POSITION STATEMENT

Clinical Recommendations for the use of Neurotropic B vitamins (B1, B6, and B12) for the Management of Peripheral Neuropathy: Consensus from a Multidisciplinary Expert Panel

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Abstract

Introduction: Peripheral neuropathy (PN) is an insidious disease that is often asymptomatic during the early stages but which can have a significant impact on quality of life at later stages when nerve damage occurs. There is currently no guidance on the use of neurotropic B vitamins (B1, B6, and B12) for the management of asymptomatic and symptomatic PN.

Objective: To provide guidance to primary care physicians on an integrated approach to managing PN with neurotropic B vitamins (B1, B6, and B12).

Materials and methods: A multidisciplinary panel of eight experts participated in an iterative quasi-anonymous Delphi survey consisting of two rounds of questions and a virtual meeting. A literature review formed the basis of the survey questions. The first round included multiple select, qualitative, and Likert Scale questions; the subsequent round consisted of 2-point scale (agree or disagree) questions that sought to develop consensus-based statements refined from the first round and recommendations derived from discussions during the virtual expert panel meeting.

Results: Clinical recommendations for the use of neurotropic B vitamins (B1, B6, and B12) have been developed for the prevention of PN progression or to delay onset in patients at high risk of developing PN. Recommendations have also been provided for the assessment of PN etiology and considerations for the use of loading dose (high dose) and maintenance dose (lower dose) of these neurotropic B vitamins (B1, B6, and B12).

Conclusion: These clinical recommendations provide an initial step towards formulating comprehensive guidelines for the early and long-term management of PN with neurotropic B vitamins (B1, B6, and B12) and move beyond addressing only neuropathic pain associated with the late stages of PN.

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Introduction

Peripheral neuropathy (PN) is a clinical condition where the nerves of the peripheral nervous system are damaged.[1] PN typically refers to symmetric and universal damage to adjacent nerves; nerve damage and clinical manifestations are usually located distally with a proximal progression.[2] Several disorders can damage peripheral nerves and cause PN; it is important to differentiate actual neuropathy from other disorders with a similar clinical presentation.[2,3]

Peripheral neuropathy (PN) is a disease that is insidious in nature.[4] Peripheral nerves serve different motor, sensory, and autonomic functions, and thus, PN onset is insidious and may show slow or no progression in the early stages.[3,4] This poses significant challenges to early intervention and timely treatment. Early treatment of PN is essential to avoid long-term consequences, including the impairment of patients' quality of life due to chronic pain, loss of sensation, and irreversible nerve damage that negatively impacts activities of daily living.[5]

Peripheral neuropathy (PN) can be caused by several conditions, but most are chronic in nature.[6] The most common cause of PN is diabetes, with up to 35% of patients experiencing PN symptoms at the time of type 2 diabetes diagnosis.[7] Up to 5% of PN cases are considered severe and irreversible, causing a significant impact on the economy through loss of productivity, disability, and increased healthcare costs.[8] However, a study of patients with diabetes and PN found 13% had never reported their symptoms to their doctors, and 39% had never received treatment for their painful symptoms.[9] Furthermore, disparities between physician and patient perceptions of diabetic PN-related neuropathic pain reflected a lack of awareness and potential loss of opportunity for early intervention.[10]

Guidance on overall PN treatment remains unclear as currently available international guidelines primarily focus on the management of neuropathic pain—one of the symptoms in late-stage PN when significant nerve damage has already occurred.[11–18] Neuropathic pain is difficult to manage as it often does not respond to conventional analgesics.[8,11] A comprehensive algorithm for neuropathic pain has been developed, with tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and α-2-Δ ligand calcium channel blockers recommended as first-line treatment.[8,19] However, TCAs are contraindicated for patients taking SNRIs, thus preventing the combined use of these drugs in patients who do not respond adequately to monotherapy.[19] These contraindications may play a role in the low number of patients (<50%) achieving good pain relief with optimum adjuvant analgesics.[20]

Guidelines for the management of nonpainful symptoms such as paresthesia, tingling, and numbness are also lacking.[21] Despite the well-known synergistic effect and broad clinical usage of neurotropic B vitamins (B1, B6, and B12) for PN management,[12] there is a paucity of literature on the use of

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neurotropic B vitamins (B1, B6, and B12) for PN management.

