Review Article

# Consensus recommendations for the management of peripheral neuropathy in India

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**Peripheral neuropathy (PN) poses a high disease burden in India as compared to developed countries, owing to higher prevalence of diabetes cases, nutritional deficiencies, infectious diseases, and exposure to toxins. There are currently no Indian clinical guidelines in place for the management of this neurological condition. Hence, there exists a need to develop standard guidelines for management of PN specific to the Indian population considering international guidelines may not be fully applicable to this patient population. To better understand the causes and management of PN in India and develop a multi-disciplinary expert consensus statement providing guidance to primary care physicians for the diagnosis and treatment of PN in India. In November 2017, a meeting of experts in the field of neuropathy, including neurologists, diabetologists, and endocrinologists was conducted in Chennai, India. The expert committee discussed underlying causes, current clinical practice(s) for diagnosis, treatment guidelines and alternative treatment options for PN in India. The group of experts arrived at consensus-based recommendations for (a) simple steps for diagnosis and (b) treatment as per the guidelines and treatment options used in clinical practice in India. Recommendations based on consensus on PN management in India were developed. The experts developed a simple, four-step, clinical diagnostic checklist as a guidance tool to help improve the diagnosis and identification of the cause of PN by primary care physicians. For treatment, the experts recommended that in addition to symptom management, treatment of underlying cause and restoration of nerve health is a vital step in PN management. The importance of alternative treatment options such as neurotropic B vitamins and alpha-lipoic acid, in the treatment of PN and nerve health restoration was highlighted. The expert group also discussed prophylactic, therapeutic and maintenance treatment options in different patient settings. This consensus statement is aimed at providing useful clinical guidance to primary care physicians on PN diagnosis, treatment and management. Nonetheless, there is a need for further experience-based cross-speciality deliberations to formulate holistic guidelines for the management and treatment of PN in India.**

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Peripheral neuropathy (PN) is a commonly encountered disorder of the nervous system in the Indian population. The disease process can start from systematic illnesses, toxins etc and leads to impairment and damage of nerves[1]. Its association with a myriad of aetiological factors makes it a diagnostic and therapeutic challenge to treating physicians, especially for those in primary care. While diabetes is recognised as the most common cause of PN, alcohol misuse, infectious diseases, deficiencies of neurotropic vitamins, toxins and many other causes, are documented to cause PN with varying prevalence numbers. Additionally, a significant number of patients suffer from PN without any identifiable cause (idiopathic neuropathy) which further complicates effective management for the treating physician[2,3]. A further barrier is the poor documentation of the disease and its respective causeleading to a lack of information on the high risk populations and possibly suffering patients.

In the Indian subcontinent, diabetes is still the most common cause of PN. However, contrary to the global picture, where diabetes remains the leading cause, in India other causes are also highly prevalent, albeit not very well documented. In view of the wide-spectrum of agents/

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factors involved in the aetiology of PN, primary care physicians (PCPs) as well as specialists like neurologists, dermatologists, endocrinologists, orthopaedics etc. play an important role in the management of PN[4,5].

In order to better understand the causes and management of PN in India and to develop a multi-disciplinary expert consensus statement providing guidance to PCPs for the diagnosis and treatment of PN in India, a group of experts including neurologists, diabetologists, and endocrinologists, formed a consensus panel and met in November 2017 in Chennai.

Although therapeutic advancement in treatment of PN is rapidly progressing, due to the insidious nature of this disease and lack of protocol/guidelines/consensus among physicians, treatment can be frustrating for both physicians and patients alike.

In India, the scientific literature on PN, to which physicians can refer for best practice, is inconsistent with regards to aetiological, diagnostic, and evidence-based recommendations[1,6-9].

This paper summarises outcomes of the discussions undertaken by the aforementioned experts along with their recommendations for best clinical practices as a guidance for PCPs and physicians from different specialties.

## *Epidemiology of Peripheral Neuropathy in India :*

**Underestimated Burden of PN and its Clinical Relevance**

PN is generally associated with symptoms of numbness, stabbing pain, tingling and burning sensation with deranged neural conduction, often affecting nerves in the extremities but also other parts of peripheral nerves. Prevalence of PN varies as a function of casual factors including the prevalence of underlying disease specifically associated with PN and environmental risk factors. Globally, different sources report different prevalence levels due to non-uniformity in case definition and case ascertainment[10,11]. Studies in different countries also report adopting the World Health Organization (WHO) protocol for diagnosis of PN which revealed variable prevalence across countries, ranging from 0.8 to 32.5 per 1,000 population[1,12,13-15].

