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Original Research Article

Expert Perspectives on Prescription Practices and Management Strategies for Neuropathy and Vitamin B12 Deficiency in Indian Settings

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Abstract: ***Objective*****:** To gather expert opinion regarding prescription practices and management strategies for neuropathy and vitamin B12 deficiency with a special focus on methylcobalamin among clinicians in Indian settings. ***Methodology*****:** This cross-sectional study utilized a 24-item, multiple-response questionnaire to gather expert opinion from specialists in managing neuropathy and vitamin B12 deficiency. The survey encompassed questions about current prescription practices, clinical observations, preferences, and experiences related to managing neuropathy and vitamin B12 deficiency in patients in routine settings. ***Results*****:** The survey included 81 experts, with more than half (62.96%) of clinicians identifying diabetes as a significant confounding factor for neuropathy in patients. As indicated by 46% and 44% of the clinicians, an appropriate diet for nutrition and maintaining glycemic levels helps to overcome the progression of neuropathy. A significant proportion of experts (60.49%) reported that 26% to 50% of patients with neuropathy have vitamin B12 deficiency. Additionally, 73% of clinicians noted that diabetes mellitus is a common co-morbid condition with vitamin B12 deficiency. In patients with neuropathy complications, 74% of clinicians preferred benfotiamine alongside vitamin B12. As stated by 44% of clinicians, besides those patients with neuropathy, elderly patients are also recommended with methylcobalamin 1500 mcg. About 43% of clinicians suggested a 12-week duration for prescribing a combination of benfotiamine and methylcobalamin for patients with neuropathy. Additionally, more than half (54.32%) of clinicians favored prescribing a combination of methylcobalamin 1500 mcg, pregabalin 75 mg, and nortriptyline 10 mg tablets to patients with chronic neuropathic pain. ***Conclusion*****:** The survey highlights diabetes as a significant factor in neuropathy management, emphasizing the importance of nutrition and glycemic control. A high prevalence of vitamin B12 deficiency is noted among diabetic patients with neuropathy, leading to recommendations for benfotiamine and methylcobalamin supplementation. Additionally, the use of combination therapy for chronic neuropathic pain demonstrates a comprehensive approach to improving patient outcomes.

Keywords: Diabetes, Methylcobalamin, Vitamin B12, Pregabalin, Nortriptyline, Neuropathy.

INTRODUCTION

Neuropathy is a condition characterized by damage to the peripheral nerves, affecting about 2.4% of the global population, with a prevalence of around 8% among the elderly.[1] Neuropathy may arise from various diseases, with diabetes mellitus (DM) being a common cause affecting up to 50% of patients with type 1 and type 2 DM [1, 2]. The Toronto Diabetic Neuropathy Expert Group defines diabetic neuropathy as symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations caused by chronic exposure to hyperglycemia and cardiovascular risk factors [3].

In India, diabetic neuropathy affects approximately 18.8% to 61.9% of individuals with DM [4]. According to recent estimates, 77 million people are affected by diabetes in India, and two-thirds of diabetic patients have clinical or subclinical neuropathy [5-7]. Neuropathy manifests through various symptoms including pain, tingling, and muscle

weakness, which can profoundly impact patients' quality of life. As shown in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial in a large cohort of patients with more advanced T2DM, 50% had confirmed diabetic neuropathy at baseline [8].

Vitamin B12 deficiency often causes blood and nerve problems, which can manifest as nerve pain and complicate diagnosis. This deficiency may lead to neurological disorders and painful neuropathy, resembling or accelerating diabetic neuropathy. Methylcobalamin, an active form of vitamin B12, is crucial for synthesizing methionine and S-adenosylmethionine, maintaining myelin integrity, neuronal function, proper red blood cell formation, and DNA synthesis. It aids in neuronal lipid synthesis and axonal nerve regeneration, with neuroprotective properties that improve neuropathic syndromes. Methylcobalamin functions in the production of myelin, which covers and protects nerve fibers, and it rejuvenates damaged neurons. Without enough methylcobalamin, myelin sheaths do not form properly, leading to nerve damage. It participates in methylation reactions to lower homocysteine levels, aids neurotransmitter synthesis, reduces inflammation, improves nerve conduction velocity, and prevents neuronal apoptosis [9-12].