In this review, consensus recommendations for the use of neurotropic B vitamins (B1, B6, and B12) for the management of PN are described to address the unmet medical need for an integrated approach to managing PN. This includes proactive prevention of PN symptom progression, active treatment with a loading dose of neurotropic B vitamins (B1, B6, and B12), and monitoring with a maintenance dose. These recommendations are applicable to patients with sensory PN due to metabolic diseases, medication/drug use, nutritional deficiency, and other causes, including critical illness, nerve entrapment, and unknown causes.

Materials and Methods

A multidisciplinary expert panel of four endocrinologists, three neurologists, and one pharmacologist from Hong Kong, India, Indonesia, Malaysia, Philippines, South Africa, Thailand, and the United Arab Emirates was convened to develop clinical recommendations on the use of neurotropic B vitamins (B1, B6, and B12) for PN management. The experts had experience in using neurotropic B vitamins (B1, B6, and B12) for PN management and were selected for their clinical expertise in PN management.

A literature review of articles published between 2002 and 2022 was conducted to evaluate current practices in PN and the role of neurotropic B vitamins (B1, B6, and B12) in the management and prevention of PN. The literature review formed the basis of the survey questions. The iterative quasi-anonymous Delphi survey approach (conducted *via* SurveyMonkey®) was used for gathering consensus (Fig. 1). The first Delphi round comprised multiple select, qualitative, and Likert Scale questions. The aim of the first round of the survey was to gather information about the expert panel's clinical practice and derive initial draft statements for consensus recommendations. The consensus was considered reached when 62.5% of panel members selected the same option or voted "agree" for a recommendation. The strong and moderate consensus was defined by >75% and between 51 and 75% agreement, respectively. Statements with strong consensus from the first Delphi round were kept and used as recommendations; statements with moderate or no consensus were redrafted in the subsequent round.

The second Delphi round included consensus recommendations refined from the first round and recommendations derived from discussions during a virtual expert panel meeting held on 26th March 2022. Each recommendation was voted on by each panel member using a 2-point scale (agree or disagree). In the case of nonconsensus (<50%), the statements were further discussed *via* email and revised accordingly until consensus was reached. A summary of the regional multidisciplinary panel recommendations for the use of neurotropic B vitamins (B1, B6, and B12) for PN management is provided in Table 1.

Consensus Recommendations

Peripheral Neuropathy (PN) as a Chronic Disease

Recommendation 1: PN is often a chronic condition that requires long-term management, except for certain acute instances of drug-induced or inflammatory neuropathy.

Peripheral neuropathy (PN) can be divided into acute and chronic forms, as well as symmetrical polyneuropathy and multiple mononeuropathy.[22] The overall prevalence of PN is difficult to establish due to the heterogeneity of etiologies and symptoms[21]—the prevalence of PN ranges from 1–3% in the general population and increases to 7% in the elderly.[7]

The onset of chronic neuropathy is often insidious and slowly progresses over the course of years.[4] While signs and symptoms of PN may take between 1 and 12 months to develop, patients with PN wait, on average, 19 weeks and up to 5 years after symptom onset before diagnosis.[21,23] Diagnostic delay can cause a delay in treatment initiation, resulting in the missed opportunity to slow down or avoid further progression of PN or prevent symptom relapses.[21] Patients suffering from painful spinal syndromes had lower relapse rates when treated for 6 months with neurotropic B vitamins (B1, B6, and B12) compared with placebo.[24]

