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EXPERT OPINION

Expert Consensus on Vitamin B6 Therapeutic Use for Patients: Guidance on Safe Dosage, Duration and Clinical Management

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Purpose: Vitamin B6 is a crucial water-soluble vitamin found in many foods and is involved in numerous physiological processes, including neurotransmitter synthesis and nervous system function. Although essential for overall health, both deficiency and excessive intake of vitamin B6 may lead to health complications, particularly peripheral neuropathy. This consensus statement aims to provide healthcare professionals with clear guidance on the safe and effective use of vitamin B6, focusing on its benefits, risks, recommended dosages, and treatment course.

Methods: This consensus statement was developed using a Delphi approach involving a panel of six experts from various medical specialties. This process includes a comprehensive literature review, two rounds of anonymous online surveys, and a virtual expert roundtable discussion. The GRADE approach was used to assess the quality of evidence for each recommendation.

Results: The expert panel reached consensus on five key statements. These key recommendations encompass the function of vitamin B6, complications due to vitamin B6 deficiency, dosage recommendations, adverse events, and monitoring guidance throughout the course of treatment. A washout period of 20–40 days for the complete clearance of vitamin B6 was calculated based on pharmacokinetic parameters. A clinical pathway for managing patients who might benefit from vitamin B6 treatment was proposed.

Conclusion: This consensus statement highlights the importance of recognizing the benefits and potential risks of vitamin B6. While the therapeutic dosage of vitamin B6 can be beneficial to treat deficiency, excessive intake can lead to adverse effects. This statement emphasizes the need for individualized patient care considering factors such as medical history, lifestyle, and potential drug interactions. Further research is needed to establish clearer dosage guidelines, understand the mechanisms of vitamin B6-induced neurological side effects, and optimize patient outcomes.

Keywords: vitamin B6, pyridoxine, safety, clinical guidance, consensus statement, neuropathy

Introduction

Vitamins are essential substances in the body that are required for all vital activities including cell structure and energy metabolism. B-group (or B-complex) vitamins specifically assist with the production of energy and biosynthesis of many physiologically vital molecules in cells.[1]

Vitamin B6, also known as pyridoxine, is a water-soluble vitamin naturally abundant in many food sources. It is crucial for over 100 enzymatic reactions in the body and is vital for various bodily functions, including amino acid, carbohydrate, and lipid metabolism, neurotransmitter (eg, serotonin and noradrenaline) synthesis, myelin formation, and haemoglobin formation.[2,3] It also functions as a coenzyme (pyridoxal phosphate) in the metabolism of amino acids, glycogen, and sphingoid bases.[4]

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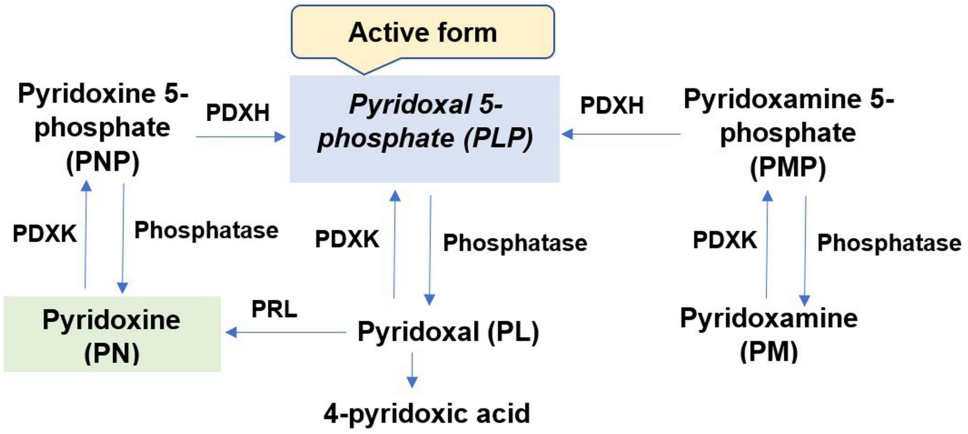

Figure 1 Vitamin B6 salvage pathway.
Abbreviations: PDXK, Pyridoxal Kinase; PDXH, Pyridoxal Oxidase; PRL, Pyridoxal Reductase.