The epidemiological picture of PN in India is somewhat different from the global context. The expert panel speculated, this may be due to presence of multiple ethnicity, culture, varied environmental factors etc. Community based studies in India show a prevalence that ranges from 0.5 (0.05%) to as high as 240 per 1,000 (24%) population[1]. The older population is affected more (30-40%) as compared to younger population (2-8%), as a result of higher prevalence of other diseases, medication intake, and other cumulating factors which are associated with the ageing process[1,16]. Geographically, significant variation in prevalence has been reported between different regions and also in urban versus rural areas[1]. While this may be attributed by location specific environmental factors, lack of clinical documentation could be another important factor leading to this observation.

The expert group at the consensus meeting expressed their concern that in India, PN is likely to be significantly under-diagnosed and hence, the burden of disease underestimated. They acknowledged thatthere is a lack of sufficient data available to understand epidemiology of PN in India creating a burden for PCPs not having a clear picture on the patients they have to identify. Negligence of mild and nagging symptoms of PN by physicians or lack of awareness on the 'at risk' population were identified as major causes for under-diagnosis of PN in India.

**Aetiology of PN is Different in the Indian Context**

Epidemiology of PN suggests involvement of a number of causative agents or pathological processes. The expert panel agreed that identifying the most common causes of PN is the first key step for PCPstowards improving the diagnosis of PN. Many studies outside India suggest that the most common cause of neuropathy as well as polyneuropathy is diabetes (34.8%), followed by alcoholic neuropathy (11.1%). The aetiology remains unknown inapproximately 22% of cases[17].

In the opinion of the experts, diabetes is the most common cause of PN in India as well. However, while prevalence of PN in diabetic patients was more than 50% in western countries[18], literature reports a prevalence of 10 to 32% in India[1]. A range is reported as different outcomes are documented in different sources, which might reflect the heterogeneity of the population across India. Whether the number differs from the globally reported prevalence due to a higher number of undiagnosed and unreported PN cases remains unknown.The experts highlighted that the documentation is not consistent and not appropriate. In their opinion diabetic patients have a higher prevalence of neuropathy than those in developed countries due to greater prevalence of concomitant causes. Furthermore, experts anticipate the incidence of PN to rise in India, as a result of increasing number of diabetic patients from 73 million in 2017 to 134 million expected in 2045[19].

Experts further highlighted that in India, unlike in western countries, infectious diseases are still highly prevalent and are one of the common causes of PN. As per available literature, inflammatory disorders like GuillainBarre Syndrome (GBS), and infectious diseases, primarily HIV and leprosy, have been found most commonly associated with PN[1]. Certain anti-retroviral drugs can also induce neuropathy[20,21]. India alone contributes to more than 55% of the global burden of leprosy, which is primarily a disease of peripheral nerves, thus making it a common cause of PN in this country[22]. Also common, and more prevalent

than in developed countries, is post-herpetic neuralgia, due to the lowervaccination rate[23].

Alcoholic abuse and environmental exposure to toxic agents like arsenic, lead, mercury and organophosphates are significant contributors to incidence of PN in India[1].

Another major cause of neuropathyis deficiency of neurotropic vitamins due to different reasons such as malabsorption and dietary restrictions[24]. In 29-40%[25-27] of the Indian population adheres to a strict vegetarian diet which leads to nutritional deficiencies, particularly vitamin B12 (cobalamin), thus affecting nerve health. Prolonged exposure to certain drugs can also deplete the B vitamin reserves in the body, leading to drug-induced deficiencies. Particularly in India, high prevalence of diseases like diabetes, tuberculosis and hypertension sees rampant use of B vitamin depleting drugs like metformin, isoniazid/cycloserine and loop diuretics, respectively[28-31]. An indicative list of causes of PN is provided in Table 1[1,17-35].

## Recommendations for Diagnosis :

**Preliminary Investigation of Patients Suffering from PN is Essential**

The experts, during the consensus meeting, acknowledged that an effective treatment of PN starts with an accurate and timely diagnosis combined with appropriate and prompt management. This necessitates the need for effective communication between physicians and their patients to drive better treatment outcomes. As such, awareness among physicians about the benefits of timely diagnosis and treatment was agreed to be of considerable value. According to a study, the median duration of symptoms was found to be 5.9 months prior to its presentation[36]. The experts estimated that the average time taken by PN patientsto get diagnosed is 5 years or more. It was acknowledged that diagnosis is a burden for majority of physicians due to limited time and availability of tools in primary care setting. According to estimation of the experts, 95% of the population in India has only access to primary care physicians and just 5% to specialists. The experts agreed that diagnosis can be done with simple tools. Developing a simple clinical checklist as a guidance tool focusing on clinical symptoms, medical history and sensory investigation and not requiring a lot of time, would improve the diagnosis of neuropathy by PCPs. Time is a critical factor in the healthcare system in India for both, patients and physicians.

To this end, the expert group proposed four basic steps in diagnosis of PN which can be used along with a simple sensory testing procedure (Table 2).