However, long-term management of PN may not be necessary for certain acute instances of PN, such as drug-induced or inflammatory neuropathy. The risk of drug-induced neuropathy is usually dose-dependent and is more likely to occur in patients with concomitant risk factors.[25] PN symptoms seen with taxanes, antimycobacterial, immunosuppressive agents, and azoles are often reversible and fully resolved following dose reduction or cessation of therapy, thus not requiring long-term management.[25] Patients with conditions in remission or controlled, that is, those where an underlying cause such as diabetic neuropathy or vitamin B12 deficiency is being treated, may also not require advanced care.[21]

Neurotropic B Vitamins (B1, B6, and B12) Prophylaxis

Recommendation 2: Neurotropic B vitamins (B1, B6, and B12) prophylaxis should be considered for the following patients at high risk of PN—over 50 years of age; diagnosed with diabetes; diagnosed with human immunodeficiency virus (HIV) or tuberculosis (TB) infection; on specific medications, for example, isoniazid or metformin; with chronic kidney disease (CKD) on dialysis; on a restricted diet.

Early intervention and timely treatment are crucial in preventing further PN progression and the development of severe or irreversible symptoms, which can result in impairment of quality of life.[1,5] The identification of patients at high risk of PN thus allows for the early recognition of and intervention in mild PN symptoms.[21]

Peripheral nerves have good regenerative capacity, with regeneration possible until approximately 50% of the fibers within a nerve are damaged.[12] By the time a reduction in nerve conduction velocity is reported,

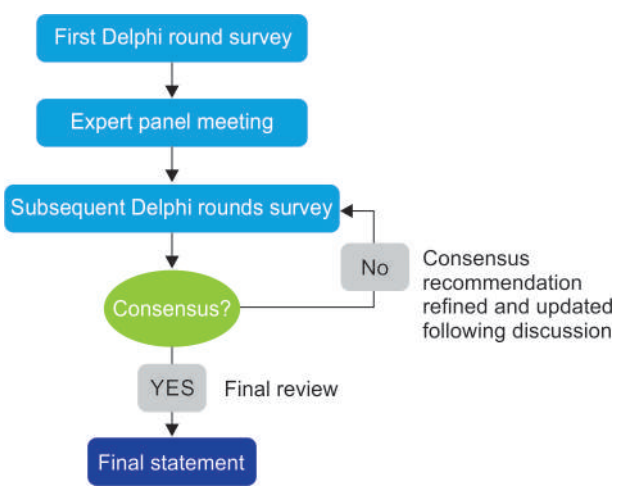

Fig. 1: Quasi-anonymous Delphi survey method used in this study

asymptomatic PN may have developed progressively, that is, nerves may already be damaged without noticeable symptoms[12]—underscoring the importance of early intervention. The neurotropic B vitamins (B1, B6, and B12) are essential for nerve regeneration and sensory nerve function restoration, representing a starting point in supporting nerve function before clinical symptoms of PN appear and worsen.[12]

Table 1: Consensus recommendations for the use of neurotropic B vitamins (B1, B6 and B12) for PN management

	Recommendations	*Level of consensus*
1	PN is often a chronic condition that requires long-term management, except for certain acute instances of drug-induced or inflammatory neuropathy.	Strong (100% agree)
2	Neurotropic B vitamins (B1, B6, and B12) prophylaxis should be considered for the following patients at high risk of PN: • Over 50 years of age • Diagnosed with diabetes • Diagnosed with HIV or TB infection • On specific medications, e.g., isoniazid or metformin • With CKD on dialysis • On a restricted diet	Strong (100% agree)
3	The initiation of neurotropic B vitamins (B1, B6 and B12) should be based on etiology and on patient risk factors (i.e., if a patient is predisposed to PN, including those with diabetes, CKD, and advanced age).	Strong (100% agree)
4	Neurotropic B vitamins (B1, B6, and B12) may be initiated for patients with sensory PN due to metabolic diseases, medication/drug use, nutritional deficiency, and other causes.	Strong (100% agree)
5	Neurotropic B vitamin (B1, B6 and B12) injections should be given to patients with PN presenting with specific B vitamin deficiency, GI tract disorders and those with acute or severe conditions.	Strong (100% agree)
6	Patients with sensory PN due to metabolic diseases, medication/drug use and nutritional deficiency could be given a loading dose (high dose) of neurotropic B vitamins (B1, B6, and B12) and transitioned to the maintenance dose (lower dose) upon the alleviation of PN symptoms.	Strong (100% agree)
7	The key criteria for dose adjustment of neurotropic B vitamins (B1, B6, and B12) from loading dose (high dose) to maintenance dose (lower dose) are symptom relief and long-term safety profile.	Strong (100% agree)