As illustrated in the vitamin B6 salvage pathway in Figure 1, vitamin B6 comprises of a group of six related compounds, including pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM), and their phosphorylated derivatives, such as pyridoxal 5′-phosphate (PLP).[5–7] Vitamin B6 is absorbed into the jejunum of the small intestine through a carrier-mediated process. Absorbed PN is converted to pyridoxine 5′-phosphate (PNP) by the enzyme pyridoxal kinase, and PNP is further converted to PLP by the enzyme pyridoxal oxidase. PLP is the predominant form in the plasma, accounting for about 70–80% of the total vitamin B6.[8] The liver is the main site of vitamin B6 metabolism and may be influenced by interindividual differences.[9] Pharmacogenomic studies have highlighted inter-individual differences in the metabolism of vitamin B6, potentially influencing its sensitivity to its effects, including neuropathy. Genetic variations involved in vitamin B6 metabolism, such as the pyridoxal kinase gene, have been associated with altered vitamin B6 levels and an increased risk of certain diseases.[9]

Although an adequate dietary intake is typically sufficient to meet daily requirements, certain medications, medical conditions, and lifestyle factors can increase the risk of deficiency. Multiple vitamin B deficiencies have been observed. Consequently, if a deficiency in one B vitamin is detected, it is generally necessary to address potential deficiencies in other B vitamins by ensuring a balanced dietary intake that includes the full spectrum of these essential nutrients unless proven otherwise.[10]

Vitamin B6 deficiency can manifest as naso-lateral seborrhoea, glossitis, peripheral neuropathy, and normocytic, microcytic or sideroblastic anaemia.[5–7,11] In these cases, administration of a therapeutic dose of vitamin B6 is essential to prevent and treat such clinical manifestations, particularly in high-risk individuals. For example, studies have reported that ensuring adequate levels of vitamin B6 is important for preventing peripheral neuropathy induced by isoniazid (INH).[12] INH is a tuberculosis medication that interferes with vitamin B6 activity, potentially leading to nerve damage. Vitamin B6, in combination with B1 and B12, have also demonstrated benefits in improving symptoms in patients with mild-to-moderate peripheral neuropathy.[13–15]

Despite the importance of vitamin B6 for these indications, excessive intake of vitamin B6 at a supratherapeutic doses over the long term has been reported to cause neurological side effects, and typical guidelines lack specific recommendations for monitoring and early detection.[16–19] Several regulatory agencies have shared safety concerns with inappropriate usage of vitamin B6-containing products upon increasing reports of toxicity development.[20,21] While the exact mechanisms of adverse events associated with supratherapeutic doses of vitamin B6 have not been fully elucidated, postulated mechanisms have been published in the current literature.[9,18,22] Hence, this expert consensus aims to provide healthcare professionals with clear guidance and specific recommendations on the use of vitamin B6, addressing its benefits, potential risks, recommended dosages, and treatment course. This comprehensive analysis of the current evidence will equip healthcare professionals with the knowledge to make informed decisions regarding the therapeutic use of vitamin B6, ultimately improving patient care.

Methods

Overview of Study Design

The approach (as summarized in Figure 2) comprised of a comprehensive literature review followed by two anonymous online surveys (one pre and one post-expert roundtable discussion) administered through Microsoft Forms, and a 2.5-hour virtual expert round table discussion (ERTD) conducted via Microsoft Teams. This study adopted a modified Delphi approach, which is a systematic process of developing consensus among a group of expert panel members through iterative discussions on a topic.[23] Similar to commonly adopted criteria, this study utilized a two-round Delphi method. In the first round of the survey, experts were asked to rate their agreement with each statement using a 5-point Likert scale independently. Based on established practices in Delphi methodologies, a statement was considered endorsed if at least 80% of the aggregated responses rated the level of agreement as 7 or above.[24,25] In cases where statements did not attain the consensus threshold, the statements were revised based on qualitative feedback provided by experts and re-evaluated in the second survey. Any divergent opinions were resolved through group discussion, leading to a consensus-driven resolution.