In the opinion of the experts, careful documentation of family, occupational, medical or previous treatment history as well as assessing any relevant drug abuse/addiction history and other factors are keyto identify the causative agents and aid in an accurate diagnosis (Step 1 – Table 2).

Presence of burning, tingling sensation or numbness in extremities indicates PN. Similarly, symptoms like hypersensitivity to touch, unsteady gait, history of fall, and presence of soreness/ulcer without any definite cause give cluestowards the diagnosis. Clinical signs differ depending on the impaired nerve which can be sensory, autonomic or motor nerves.Therefore, clinical evaluation of signs and symptoms was ascertained to be the next important step for diagnosis(Step 2.1 – Table 2).

Site and pattern of nerve involvement can also give a diagnostic clue to physicians. Nerve involvement can be single or multiple, large fiber or small fiberwhich have different conduction capacities.Localizing the pattern was also considered important by the expert group. For example, symmetrical distribution of symptoms would be a very typical sign of neuropathy (Step 2.2 – Table 2)[37].

The time line or the course of development of signs and symptoms classifies PN into three categories i.e. acute (<4 weeks), sub-acute (4-12 weeks) and chronic (>12

Table 1 — *Indicative list of causes of Peripheral Neuropathy in India*[1,17-35]

| Disease-induced PN | Deficiency-induced PN | Drug-induced PN |
|---|---|---|
| • Diabetes (10-32%)<br>• Guillian-Barre Syndrome (38.2-73.8%)<br>• HIV (>50%)<br>• Leprosy (4-8%)<br>• Post-herpetic Neuralgia<br>• Hypothyroidism<br>• Glucose-intolerance<br>• Chronic Kidney Disease (65%)<br>• Carpel Tunnel Syndrome<br>• Cancer-related neuropathy (15-50%)<br>• Critical illness related Neuropathy (25-36%)<br>• Chronic inflammatory demyelinating polyneuropathy<br>• Vasculitic neuropathy<br>- Rheumatoid arthritis (39.2%)<br>- Systemic lupus erythematosus (3.3%) | PN caused by low levels of neurotropic B vitamins due to:<br>• **Nutritional deficiencies**<br>- Malnutrition<br>- Vegetarianism<br>- Tropical ataxic neuropathy<br>- Deficiencies due to GI malabsorption<br>• **Drug-induced deficiencies**<br>• Metformin-induced vitamin B12 deficiency<br>• Isoniazid-induced vitamin B6 deficiency<br>• Vitamin B3 deficiency due to Loop Diuretics<br>• Others | • Cardiovascular agents<br>- Statins<br>- amiodarone<br>• Chemotherapy agents<br>- Vince-alkaloids (vincristine, vinorelbine, etc)<br>- Taxanes (paclitaxel, docetaxel)<br>- Platinum compounds (cisplatin, oxaliplatin, carboplatin)<br>• Antifungal agents-Triazoles (itraconazole, voriconazole) |
| **Other causes** | | |
| • Heavy metals (such as lead, arsenic, mercury, etc) through<br>- Environmental exposure<br>- Herbal medicines<br>• Organophosphates<br>• Alcohol (13-66%)<br>• Smoking (including passive smoking and chewing tobacco)<br>• Hereditary Neuropathies<br>- Charcot–Marie–Tooth disease (4.8%)<br>- Amyloid neuropathy | | |

weeks). For example, vasculitis-related neuropathy presents as acute symptoms mostly within 1 to 3 days, symptoms of acute inflammatory demyelinating polyneuropathy (AIDP) peak within 4 weeks of onset, while chronic inflammatory demyelinating polyneuropathy (CIDP) takes more than 8 weeks. Experts recommended that understanding the course of the disease minimises diagnostic choices and, therefore, helps in accurate diagnosis and management procedure (Step 2.3 – Table 2).

Presently, standardised assessment tools are not available for diagnosis of PN in India. Expert group further recommended the inclusion of simple and easy to perform 2-minute sensory tests (Step 3 – Table 2) as a standard diagnostic procedure for PN which should be practical and feasible for all GPs. Sophisticated/ state of the art diagnostic or laboratory facilities may not be easily accessible in a resource-poor nation like India. The recommendation includes temperature and pinprick sensation assessment for small nerve fibre function and assessment of vibration sensation using 128 Hz tuning fork for large nerve fibres. Additionally, use of 10-g monofilament test for screening of large nerve fibre function in patients with diabetic neuropathy is also recommended. Physicians can even use very simple tools such as a cotton wool piece, small brush, toothpick, a wooden stick or a feather to test sensation impairment when they do not have a tuning fork or monofilament. These tests are in line with published literature where simple sensory tests and screening tools applied by general physicians have been used to facilitate preliminary assessment and for diagnosis of PN in the primary care setting[5,38-44]. In the current scenario, use of these simple tests/ screening tools was considered a practical solution for health care professionals at grass root level.