CKD, chronic kidney disease; GI, gastrointestinal; HIV, human immunodeficiency virus; PN, peripheral neuropathy; TB, tuberculosis

The expert panel agreed that there is a need for neurotropic B vitamins (B1, B6, and B12) prophylaxis in high risk populations as long as risk factors are still present. An algorithm to evaluate a patient's condition to identify those at high risk of PN has been developed—thereafter referred to as CONDITION (Fig. 2). The CONDITION algorithm was developed based on the current management practice of patients with sensory PN, that is, PN due to insufficient intake, impaired absorption, or increase in loss of neurotropic B vitamins (B1, B6, and B12).

The incidence of PN increases with age, commensurate with the high prevalence of chronic diseases like diabetes and renal impairment.[26] Furthermore, age-related changes in organs may cause not only malabsorption and result in nutritional or polyvitamin deficiency but may also worsen changes in the structure and function of peripheral nerves.[27] This leads to an increased risk of PN in older patients. PN affects patients with noncommunicable and communicable diseases alike.

Peripheral neuropathy (PN) affects 60–70% of patients with diabetes, and metformin use is a risk factor for the development of diabetic PN.[28] The global incidence of PN is expected to rise as a result of the projected increase in the number of patients with diabetes, from 451 million people in 2017 to 693 million people by 2045.[29] Furthermore, an estimated 49.7% of the people living with diabetes remain undiagnosed. Although metformin is recommended as the first-line treatment for patients with type 2 diabetes for as long as it is tolerated.[30] Patients aged 50 years and above treated with metformin for at least 18 months