Expert Panel Selection

A diverse group of experts listed in Table S1 were involved in capturing a wide range of perspectives. The multi-disciplinary expert panel consisted of six experts from five countries: Australia, Malaysia, Thailand, United Arab Emirates and South Africa. Of the 6 experts, there were 3 neurologists, 1 endocrinologist, 1 pharmacologist, and 1 pharmacist. Experts were selected based on a pre-defined inclusion and exclusion criteria. The inclusion criteria include experts with experience prescribing, managing or researching high-dose vitamin B6 therapy, and experienced neurologist/ endocrinologist/ pharmacologist/pharmacist with more than 20 years of experience in their current specialty, have seen more than 30 peripheral neuropathy or nerve damage patients in the past month (neurologist/ endocrinologist only), good familiarity with the current landscape and management of peripheral neuropathy or nerve damage in respective countries. Exclusion criteria would be experts unwilling to provide informed consent.

Targeted Literature Review

An initial targeted literature review search was conducted using publicly available sources (eg PubMed, Google, government websites) to establish a comprehensive understanding of Vitamin B6 clinical data, management, and usage. The search terms used are listed in Table S2.

The PRISMA diagram in Figure 3 summarized the total number of identified, reviewed, and included articles. A total of 58 articles identified from the literature review were utilized as the basis for developing the consensus statements.

The GRADE approach was used to systematically assess the quality of evidence for each included article, considering factors such as risk of bias, inconsistency, indirectness, and publication bias.[26] Two reviewers (JHW and MT) independently screened and reviewed the full-text articles and assigned an evidence grade to the articles based on the GRADE definition. Any discrepancies in the article grading were resolved by a third reviewer (KT).

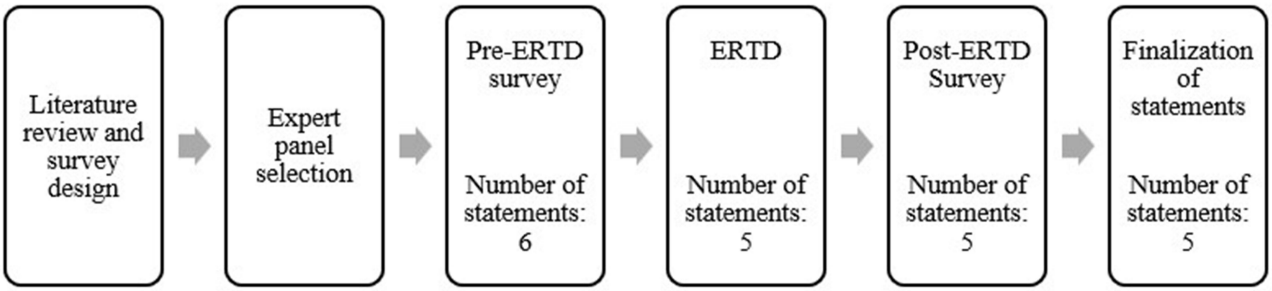

Figure 2 Two-round Delphi approach workflow.
Abbreviation: ERTD, Expert round table discussion.