Since vitamin B12 deficiency is common in T2DM patients, vitamin B12 supplementation is often combined with anti-glycemic therapy to achieve strict glycemic control. The American Diabetes Association (ADA) recommends periodic screening of diabetic neuropathy patients for vitamin B12 levels. Methylcobalamin is frequently prescribed for diabetic neuropathy, taken orally by both type 1 and type 2 diabetes patients, and its impact on neuropathy pain, particularly in homocysteine metabolism, has been examined [12-16]. In addition, long-term use of metformin has been associated with vitamin B12 (also known as cobalamin) malabsorption. Studies have reported that 5.8–33% of T2DM patients receiving metformin experience vitamin B12 deficiency. A recent meta-analysis of 29 studies involving 8,089 participants showed that patients receiving metformin therapy had a 2.45-fold increased risk (95% CI 1.74–3.44, P <0.0001) of developing vitamin B12 deficiency compared to non-metformin users [17-19].

Prescription practices play a pivotal role in the management of these conditions, requiring a careful approach to medication selection, dosage adjustment, and monitoring for potential side effects. Moreover, addressing vitamin B12 deficiency through appropriate supplementation and dietary interventions is crucial in preventing irreversible neurological damage and improving overall patient outcomes. The present cross-sectional survey aims to gather expert opinion on the prescription practice for the management of neuropathy in Indian settings.

METHODOLOGY

A cross sectional, questionnaire-based survey was carried out among physicians specialized in managing neuropathy in the major Indian cities from June 2023 to December 2023.

Questionnaire

The questionnaire booklet named MORE (Methylcobalamin in Neuropathic Pain: Expert Perspective Study) study was sent to the clinicians who were willing to participate in this study. The MORE study questionnaire consisted of 24-item questions primarily focused on current practices, clinical observations, and experiences related to neuropathy and vitamin B12 deficiency used in routine settings, specifically methylcobalamin, for managing neuropathy. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to leading clinicians in managing neuropathy in the month of March 2023 for participation in this Indian survey. About 81 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Practitioners were requested to complete the questionnaire without discussing with peers. A written informed consent was obtained from each clinician before initiation of the study.

Statistical Methods

Descriptive statistics were used to analyze the data, with percentages representing categorical variables. The distribution of each variable was illustrated using both frequency and percentage distributions. Furthermore, bar and pie charts were generated using Excel 2013 to represent the data findings (version 16.0.13901.20400) visually.

RESULTS

This study involved 81 clinicians, and more than half (61.73%) of them reported that on average, more than 20 patients are diagnosed with neuropathy in a month in routine practice. Almost 49% of the clinicians opined that around 51 to 75% of the patients with neuropathy are diagnosed with diabetes. The majority (66.67%) of the participants indicated that neuropathy is diagnosed equally in both genders. As reported by 52% of the respondents, neuropathy is diagnosed in

individuals aged between 50 to 60 years. According to 83% of the clinicians, numbness and tingling in the feet or hands are the most common symptoms observed in patients with neuropathy.

As reported by 41% of the participants, about 21 to 30% of the patients with neuropathy are obese, while 38% reported that only 11 to 20% of the patients are obese. More than half (62.96%) of the clinicians indicated that diabetes is the confounding factor for neuropathy in patients (Figure 1).