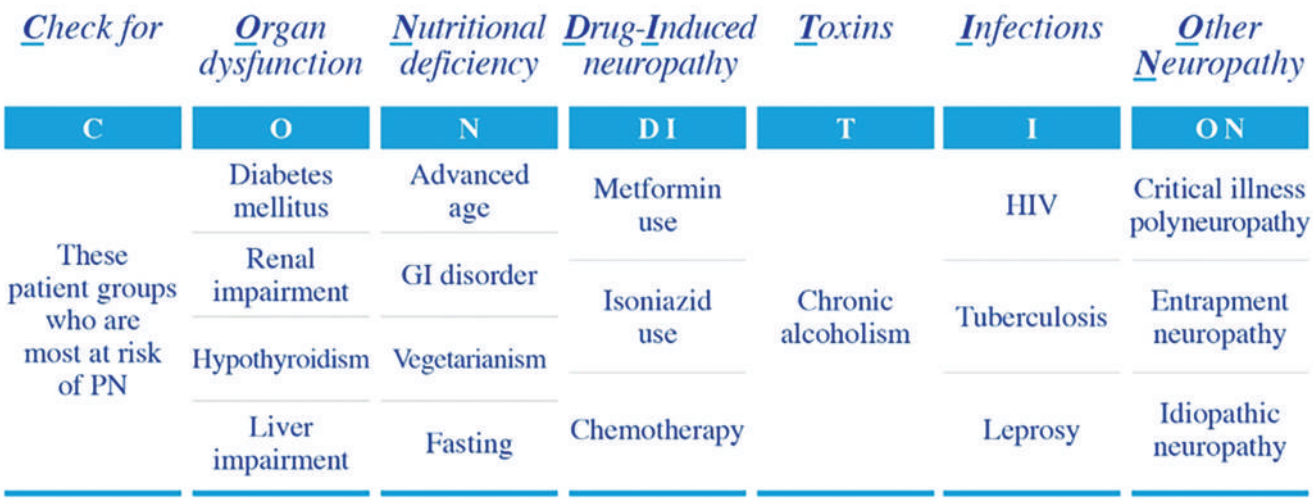

Fig. 2: CONDITION algorithm for the identification of patients at high risk of PN; GI, gastrointestinal; HIV, human immunodeficiency virus; PN, peripheral neuropathy

have been reported to be two to three times more likely to develop PN.[31] Prolonged use and higher doses of metformin in patients with diabetes were also associated with vitamin B12 deficiency, increased homocysteine (Hcy) and methylmalonic acid (MMA), which are associated with increased diabetic PN severity.[28] The metformin usage index (MUI) can be used as a risk assessment tool for the evaluation of vitamin B12 deficiency and PN in patients with type 2 diabetes. For instance, an MUI > 5 suggests a high risk of vitamin B12 deficiency.[32]

Patients with TB and HIV infection may also be predisposed to developing PN.[3] In patients with TB, the development of PN can be caused by the condition itself, comorbid conditions associated with TB, or the front-line anti-TB drug isoniazid.[3] Isoniazid depletes vitamin B6 by interference with the metabolism of vitamin B6, which may result in the development of PN.[3] Isoniazid-induced PN often presents as paraesthesia beginning from the lower extremities and is commonly seen in slow acetylators of isoniazid, patients with HIV infection, diabetes, renal failure, chronic hepatic failure, malnourished patients, alcoholic patients, the elderly, and pregnant women.[33,34]

Chronic kidney disease (CKD) with a glomerular filtration rate of <12 mL/minute is associated with clinically significant PN.[35] While PN may develop early in the course of CKD, several studies have reported that 70–100% of patients with end-stage renal disease experience neuropathic symptoms.[35]

Patients on a restricted diet, including vegetarians, have been shown to be at high risk of vitamin B12 deficiency.[36] For instance, 29–40% of the population in India are strict vegetarians, leading to an increased prevalence of vitamin B12 deficiency and an increased risk of nerve-related conditions.[21]

PN Management with Neurotropic B Vitamins (B1, B6, and B12)

Recommendation 3: The initiation of neurotropic B vitamins (B1, B6, and B12) should be based on etiology and on patient risk factors (i.e., if a patient is predisposed to PN, including those with diabetes, CKD, and advanced age).

Recommendation 4: Neurotropic B vitamins (B1, B6, and B12) may be initiated for patients with sensory PN due to metabolic diseases, medication/drug use, nutritional deficiency, and other causes.

International guidelines focus primarily on the management of neuropathic pain—providing treatment recommendations for pain relief in patients with PN, with a lesser focus on treating underlying causes of PN.[11,13–18,21] While guideline-recommended first-line treatments offer effective symptom relief in patients with painful PN,[19] they do not restore nerve function and health.[21]

The expert panel agreed that the etiology of PN should be identified, and treatment of PN with neurotropic B vitamins (B1, B6, and B12) should be initiated. Neurotropic B vitamins (B1, B6, and B12) are a well-established and commonly used treatment in clinical practice for PN management, albeit with limited published scientific evidence.[1] Individually, the neurotropic B vitamins (B1, B6, and B12) have been shown to provide symptomatic relief and act synergistically to improve nerve function and promote nerve regeneration.[12,21] In the prospective, open-label, multicenter, single-arm observational Neurobion noninterventional (NENOIN) study, a significant reduction in overall Total Symptom Score for stabbing pain, burning pain, paresthesia, and numbness were observed within 14 days of treatment with a fixed dose combination of neurotropic B vitamins (100 mg B1, 100 mg B6, and 5000 µg B12) ($p < 0.0001$).[1] The study population of the NENOIN study was patients with mild-to-moderate PN of different etiologies, including diabetes mellitus, nutritional deficiency, alcoholism, carpal tunnel syndrome, idiopathic PN, and others.[1]

