin B complex	Milgamma resulted in Significant relief of both background and peak neuropathic pain Improved vibration perception thresholds
Kuwabara *et al*. (1999)[95]	OL *n*=9 6 months	IV methylcobalamin (500 µg, three times/ week) for 6 months after each hemodialysis	Relieved pain and paraesthesia Improved motor and sensory nerve conduction velocity No side effects
In LBP/neck pain			
Waikakul and Waikakul (2000)[96]	RCT *n*=152 2 years	Oral methylcobalamin (0.5 mg, TDS) versus placebo (as an adjuvant to conventional management [patient education, physical therapy, and medication] for 6 months)	No effect on pain improvement and neurological signs Amelioration of neurogenic claudication distance
Chiu *et al*. (2011)[97]	RCT *n*=60 2 weeks	IM methylcobalamin (500 µg, TDS) versus placebo	Methylcobalamin resulted in significant (*P*<0.05) improvement of Oswestry Disability Index score Visual Analog Scale pain scores
As combination with other agents			
Xu *et al*. (2013)[98]	RCT *n*=98 PHN 4 weeks	Local injection of methylcobalamin/ oral methylcobalamin/subcutaneous 1% lidocaine injection	Injectable methylcobalamine was better than other treatments in reducing Overall pain (*P*<0.0001) Continuous spontaneous pain (*P*<0.05) Paroxysmal pain (*P*<0.05) Allodynia (*P*<0.05) Safe and well tolerated
Singh *et al*. (2013)[99]	RCT *n*=30 GN 3 months	Group A: Oral gabapentin (300 mg), tramadol (50 mg TDS), and methylcobalamin (0.5 mg) Group B: Group A treatment positive extraoral glossopharyngeal nerve block	Both groups Lowered pain intensities Improved pain relief Improved quality of life

DPN=Diabetic peripheral neuropathy, PHN=Postherpetic neuralgia, RCT=Randomized controlled trial, OL=Observational, IM=Intramuscular, IV=Intravenous, TDS=Three-times daily, GN=Glossopharyngeal neuralgia, LBP=Low back pain, QID=Four times daily

treatments is lacking and needs further focused research. Though the evidence on Vitamin B12 is encouraging, utility of such adjuvant therapies requires further in-depth evaluation.

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Conflicts of interest

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