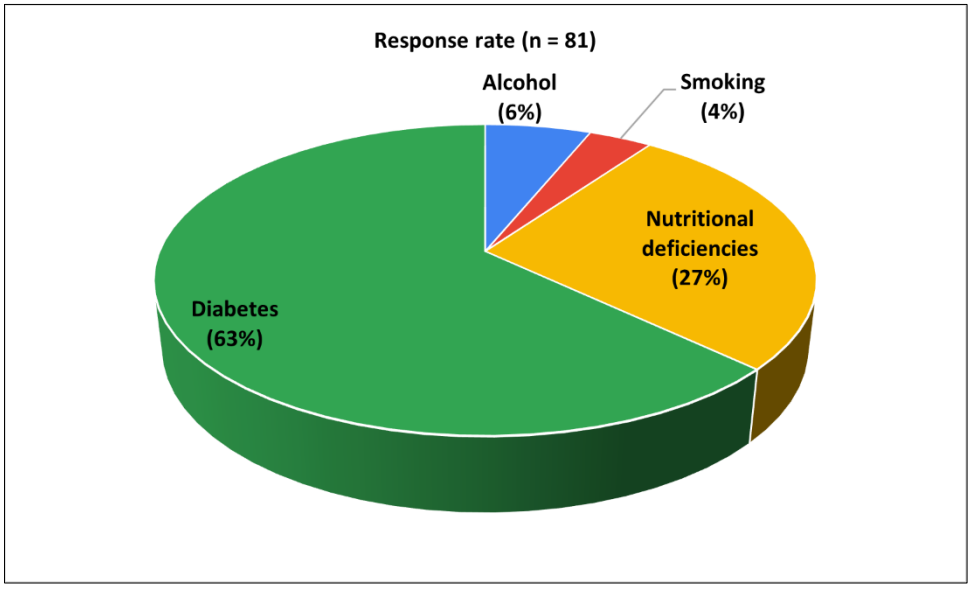

Figure 1: Distribution of response to the prevalence of confounding factors in neuropathy cases

As opined by 36% of the clinicians, around 21 to 30% of neuropathy patients consume a vegetarian diet. According to 46% and 44% of the clinicians, respectively, an appropriate diet for nutrition and maintaining glycemic levels are recommended to overcome the progression of neuropathy (Figure 2). Around 47% of the clinicians opined that about 21 to 30% of the patients with neuropathy have complications of disturbed sleep.

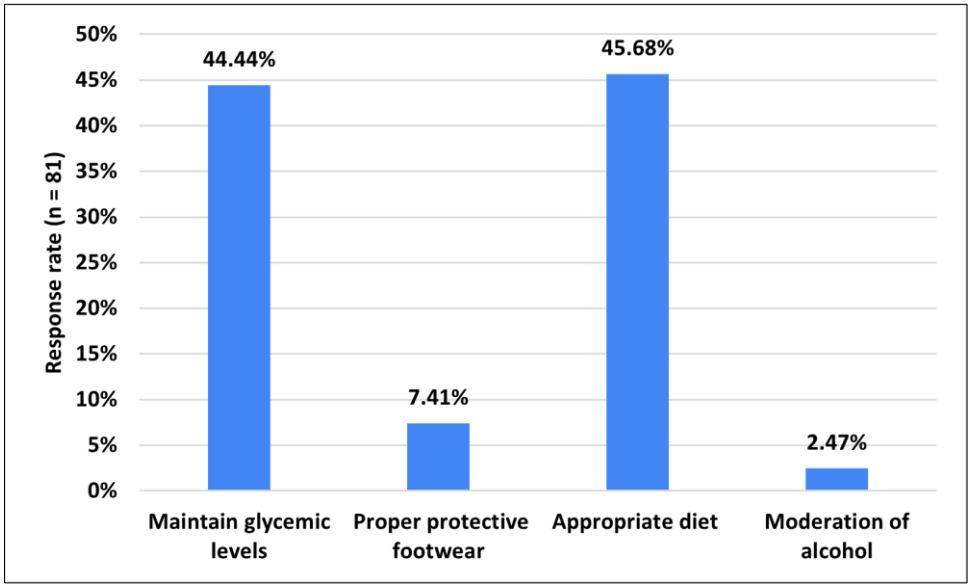

Figure 2: Distribution of response to the recommendations for overcoming the progression of neuropathy

A significant proportion (60.49%) of clinicians reported that 26 to 50% of patients with neuropathy have vitamin B12 deficiency (Figure 3). According to 53% of respondents, elderly patients are usually diagnosed with vitamin B12 deficiency. As indicated by 73% of clinicians, DM is a common co-morbid condition observed with vitamin B12 deficiency (Table 1). As reported by 46% and 60% of clinicians, respectively, about 21 to 30% of patients with vitamin B12 deficiency experience complications of burning and numbness of the feet. Additionally, 44% and 41% of clinicians reported that

intravenous (IV) injections and capsules are the most preferred formulations for patients with severe vitamin B12 deficiency.