The final step recommended for diagnosis is to identify the cause of the presenting PN. It is important to determine the underlying cause and treat it accordingly in order to check the progression of symptoms and restrict further nerve damage (Step 4 - Table 2).

Table 2 — *Proposed Steps in Diagnosis of Peripheral Neuropathy for Clinical Practice in India*

| Steps in diagnosis | Description |
|---|---|
| Step 1 | **Careful analysis of medical history** (disease history, co-medications, etc) should be carried out. Examples of pertinent questions that should be asked are as follows (not an exhaustive list):<br>• Is there a history of Diabetes in your family?<br>• Is there a history of peripheral neuropathy in your family?<br>• Do you use tobacco in any form? Smoking Bidis/cigarettes/tobacco containing chews/Khaini/Pan Masalas/tobacco containing tooth powders?<br>• Do you use alcohol? How much and how often in a month?<br>• Do you take medicines from Ayurvedic/Unani medical practioners?<br>• What is your occupation? Is there any exposure to chemicals?<br>• Are you exposed to toxin /heavy metal laden well water?<br>• Is there a history of leprosy amongst your family/associates?<br>• List the medications that you regularly use. |
| Step 2 | **Checking for currently experienced symptoms, localisation of symptoms and determining time course** |
| 2.1 | Checking for symptoms experienced<br>• Do you experience symptoms such as tingling, burning, numbness, etc in your upper or lower extremities (fingers, hands, toes, and feet)?<br>• Do you feel pain even when lightly touched in a certain area?<br>• Do you experience a sense of dizziness? Especially in the dark?<br>• Have you had falls?<br>• Do you feel hesitant or unsteady on walking?<br>• Do you ever find blisters/sores/cracks/ulcers on your feet whose cause you do not know or which you did not notice when they developed?<br>• Do you sometimes discover foreign objects in your shoes that you had not been aware of?<br>• Any other unusual sensation (Please describe) |
| 2.2 | Localisation of symptoms, if reported<br>• Are these symptoms in the upper or lower limbs, or both?<br>• Can you draw the areas of your body where these sensations occur? (Human body sketch to be provided for shading in affected areas by the patient, as it is sometimes difficult for a patient to specify the location by verbal description) (Figure 1)<br>• Are they on the right side or left side or both sides?<br>• Do you ever feel difficulty in putting on your shoes or slippers? |
| 2.3 | Determining the time course of symptoms<br>• When did you first experience the symptoms described by you?<br>• Do these symptoms increase in cold weather/hot weather/summer/winter?<br>• Has the intensity of these symptoms increased since their onset?<br>• Are these symptoms persistent? |
| Step 3 | **Conduct sensory testing**<br>• Temperature or pinprick sensation (small fibre function)<br>• Vibration sense using a 128Hz tuning fork; sensation test using a 10-g monofilament (large fibre function) |
| Step 4 | **Identify probable cause(s) of the neuropathy, if possible**<br>• Ascertain whether the neuropathy is due to existing systemic conditions (infections; other neurological conditions like GBS, etc; metabolic causes like diabetes, nutritional deficiencies, etc)<br>• Determine if there might be deficiency of neurotropic vitamins on account of treatment-related factors such as use of metformin (diabetes), isoniazid (tuberculosis), etc<br>• Look for nerve thickening/skin patches suggestive of leprosy<br>• If the cause of neuropathy cannot be determined, consider specialist referral for further diagnosis |

Given many cases of PN are a result of other systemic conditions, the importance of seeking expert help and accurate referral services for such patients cannot be denied[40]. In this context, the expert group proposed an algorithm incorporating diagnosis and referral services of patients suffering from PN with associated symptoms of neuropathic pain (Fig 2).

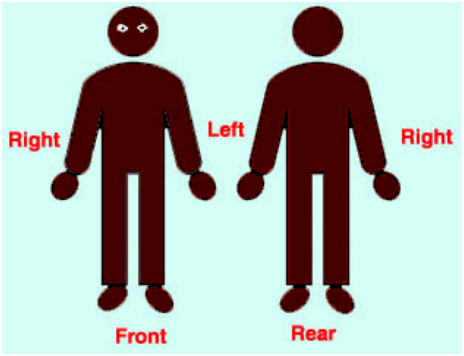


Fig 1 — Proposed Diagnostic Tool to Aid in Localization of Symptoms

Treatment and Prevention of Peripheral Neuropathy

Treatment of PN is still unclear for many GPs in India due to lack of well-structured treatment guidelines. Current international guidelines primarily focus on management of neuropathic pain, and not targeting the underlying cause of the disease. No guidelines exist for non-painful symptoms like tingling, numbness or autonomic symptoms etc. This leaves many PN patients unsatisfied and untreated, withpoor quality of life or treated with inappropriate agents[40,45,46].