The initiation of neurotropic B vitamins (B1, B6, and B12) in patients after bariatric surgery has also been proven beneficial.[37] PN has been reported in 10–33% of patients who have undergone bariatric surgery, with an average time to onset of 3.7 years postsurgery.[38] The extent to which bariatric surgery can cause B vitamin deficiencies and thus an increased risk for PN depends on the type of surgical procedure performed.[37,38]

The dose-dependent effect of neurotropic B vitamins (B1, B6, and B12) makes them suitable for a regimen that includes a loading dose with a subsequent transition to an ongoing maintenance dose. The loading dose, a high dose, is necessary to achieve the minimum effective concentration and attain a fast therapeutic response, whereas the maintenance dose is required to maintain the minimum effective concentration in the long-term.[39] A dose-finding study has demonstrated a dose-dependent increase in absorption of vitamin B12 in older people aged 70 years and above with mild vitamin B12 deficiency (defined as serum vitamin B12 level of 100–300 pmol/L).[40] Vitamin B12 levels were found to increase more effectively with daily oral doses of 1000 µg vitamin B12 compared with 200 µg of vitamin B12, increasing by 167% over 16 weeks.[40] Another study has also shown that patients with symptomatic diabetic PN experienced greater symptom relief with the high dose treatment of 25 mg B1 and 50 mg B6 compared with the lower dose of 1 mg B1 and 1 mg B6.[41]There were also more patients (48.9%) in the higher dose treatment group who experienced a reduction in the severity of PN symptoms compared with those in the low-dose treatment group (11.4%).[41]

A loading dose (high dose) of neurotropic B vitamins (B1, B6, and B12), individually administered or as a combination, led to better treatment outcomes compared with treatment commencement at a maintenance dose (lower dose).[42] In patients aged 55–56 years with diabetic PN, a high initial parenteral dose (daily intramuscular injection for 1 week followed by twice weekly intramuscular injection for 3 weeks) of neurotropic B vitamins (100 mg B1, 100 mg B6, and 1000 mg B12) resulted in significant increases in nerve conduction velocities in the posterior tibial nerve (5.0 m/second; $p \leq 0.01$) and lateral popliteal nerve (8.5 m/second; $p \leq 0.01$)–which were in the median and upper normal range of normal nerve function, and thus indicative of nerve regeneration.[42]

Recommendation 5: Neurotropic B vitamins (B1, B6, and B12) injections should be given to patients with PN presenting with specific B vitamin deficiency, gastrointestinal (GI) tract disorders and those with an acute or severe condition.

The expert panel agreed that an injectable preparation might be given to patients with PN presenting with B deficiency (e.g., vitamin B12), GI tract disorders, and those with an acute or severe condition. Injectable neurotropic B vitamins (B1, B6, and B12) are useful to ensure rapid restoration of B vitamin levels, particularly in patients with severe deficiency or severe PN symptoms.[21,43] In patients with vitamin B12 deficiency with neurological deficits, the British Society for Haematology recommends intramuscular injections of 1000 µg hydroxocobalamin every other day for up to 3 weeks or until no further improvement is noted and oral tablets for patients with an asymptomatic, mild disease without absorption concerns.[44] A Cochrane review found that a high oral dose of vitamin B12 was as effective as injections in achieving hematological and neurological responses in patients with vitamin B12 deficiency.[45]

Transitioning from Loading (High Dose) to Maintenance Dose (Lower Dose)

Recommendation 6: Patients with sensory PN due to metabolic diseases, medication/drug use, and nutritional deficiency could be given a loading dose (high dose) of neurotropic B vitamins (B1, B6, and B12) and transitioned to

a maintenance dose (lower dose) upon the alleviation of PN symptoms.