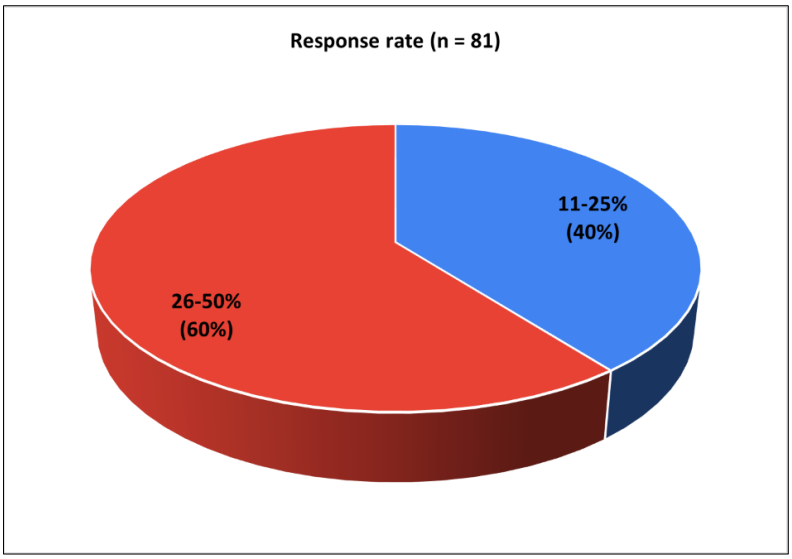

Figure 3: Distribution of response to the proportion of patients with neuropathy have vitamin B12 deficiency

Table 1: Distribution of response to the common co-morbid conditions that are usually observed with vitamin B12 deficiency

Co-morbid conditions	Response rate (n = 81)
Diabetes mellitus	72.84%
Dyslipidemia	1.23%
Obesity	9.88%
Hypertension	6.17%
Hypothyroidism	1.23%
Chronic kidney disease	1.23%
Osteoporosis	7.41%

According to 74% of clinicians, benfotiamine is the preferred molecule along with vitamin B12 for patients with neuropathy complications (Figure 4). Around 72% reported that vitamin B12 deficiency is mostly seen in patients using drugs like ethambutol, metronidazole, and isoniazid. Additionally, 59% of participants indicated that the biothesiometer is the most common method to investigate neuropathy.

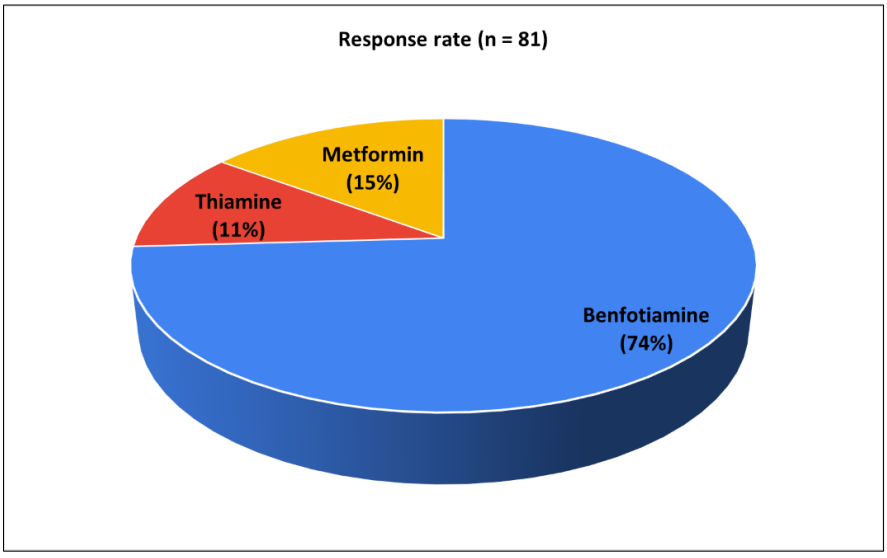

Figure 4: Distribution of response to the preferred supplementary molecule along with vitamin B12 for neuropathy complications in clinical practice