The experts agreed that the guidelines for neuropathic pain management devised by international associations like American Diabetic Association (ADA) and International Association for the Study of Pain (IASP) are commonly being followed for managingpain associated with PN. However, these guidelines may not be fully applicable to the clinical practice in India due to issues pertaining to accessibility and/or cost of therapies. In addition, for a developing country like India, where toxic, infective and metabolic causes contribute heavily to the burden of neuropathy, treatment guidelines should take into consideration these elements as well. PN was recognised as one of the few conditions for which Indian clinical guidelines do not exist, and hence reinforced to the expert panel that an unmet need exists for guidance on the treatment and management of PN for GPs/PCPs across India.

Different recommendations from international organizations, like the Neuropathic Pain Specialist Interest Group of IASP (2007) and the European Federation of Neurologic Society (2010), suggest line-wise treatment modalities for neuropathic pain. They also recommend specific pharmacotherapies depending on different underlying causes of PN[47,48]. According to mentioned guidelines, first line treatment options are pregabalin and gabapentin, second line are tramadol and capsaicin 8% patch while opioids are used as a third line option. Worldwide, particularly in Western countries, the first line treatments are commonly used agents for the treatment of neuropathic pain. Similar clinical practice is followed in India as well, especially in patients treated by specialists. However, this differs from the situation in primary care where access to these treatment options might be limited.

The above referencedtreatment options offer effective symptomatic relief in most patients and focus on management of neuropathic pain. They do not contribute to restoration of nerve functionality and health. Additionally, numerous side effects have been found associated with the use of these medicines which can become a treatment burden for the patient.

It was agreed by the experts that instead of focusing on pain management, the primary goal should be to identify the cause of PN and treat the underlying aetiology. If the underlying cause is treated, like in cases of diabetic neuropathy, toxic exposure or vitamin B12 deficiency, further progression of the disease might be slowed down or even avoided. However, in cases where the cause cannot be identified, i.e. idiopathic PN, or in patients suffering from symptoms even after treatment, symptom management becomes the primary and the only approach to provide relief to the patients[49,50]. Nonetheless, in both scenarios, restoration of nerve health was agreed to be the next vital step in the treatment algorithm.

To this end, the experts highlighted the importance of alternative treatment options that include neurotropic B vitamins, alpha-lipoic acid (ALA) and other agents. These therapies have been shown to provide symptomatic relief in earlier stages of neuropathy, are well tolerated and additionally, play a significant role in nerve regeneration[11,51].

## *Alternative Treatment Options :*

### (1) Neurotropic B Vitamins

There was general consensus that the majority of physicians across relevant therapeutic disciplines are prescribing vitamin B combination products based on clinical experience of treating PN. Dosage, formulation and combi-

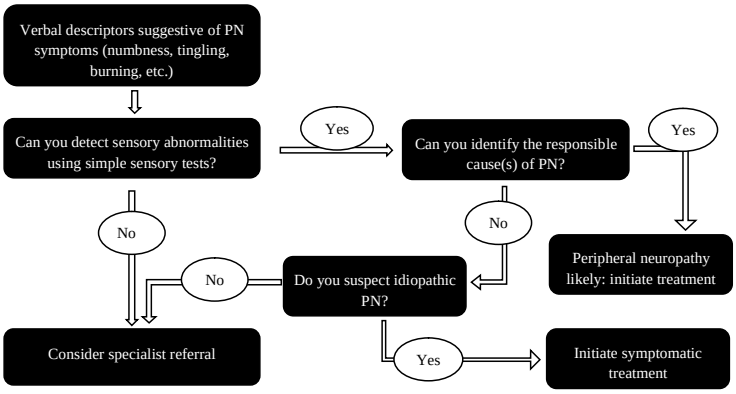


Fig 2 — Proposed Algorithm for Diagnosis and Referral of Patients presenting with Peripheral Neuropathy Symptoms in India

nation of B vitamins is selected on the basis of individual patient case requirements. The experts agreed on the benefits of using B -vitamin combination over mono-therapy approaches specifically complexes of B1/B6/B12 as these three vitamins are documented to play an important role in nerve health and are well-established globally for treatment of PN.