The expert panel recommended patients transition from loading dose to maintenance dose upon the alleviation of PN symptoms. The recommendations for the initiation of neurotropic B vitamins (B1, B6, and B12) for PN management are summarized in Figure 3. As PN has been associated with reduced plasma vitamin B12, elevated MMA and total Hcy concentrations,[46] vitamin levels may be valuable in guiding treatment. In regions where B vitamin level testing is not routinely performed due to cost concerns, the panel recommended symptom relief and long-term safety profile as the key criteria for dose adjustment of neurotropic B vitamins (B1, B6, and B12) from loading dose to maintenance dose.

Recommendation 7: The key criteria for dose adjustment of neurotropic B vitamins (B1, B6, and B12) from loading dose (high dose) to maintenance dose (lower dose) are symptom relief and long-term safety profile.

High dose neurotropic B vitamins (B1, B6, and B12) have been shown to be advantageous for PN management if dosing recommendations are followed alongside monitoring of serum levels, particularly in patients with diabetic nephropathy—considering the water-solubility of these vitamins that are predominantly renally excreted.[47] No reports of adverse effects with vitamin B1 have been reported, although parenteral administration has been associated with phlebitis and rarely with hypersensitivity reactions.[47]

The Filipino Neuropathic Pain Technical Committee has cautioned against the use of vitamin B6, in which high doses (>250 mg/day) may induce neuropathy.[48] Even though neurological side effects of vitamin B6 are rare and may resolve after treatment cessation, a high daily dose of >500 mg/day and/or a long treatment duration (>6 months) should be avoided. Various studies and case reports have suggested an association between PN and the dose or duration of vitamin B6, but it is generally well-tolerated at 50 mg/day for up to 6 months.[47] Vitamin B6 alone at 250 mg/day for a few weeks has been shown to reverse PN associated with isoniazid treatment, whereas a dosing schedule of 30 mg daily for 1 month has shown improvement in PN associated with vitamin B6 deficiency in patients with uremia.[49] There have been no side effects or overdosing reported with oral high dose vitamin B12 (500–1000 µg) for up to 7 years.[47] Correlation between vitamin B6 and/or B12 and hip fracture risk and lung cancer was not conclusive[47]. Conversely, 1000 µg of vitamin B12 has been shown to be the optimal dose to restore vitamin B12 levels.[40,50]

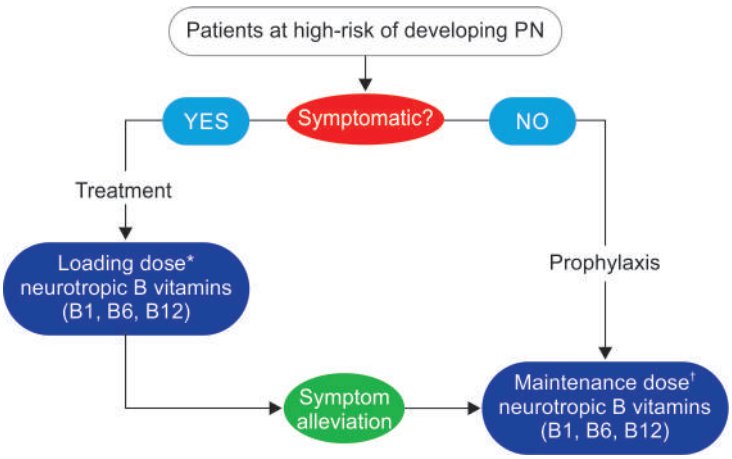

Fig. 3: Algorithm for the management of PN with neurotropic B vitamins (B1, B6, and B12) in patients at high risk of PN; *high dose; †lower dose; PN, peripheral neuropathy

Neurotropic B vitamins (B1, B6, and B12) are available in various dosages and preparations. These include an oral high dose formulation composed of 100 mg B1, 100 mg B6, and 5000 µg B12, with a recommended dosing of one tablet daily for up to 3 months, and ampules composed of 100 mg B1, 100 mg B6, and 1000 µg B12. Oral lower dose neurotropic B vitamins are available as 100 mg B1, 200 mg B6, and 200 µg B12 with a recommended dosing of 1–3 tablets daily.