About 52% of the clinicians responded positively to vitamin B12 medications in 21-30% of the patients. The majority (61.73%) of the clinicians opined that they prescribe the consumption of methylcobalamin (1500 mcg) at night. As stated by 44% of clinicians, elderly patients, apart from those with neuropathy, are recommended with methylcobalamin 1500 mcg (Table 2).

Table 2: Distribution of response to the patient population recommended with methylcobalamin 1500 mcg other than neuropathy patients

Recommendation	Response rate (n = 81)
Elderly patients	44.44%
Patients recovering from illness	16.05%
Pregnancy	3.7%
Anaemia (B12 deficiency)	35.8%

About 43% of the clinicians recommended prescribing a combination of benfotiamine and methylcobalamin for 12 weeks in patients with neuropathy (Table 3). More than half (54.32%) of the clinicians favored prescribing a combination of methylcobalamin 1500mcg + pregabalin 75mg + nortriptyline 10mg tablets to patients with chronic neuropathic pain (Table 4).

Table 3: Distribution of response to the duration of prescribing benfotiamine and methylcobalamin combination in patients with neuropathy

Duration	Response rate (n = 81)
2 weeks	2.47%
4 weeks	9.88%
8 weeks	34.57%
12 weeks	43.21%
24 weeks	9.88%

Table 4: Distribution of response to the patient categories prescribed with methylcobalamin 1500 mcg + pregabalin 75 mg + nortriptyline 10 mg tablets

Category of patients	Response rate (n = 81)
Chronic neuropathic pain	54.32%
Postherpetic neuralgia	11.11%
Sciatica	14.81%
Fibromyalgia	11.11%
Radiculopathy	4.94%
All of the above	3.7%

DISCUSSION

The survey findings highlighted the importance of a multifaceted approach to managing neuropathy, integrating medical treatment, lifestyle changes, and patient education. The current study findings indicated that diabetes is a confounding factor for neuropathy in patients. According to the American Diabetes Association, neuropathy is one of the most prevalent and expensive microvascular consequences of DM [20]. Callaghan *et al*., stated that diabetes can damage peripheral nerves, contributing to the development of neuropathy through metabolic and vascular pathways. The study highlights that diabetes worsens neuropathic symptoms and complicates diagnosis [21]. Studies have shown that diabetic patients are 11 times more likely to develop neuropathy than those without diabetes, due to macrovascular complications. The duration of diabetes and levels of glycated hemoglobin have been strongly linked to a high incidence of neuropathy [22-24].

The latest survey results indicate that maintaining an appropriate diet and controlling glycemic levels are recommended strategies for managing and preventing the progression of neuropathy. Studies have shown that making dietary changes can effectively modify diabetic neuropathy. Strict control of glycemic levels is the most convincing strategy in preventing or delaying the development of neuropathy in patients with type 1 diabetes and in slowing its progression in some patients with T2DM [25, 26].

A significant proportion of the current survey clinicians reported that 26 to 50% of patients with neuropathy have vitamin B12 deficiency. A systematic meta-analysis by Stein *et al*., reported an association between neuropathy and decreased levels of vitamin B12 and emphasized the significance of treating nutritional deficiencies for the optimal management of neuropathy and associated morbidities [27]. Oberlin *et al*., also reported similar association between

vitamin B12 deficiency and neuropathy [28]. Fakkar *et al.*, too reported similar findings regarding the prevalence of vitamin B12 deficiency among elderly patients with peripheral neuropathy [19].