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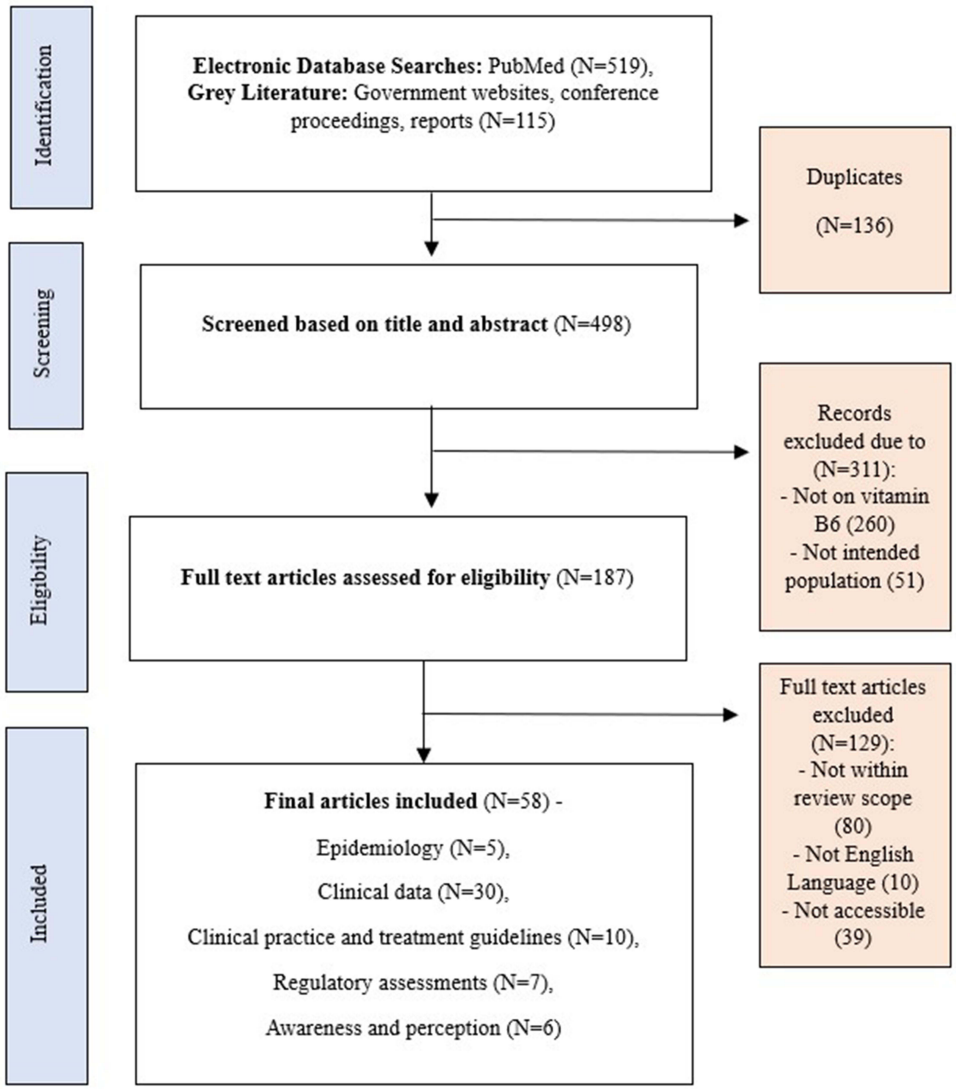

Figure 3 Study selection flow (PRISMA diagram).

Vitamin B6 usage, like other vitamins, is often hampered by the lack of high-quality randomized controlled trials (RCTs) with robust sample sizes and clinically significant outcomes. This scarcity necessitates the reliance on expert clinical opinions to provide guidance and consensus recommendations. Hence, it is important to emphasize that the GRADE system provides a comprehensive framework for evaluating evidence from a variety of sources and is not strictly dependent on the study design.

Results

Based on initial literature review, six consensus statements were initially developed and maintained during the first Delphi survey. The statements were then evaluated by experts during the ERTD and second Delphi survey to yield five key statements covering the function of Vitamin B6, effects of vitamin B6 deficiency, vitamin B6 dosage, adverse effects, and the recommended treatment course for the therapeutic use of vitamin B6.

The final list of statements and references can be found in Table S3.

Table 1 presents the final consensus statements and average strength of the recommendations of all experts (rated out of 10) assigned to each statement.

Table 1 Summary of Endorsed Consensus Statements

No.	Consensus Statement	Strength of Recommendation
1	Vitamin B6 and its metabolites are essential for the functioning of the nervous system, as a coenzyme for metabolic reactions that is crucial for synthesis of neurotransmitters such as γ-aminobutyric-acid (GABA), dopamine, norepinephrine and serotonin.	9.8
2	Vitamin B6 deficiency may result in peripheral neuropathy, seborrheic dermatitis, microcytic anaemia, glossitis, seizures, depression, confusion and associated with impaired immune function.	9.2
3	Clear dose and duration recommendations associated with neuropathy aetiology, patient risk groups, or symptoms severity have not been established. Clinicians should carefully evaluate each patient's individual condition when deciding dosage and duration. Based on published literature and expert clinical practices, the following tolerable (maximum) daily dosage and associated duration of vitamin B6 intake is recommended for peripheral neuropathy as shown in Table 2.	8.3
4	Vitamin B6-induced neurological adverse events have been reported in high therapeutic dose and long-term usage. However, these are generally rare, and may be reversible upon treatment cessation when recognized early. Regular monitoring by healthcare professionals, screening for history of vitamin consumption is key to early detection of adverse events.	9.2
5	For patient usage duration of longer than 6 months, and over 50 mg/day vitamin B6, regular monitoring by healthcare professionals is recommended. If patients develop neurological side effects, a washout period of 20 ~ 40 days (3 ~ 6 weeks) is recommended before considering resuming vitamin B6 treatment. For some cases with prolonged symptoms, extend to 3–6 months for recovery depending on patient's neurological side effect.	7.3