Other considerations for dose adjustment from the loading dose (high dose) to the maintenance dose (lower dose) include the onset of therapeutic response. A prospective noninterventional study using a fixed-dose combination of high dose neurotropic B vitamins (100 mg B1, 100 mg B6, and 5000 µg B12) has reported an onset of action between 8 and 14 days.[1] The rapid onset of effect is also an important factor for treatment adherence.[21] Adherence to treatment is crucial in the management of chronic diseases, including PN—discontinuation of treatment has been shown to lead to symptom relapse.[24] Communication by the healthcare provider also plays an important role in communicating the rationale for dose adjustment, thus ensuring treatment adherence and maximizing patient outcomes—particularly for a chronic and debilitating disease like PN.[10] While strategies to improve uptake and adherence to long-term management should be evaluated and established, primary care physicians will have the discretion to make appropriate dose adjustments based on patient's current status, underlying medical conditions or other environmental factors.

Conclusion

Based on the clinical experiences of the expert panel as well as evidence from clinical studies, neurotropic B vitamins (B1, B6, and B12) can effectively provide symptomatic relief in PN and can help to restore nerve health and function.[21] The seven recommendations presented in this article provide practical guidance on the following:

- The prophylactic use of neurotropic B vitamins (B1, B6, and B12).
- The use of a loading dose (high dose) for active treatment of PN and maintenance dose (lower dose) regimen for proactive prevention of PN relapse and long-term nerve care.
- Key considerations for the transition from the loading dose to the maintenance dose.

While the CONDITION algorithm developed by the expert panel is helpful in identifying different risk groups for early treatment initiation with neurotropic B vitamins (B1, B6, and B12), clinical awareness and easily available laboratory tests are essential to confirm vitamin B1, B6, or B12 deficiency and potentially detect PN at an early stage. Until more specific tests are available to quantify deficiencies, current recommendations on the dosage of neurotropic B vitamins (B1, B6, and B12) are mostly empirical—thus, primary care physicians are urged to be vigilant for signs of potential overdose with long-term use. Further research into early detection of PN via cutaneous nerve density testing or fully automated confocal microscopy corneal nerve quantifications is warranted to improve the detection of diabetic neuropathy and to further examine the clinical applications of nerve stimulation or regeneration factors.

Assessing the etiology of PN and recognizing patients at high risk of PN is crucial, and treatment goals for PN should include symptomatic relief and restoration of nerve health. After the initial loading dose (high dose), the maintenance dose (lower

dose) should be tailored to individual patients while accounting for the tolerability and differences in the preparations of neurotropic B vitamins (B1, B6, and B12). Oral dosage of vitamin B1 is generally safe, whereas dosage recommendations for vitamin B6 should be followed to ensure an advantageous benefit-risk ratio.[47] B vitamin levels should be subject to ongoing monitoring in specific patient groups, including those with diabetic nephropathy.

The heterogeneity of etiologies and symptoms of PN also highlights the need for a personalized treatment rather than a "one size fits all" treatment approach. The current consensus substantiates the use of adjunctive neurotropic B vitamins (B1, B6, and B12) for the management of PN and supplements existing guideline recommendations for PN-related neuropathic pain. An important consideration for prescribing neurotropic B vitamins (B1, B6, and B12) adjunctively for PN management is the different mode of action of the individual B vitamins and their synergistic effect in improving nerve function and nerve regeneration.[12]

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