Vitamin B12 (cobalamin) improves the symptom of PN by regenerating or re-myelinating nerves through increased protein synthesis. Selective blockade of sensory nerve conduction by vitamin B12 also helps in alleviating the symptoms[52]. Deficiency of vitamin B12 has been shown to result in increased levels of neurotoxic cytokine TNF-alpha and decreased levels of neurotropic epidermal growth factor and neurotropic cytokine IL6 leading to PN symptoms[53]. Supplementation by vitamin B12 corrects the deficiency and benefits PN patients. Studies on vitamins like vitamin B1 (thiamin) and B6 (pyridoxine) also suggest their role in PN[51,54-58]. Biochemically, vitamin B1 acts through diacylglycerol protein kinase C pathway, glycation end-product formation pathway and the hexamine pathway to reduce pain. It also modulates neural excitability and Na+ currents in injured dorsal root ganglions to improve symptoms of neuropathy[59-61]. Role of vitamin B6 in PN includes inhibition of presynaptic transmitter release from nociceptive afferent fibres carrying excitatory input to the spinal dorsal horn and thalamic neurons[62]. Vitamins B1, B6 and B12 act synergistically in terms of their mechanism of action, thus complementing the neurotropic activity of each other. Use of combination of these neurotropic vitamins has been shown to improve the nerve conduction velocity and also improves the vibration threshold[63]. The fixed dose combination of these vitamins has been found to be well-tolerated and effective for the treatment of mild to moderate PN of various aetiologies[64]. Evidence suggests thatcombination use of vitamin B1, B6 and B12, was also efficacious in more than 80% of cases of diabetic neuropathy[65,66].

**Posology of Neurotropic B Vitamins**

The expert group recommended that parenteral approaches such as injectable formats be prescribed for the treatment of hospitalized patients with neuropathy eg, diabetic PN[67] and acute PN symptoms. Similarlyuseful for patients with neurological symptoms related to acute neuralgia eg, trigeminal or plantar neuralgia[68], acute symptoms related to herpes zoster, lumbago, sciatica, shoulder-arm syndrome[52], diabetic cranial neuropathy and neuropathic pain associated with cancer pain/cancer treatment or in any other case where rapid relief is required. In addition, injectable is preferred in patients with impaired absorption due to gastrointestinal disorders such as Irritable Bowel Syndrome (IBS), colitis, H pylori infection, gastritis etc[69,70] to ensure a fast restoration of B vitamin levels. However, evidence shows that high dose oral vitamin application can also restore the levels as effectively as injections[71]. In various studies, oral dosages of 1500 mcg and higher were found to be therapeutically useful[11,64,70,72]. The decision to administer injectable and/or oral therapy should lie with the PCP based on their assessment of what will work best for patients based on their current status and the desired

Table 3 — *Recommendations for Prophylactic, Therapeutic and Maintenance Therapies of Peripheral Neuropathy Patients*

| | | Prophylactic | Therapeutic | Maintenance |
|---|---|---|---|---|
| Diabetic Patients* | Patient Segment | • Patients at risk of developing PN, currently not showing PN symptoms, including:<br>• Asymptomatic patients, at high risk of vitamin B deficiency<br>• Asymptomatic patients who frequently take tuberculosis drugs which cause deficiency<br>• Orthopedic patients, facing mild symptoms related to sciatica pain, low back pain, CTS<br>• Older patients<br>• Alcoholics | • Patients presenting acute/moderate to severe symptoms of neuropathy<br>- With neuropathic pain<br>- Without neuropathic pain, but present moderate-to-severe numbness, burning, tingling, atrophy, etc.<br>• Patients hospitalized due to neuropathy<br>• Patients with mild-to-moderate symptoms | • Patients who feel better with PN treatment, may be still suffer from mild-to-moderate symptoms<br>• Patients who have been cured and want to avoid reappearance of PN symptoms<br>• Chronic or acute PN patients with mild symptoms |
| | Recommendation | • Low therapeutic dose of neurotropic B vitamins<br>• Low dose of other alternative therapies | • For neuropathic pain relief, pregabalin or gabapentin as first line.<br>• Therapeutic doses of neurotropic B vitamins:<br>- Injectable is preferred in acute cases or GI malabsorption or more control is needed (e.g. a rural primary care center)<br>- In other cases, orals with high dose neurotropic B vitamins<br>• High dose of other alternative therapies | • Maintenance dose of neurotropic B vitamins (preferably orals) or other treatment options |
| | Patient Segment | • Patients diagnosed with pre-diabetes<br>• Asymptomatic patients taking metformin<br>• Asymptomatic patients, at risk of vitamin B deficiency | • Patients presenting acute/moderate to severe symptoms of neuropathy<br>- With neuropathic pain<br>- Without neuropathic pain, but moderate-to-severe numbness, burning, tingling, etc.<br>• Patients hospitalized due to neuropathy<br>• Patients with mild-to-moderate symptoms | • Patients who feel better with PN treatment, but still suffer from mild-to-moderate symptoms<br>• Patients who have been cured and want to avoid reappearance of PN symptoms<br>• Chronic PN patients with mild symptoms |
| | Recommendation | • Low dose of neurotropic B vitamins<br>• Low dose ALA (100mg daily), especially recommendable in patients with high CVD risk<br>• Low dose of other alternative therapies | • For neuropathic pain relief, pregabalin or gabapentin as first line.<br>• Therapeutic doses of neurotropic B vitamins:<br>- Injectable is preferred in acute cases or GI malabsorption or more control is needed (e.g. a rural primary care center)<br>- In other cases, orals with high dose neurotropic B vitamins<br>• Therapeutic dose of ALA (600mg daily)<br>• High dose of other alternative therapies | • Maintenance dose of neurotropic B vitamins (preferably orals) or other treatment options<br>• Maintenance dose of ALA (100-300mg daily) |

*Experts recommended prescribing ALA to non-diabetics patients also, owing to its anti-oxidative properties.