Clinical Pathway: A Guide for Primary Care Physicians

The proposed treatment pathway in Figure 4 offers clinicians a guide for managing patients at high risk of vitamin B6 deficiency or presenting with clinical symptoms potentially requiring therapeutic usage of vitamin B6 (refer to consensus

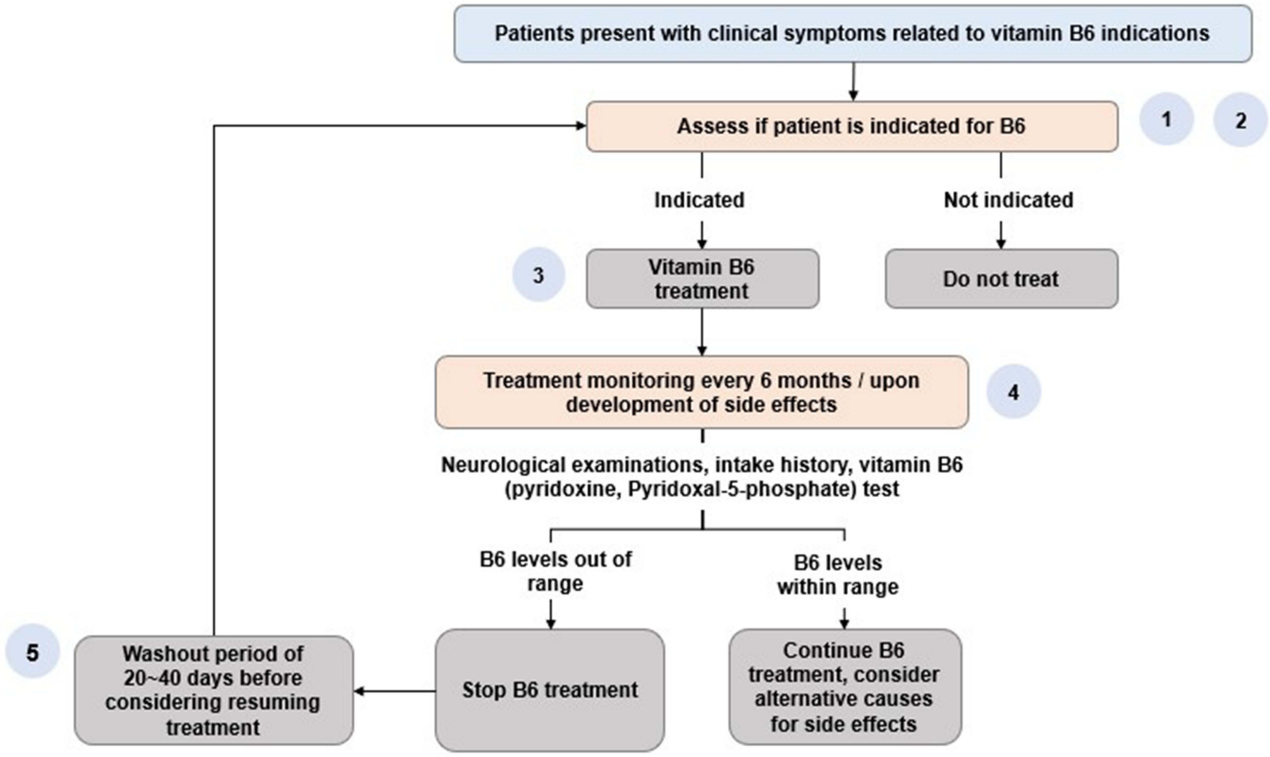

Figure 4 Clinical pathway for management of patients presenting with clinical symptoms related to indications of vitamin B6 treatment. 1) Consensus statement #1. 2) Consensus statement #2. 3) Consensus statement #3. 4) Consensus statement #4 5) Consensus statement #5.