The prevalence of vitamin B12 deficiency is relatively high in T2DM patients that are on medication (metformin) [29]. Alvarez *et al*., concluded that vitamin B12 deficiency is highly prevalent, especially in patients with diabetic neuropathy [30]. A meta-analysis by Niafar *et al*., revealed that patients with T2DM undergoing metformin therapy had a significantly higher risk of vitamin B12 deficiency and lower serum vitamin B12 concentrations [17]. Vitamin B12 deficiency is a significant concern in diabetic patients, particularly those treated with metformin. Several studies have highlighted the association between metformin use and vitamin B12 deficiency in individuals with T2DM [31, 32]. This aligns with the present survey results. In a double-blinded investigation, Stracke *et al*., reported that a combination of benfotiamine and vitamin B12 improves nerve function and reduces neuropathic symptoms more effectively [33]. Similar results have also been reported in the present study.

Methylcobalamin 1500 mcg is recommended for elderly patients other than neuropathy patients. The drug has been shown to have significant pain-relieving effects in conditions such as diabetic neuropathy, nutritional diseases, Alzheimer's disease, rheumatoid arthritis, and neuralgia. It acts by enhancing nerve conduction velocity, promoting nerve regeneration, reducing pain sensitivity, and suppressing abnormal nerve discharges that cause neuropathic pain. It is a potentially safe treatment for neuropathy [16]. In acute cases of neuropathy, a dose of 1500 mcg per day is considered safe [11]. Didangelos *et al*., suggested that treating patients with diabetic neuropathy with 1 mg of oral methylcobalamin for twelve months increased plasma vitamin B12 levels and improved all neurophysiological parameters [10]. The study published by David *et al*., in the *American Journal of Clinical Nutrition* found that vitamin B12 supplementation can improve cognitive function in older adults with mild cognitive impairment [34].

A randomized, double-blind, placebo-controlled trial demonstrated significant improvement in neuropathic symptoms in patients treated with benfotiamine over 12 weeks. The study suggested that this duration was effective for symptom relief and improvement in nerve conduction [33]. Another study showed that a 12-week course of benfotiamine combined with methylcobalamin significantly improved neuropathic symptoms and quality of life in patients with diabetic neuropathy. This supports the effectiveness of a 12-week duration for benfotiamine treatment [35]. These findings align with the present survey results.

The survey findings reported methylcobalamin 1500 mcg + pregabalin 75 mg+ nortriptyline 10 mg tablets as the commonly prescribed combination in patients with chronic neuropathic pain. In line with this finding, Dongre and Swami demonstrated that the combination of methylcobalamin and pregabalin effectively improved neuropathic symptoms and quality of life in patients with diabetic neuropathy. This treatment showed significant improvement in both the positive and negative symptoms associated with neuropathy in Indian patients, and it was well tolerated [36]. Prabhoo *et al*., concluded that the fixed-dose combination of pregabalin and methylcobalamin was efficacious and well tolerated in neuropathic pain with minimal adverse effects [37]. Raju *et al*., reported that pregabalin 75 mg+ nortriptyline 10 mg + methylcobalamin 1500 mcg combination was a more effective and convenient treatment for neuropathic pain [38].

The findings of the current survey could help clinicians make better-informed clinical decisions and improve patient care by incorporating preferences and practices related to neuropathy and vitamin B12 management in Indian healthcare settings. A major strength of the current survey is the use of a well-designed and validated questionnaire to collect data from clinicians. However, there are some limitations to consider. The results may be biased due to their reliance on expert opinions, and the diverse perspectives among clinicians could impact the outcomes. It is important to take these limitations into account when interpreting the findings. To address these limitations, it is recommended to conduct prospective trials or real-world observational studies to validate the survey results and gain a more comprehensive understanding of optimal treatment approaches.

CONCLUSION

The survey results indicate that managing diabetes and vitamin B12 deficiency is critical for treating neuropathy. Key recommendations include making dietary adjustments and controlling blood sugar levels. The high prevalence of B12 deficiency among patients with diabetes emphasizes the importance of targeted nutritional interventions. Combining benfotiamine with vitamin B12 can help manage neuropathy complications.

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DECLARATIONS

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- **Conflict of Interest**: None declared
- **Ethical Approval**: This study was approved by the Independent Ethics Committee.

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