Note : Dose, treatment duration, formulation is as directed by the physician.

outcome. PCPs can ensure better compliance control (eg, a rural primary care centres) with injectable formulations and in cases where they do not foreseeproblems with compliance, oral pills can be prescribed. In other mild-to-moderate cases of PN, oral doses of vitamin B12 in the range of 1000-1500 mcg are able to impart therapeutic effect[73-76].

In cases of chronic conditions leading to neuropathy, like diabetes, the dosing pattern can determine the patient's adherence to medications. Long term diabetic patients may require multiple dosing of diabetic medications. In addition, they may also require additional drugs like anti-hypertensive orcholesterol reducing agents etc. depending on associated co-morbidities. Further addition of multiple dose schedule of neurotropic vitamins can hamper compliance[77]. In clinical practice, it is seen that prescribing vitamin B 12 (500 mcg) thrice daily (TID) decreases compliance after 6 months. The twice daily (750 mcg) (BD) regimen improves compliance while once daily (1500 mcg) (OD) dosing demonstrates highest patient compliance. It was recommended to give multiple dose of vitamin B12 during the treatment period followed by single dose regimen for maintenance.

**Monitoring of Neurotropic B Vitamin Levels**

Regular follow-up and monitoring of patients taking higher doses of vitamin B6 (>50 mg) for periods of more than 6 months is recommended.In various long-term clinical studies, it was established that both vitamins B1 (100 mg/day or more)[67,78,79] and B12 (up to 6000 mcg/day)[80,81] have favourable safety profile and are very well tolerated over a long treatment period. No upper limits (UL) are established for vitamin B1 and B12. (82) However, in clinical practice in India, a safety concern exists among PCPs while prescribing prolonged high vitamin B12 doses (>2000 mcg). The experts recommend monitoring the patient with a high dose therapy for any side effects and potentially of vitamin B12 levels if the patient experiences any side-effects with prolonged use. The panel recommended Mean Corpuscular Volume (MCV) as an efficient, reliable and cost effective test in quantifying vitamin B12 level in the body instead of assessment of serum vitamin B12 for diagnosis and monitoring[83].

The experts agreed that guidance on the correct dose, duration of use and even combination of B vitamins should be provided based on general patient type and associated clinical status e.g. acute vs chronic[24,84]. Additionally, the expert group suggested prophylactic, therapeutic and maintenance usage in different patient settings (Table 3).

**(2) Alpha-Lipoic Acid (ALA) in Treatment of PN**

Evidence from clinical trials suggest that diabetic patients with neuropathy treated with ALA daily have reduced numbness, pain and paraesthesia. ALA is discussed to improve insulin sensitivity and is therefore most suitable for diabetic PN patients[85]. ALA can also reduce levels of interleukin 6 and plasminogen activator 1 in plasma, suggesting that it may improve endothelial dysfunction through anti-inflammatory and anti-thrombotic mechanisms. It is notable that ALA may improve nitric oxide-mediated endothelium-dependent vasodilation in diabetic patients[86]. ALA may also have the potential beneficial effect in cases with high CVD risk, by decreasing the plasma level of ADMAconsidering that ADMA is an independent risk factor for cardiovascular outcome in ESRD patients[87].

**Posology of ALA**

A meta-analysis from 6 randomised controlled trials concluded that ALA, administered intravenously for 3 weeks at a strength of 600 mg per day, resulted in significant clinical improvement[88]. Additionally, an oral dose of 600 mg /day is also reported to have the optimal risk/benefit ratio[89,90]. Evidence exists which indicates that 300 mg ALA is capable of exerting a therapeutic effect and benefit has also been observed with doses of more than 600 mg, administered orally for at least 5-8 weeks[88,91-93]. However, high ALA dose (>600 mg/day) has been found to increase gastrointestinal side effects like nausea, vomiting and dizziness[73,88,91]. During the sub-acute or chronic phase, maintenance dose of 300 mg could be used. In line with current evidence, expert group suggested that ALA should be prescribed alone or in combination with vitamin B12 for diabetic PN (Table 3). Experts were in consensus that patients with acute diabetic neuropathy should be prescribed 600 mg ALA initially for 3-months duration followed by 100-300mg ALA in maintenance. It is important to note that the 100 mg dose of ALA is prescribed only during maintenance for its anti-oxidative neuro-protective benefits and not for therapeutic benefit.

It has been observed that ALA is also prescribed to non-diabetics in practice primarily owing to its anti-oxidant properties. However, there is a dearth of scientific evidence for the effective use of ALA in non-diabetics.