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statements 1 and 2 for specific benefits and deficiency risks). Clinical judgement and detailed medical history assessments are paramount in determining the appropriate dosage and duration of treatment. Regarding tolerability, published literature and expert opinions have suggested tolerable (maximum) dosages and durations for patients with peripheral neuropathy (consensus statement #3). In the opinion of the experts, monitoring and treatment can proceed without interruption in the absence of side effects. While generally rare, adverse events may occur with supratherapeutic doses and long-term usage. In addition to the recommended treatment, timely monitoring, testing to determine vitamin B adequacy, and early detection of side effects are key (consensus statement #4). In rare cases where side effects arise, a washout period of 20–40 days (consensus statement #5) is recommended. However, clinical judgement should be practiced on a case-by-case basis to determine the appropriate duration of the washout period. A preventive washout period is not recommended in cases where no side effects are observed.

Discussion

Vitamin B6 Function

Statement 1: Vitamin B6 and its metabolites are essential for the functioning of the nervous system, as a coenzyme for metabolic reactions that is crucial for synthesis of neurotransmitters such as γ-aminobutyric-acid (GABA), dopamine, norepinephrine and serotonin.

Strength of Recommendation: 9.8/10

Since its discovery by Birch et al in 1935, vitamin B6 has been recognized as a crucial compound in cellular processes.[27] PLP, the active form of vitamin B6, serves as a coenzyme in the synthesis of many key neurotransmitters and metabolism of macromolecules within the human body.[5,7] Dopamine, γ-aminobutyric-acid (GABA), epinephrine and serotonin are essential neurotransmitters involved in neuronal processes.[11] Dopamine plays a vital role in motor activity, reward control and cognitive function,[28] GABA is known to modulate synaptic transmission and plays an important role in preventing neuronal hyperexcitability,[29] epinephrine is critical during acute stress situations and triggers fight-or-flight responses,[11] and serotonin regulates emotions and promotes well-being, among many other functions.[30] Additionally, these neurotransmitters are integral to maintaining the body's healthy functions in areas such as metabolism, immunity and haematology.[11,12] The emergence of neurological symptoms as a consequence of vitamin B6 deficiency highlight the critical role of vitamin B6 in maintaining nervous system health.

Statement 2: Vitamin B6 deficiency may result in peripheral neuropathy, seborrheic dermatitis, microcytic anaemia, glossitis, seizures, depression, confusion and associated with impaired immune function.

Strength of Recommendation: 9.2/10

Vitamin B6 is widely available in various natural dietary sources including eggs, fish, soybeans and corn.[31] However, deficiency can occur due to medication use, poor renal function, autoimmune diseases, metabolic diseases, impaired absorption, increased alcohol intake and other causes.[5,12,32–35] Vitamin B6 deficiency impairs the production of neurotransmitters in the body as it is a key component of cellular processes. Various clinical conditions, such as peripheral neuropathy, dermatitis, anaemia, glossitis, seizures, depression, confusion, and weakened immune system, are known to manifest due to vitamin B6 deficiency.[5,11,16,36]

Vitamin B6 Dosage Recommendations

Statement 3: Clear dose and duration recommendations associated with neuropathy aetiology, patient risk groups, or symptoms severity have not been established. Clinicians should carefully evaluate each patient's individual condition when deciding dosage and duration. Based on published literature and expert clinical practices, the following tolerable (maximum) daily dosage and associated duration of vitamin B6 intake is recommended for peripheral neuropathy as shown in Table 2.

Table 2 Tolerable (Maximum) Daily Dosage and Duration of Vitamin B6

Tolerable (Maximum) Dosage and Duration According to Literature	
Daily Dose of Vitamin B6	**Duration of Vitamin B6 Intake**
	Patients with Peripheral Neuropathy
50 mg	Long term use possible
100 mg*	Up to 5 years
200 mg	Up to 200 days
Up to 600 mg	Up to 18 weeks

Notes: *cap doses at 100 mg/day, as evidence indicate Peripheral Neuropathy risk even at 50–100 mg/day in susceptible individuals.

Strength of Recommendation: 8.3/10

The recommended dietary allowance (RDA) for adults at different life stages averages between 1.3–1.7 mg per day, which is an amount generally achievable through adequate food intake.[4,37] Among peripheral neuropathy patients with vitamin B6 deficiency, oral therapeutic doses of vitamin B6 are typically required.