**(3) Other Alternative Treatments for PN**

In addition to the above listed therapies, several other alternative treatments have been identified and with varied efficacies established in different PN patient segmentsthrough various clinical studies. The potential mechanisms by which these therapies act, include deficiency correction, oxidative stress reduction, nerve growth factor stimulation etc[11]. Therapies like Acetyl-L-Carnitine, opioids, botulinum toxin A, mexidol, reflexology etc., have shown improvements in diabetic PN symptoms in some studies[11,92,93]. Preliminary studies with therapies involving treatment or supplementation with Acetyl-L-Carnitine, vitamin E, minerals like calcium and magnesium, glutathione, glutamine, N-Acetyl-Cysteine etc have also shown positive results for chemotherapy-induced PN[11,94,95].

**Vitamin B Deficiency :**

The experts acknowledged that Indian patients are likely to have deficiencies for multiple B vitamins owing to various underlying causes including malnutrition, veg-

etarianism, alcoholism and drug-induced or 'iatrogenic' causes(due to a disease) eg pernicious anemia[96]. The clinical manifestations for vitamin B deficiency varies drastically from mild conditions such as neuropathy with symptoms like ataxia, sensation disturbance, weakness, etc. to more severe disorders such as combined sclerosis of the spinal cord, haemolytic anaemia and even pancytopenia[96].

Although India is taking several measures to fight against malnutrition, micronutrient deficiency is widespread in India. In 38.7% of Indian children aged 0–59 months are stunted, and stunting is prevalent across all socioeconomic groups. 44–66% of the affluent schoolchildren had vitamin A, B2, B6, B12, and C deficiencies[97]. Median intakes of all nutrients, except vitamin B1, were below the RDAs for Indians. Another significant reason of high prevalence of vitamin B deficiencies in India is the significantly higher number of vegetarians as compared to other western countries[51,69,98].

Chronic diabetes or gastritis patients are very often poly-medicated; intake of several active ingredients can lead to drug-interactions leading to vitamin B deficiency. Long-term use of metformin, widely used as a first-line treatment for type 2 diabetes in India, can cause vitamin B12 deficiency[28-30,54,96,99,100]. Therefore, metformin treatment should be supplemented with an adequate dose of vitamin B12in type 2 diabetes patients. Tuberculosis (TB) drugs likeisoniazidare linked with vitamin B6 deficiency. According to World Health Organization TB Statistics, 2.79 million new TB cases, ~27% of worldwide new cases, were estimated in 2016[101], indicating a very heavy usage of TB drugs in India. Use of H2-antagonists such as ranitidine, cimetidine and proton pump inhibitors such as omeprazole are significantly associated with vitamin B12 deficiency[102]. Prolonged treatment with loop diuretics is associated with urinary loss of vitamin B1 and deficiency[31]. Treatment with anticonvulsants including phenobarbital, primidone, pregabalin andtopiramate is associated with vitamin B6 and B12 deficiency[103,104]. Vitamin B12 deficiency is common in patients with pernicious anaemia and elderly patients and its incidence increases with age[95].

A significant portion of the Indian population is at high risk of developing deficiencies of multiple B vitamins, and therefore, remains at risk of developing PN and should be monitored carefully.

While vitamin B12 can be measured through tests, those for measuring vitamin B1 and B6 are either not accessible for the patient due to availability or costs or not established. The experts agreed on the benefits of using combination of B1/B6/B12 vitamins in patients where a deficiency is suspected due to a present risk, symptoms or other factorsas cautionary measure even without quantifying levels in order to prevent further development of diseases affecting the nervous system or other health areas.

## *Conclusion :*

The burden of PN in India is significant due to higher prevalence of diabetes cases, nutritional deficiencies, infectious diseases, and exposure to toxic substance in India as compared to developed countries. In light of this fact, primary care physicians should carefully evaluate underlying causes by documenting complete patient history and utilizing available diagnostic facilities to confirm diagnosis of PN. Management should be focussed on treating the underlying cause and symptomatic relief, followed by restoration of nerve health.First line pharmacological treatments like pregabalin and gabapentin show a higher efficacy in neuropathic pain, and expert group was in consensus that judicial use of these drugs will definitely ameliorate neuropathic pain symptoms. Neurotropic vitamins like vitamin B1, vitamin B6 and, most importantly, vitamin B12 are recommended in the treatment of PN, considering their role in nerve regeneration. Alpha-lipoic acid is also considered effective in treatment especially in DPN, owing to its antioxidant properties.

This advisory board meeting was an initial yet important step towards bringing multi-disciplinary experts on a common platform to discuss the management of PN in India. While the meeting outcomes provided useful guidance on PN diagnosis, treatment and management, more of such experience-based cross-speciality deliberations are required to formulate holistic guidelines for the management and treatment of PN in India.

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