Several studies have investigated the dosing range and potential adverse effects of Vitamin B6. Bernstein et al monitored 70 patients receiving 100–150 mg of Vitamin B6 for the treatment of carpal tunnel syndrome and diabetic neuropathy in a neurology clinic.[38] Over a 5-year period, the clinical and electrical status of the peripheral nerves were assessed, and it was concluded that there was no evidence of neurotoxicity from pyridoxine at these dosages. Pietrzik et al tested the dose limit for Vitamin B6 and suggested that its intake should not exceed 200 mg for more than 200 days.[39] For a usage duration of less than 200 days, the dosage of Vitamin B6 could reach up to 500 mg/day. Both studies align with a recent consensus guideline published by Coughlin et al, suggesting that patients treated with less than 500 mg of Vitamin B6 per day are at a lower risk of developing neurological side effect.[40] In a separate study, Janka et al administered 200 mg of Vitamin B6 three times a day (total of 600 mg/day) for 18 weeks, in combination with vitamins B1 and B12 to diabetic patients.[41] This study demonstrated significant symptom relief from neuropathy without adverse effects attributable to vitamin B therapy.

While the above reports suggested tolerable dosages of up to 600 mg/day, the overall quality of evidence regarding the dosage regimen and duration remains inconclusive owing to the limited studies available. It is crucial to understand that uncertainty remains regarding the optimal dosage regimen and duration for specific population subgroups, such as patients with peripheral neuropathy of various aetiologies or patients with different levels of symptom severity.[16] Additionally, Van Hunsel et al reported that a high therapeutic dosage and prolonged use of vitamin B6 (above the suggested tolerable amount) may be associated with an increased incidence of adverse events.[17] However, high-quality long-term studies are lacking and represent a gap in the scientific evidence required to draw valid conclusions.

In certain indications, parenteral administration of vitamin B6 may be required to achieve an adequate level of pyridoxine in the plasma rapidly.[5,42] Intravenous pyridoxine is administered as an antidote for isoniazid (INH) poisoning and for treatment of acute seizures for patients with vitamin B6-dependency syndromes.[5] Typically, these treatment regimens require high dosages of pyridoxine (>500mg), are administered in an acute setting, and are under the supervision of a healthcare professional for any potential adverse events induced by pyridoxine administration. On the other hand, oral administration of pyridoxine is typically consumed independently by patients on a chronic basis and there are reported clinical cases where patients consume pyridoxine unknowingly from multiple sources and therefore leading to excessive intake of pyridoxine.[17,43]

In light of post-marketing reports of vitamin B6-induced neurological side effect associated with supratherapeutic doses of vitamin B6,[17] several regulatory agencies had issued regulations permitting a maximum daily dose of 100 mg for listed medicines containing vitamin B6.[20,21] Clinicians should generally follow the dosage and duration recommendations for vitamin B6 as outlined by Bernstein et al, Pietrzik et al, and Janka et al when treating patients as a reference point.[38,39,41] However, clinicians must also use their clinical judgment, considering each patient's unique situation,

especially for those at high risk of vitamin B6 deficiency or for whom vitamin B6 is clinically indicated. Careful monitoring for treatment progress and any adverse reactions is essential in these cases.

Vitamin B6 Adverse Events

Statement 4: Vitamin B6-induced neurological adverse events have been reported in high therapeutic dose and long-term usage. However, these are generally rare and may be reversible upon treatment cessation when recognized early. Early detection of adverse events is key to management of neurological adverse events.

Strength of Recommendation: 9.2/10

Adverse events arising from the prolonged use of vitamin B6 have been reported in reviews, case reports, and post-marketing surveillance data.[16,17,24,43–48] Patients have developed vitamin B6-induced neurological symptoms at high doses and long-term usage of pyridoxine. The incidence rate of such vitamin B6-induced neurological side effects is low and remains unclear, given the lack of comprehensive data on vitamin B6 usage and total reported cases of adverse effects.[17,18] Dalton et al, Hunsel et al, and Sathienluckana et al noted the resolution of adverse effects upon cessation of pyridoxine treatment, albeit to varying degrees.[17,24,47] Early detection of adverse effects and therapy cessation have also been noted to improve symptom resolution in reported cases. The panel recommends regular monitoring of neurological adverse events, with healthcare professionals monitoring for severe symptoms or unexpected development of new symptoms in patients prescribed with vitamin B6. Screening and history-taking of vitamin B6 consumption would allow early detection of adverse events. Patients with prolonged symptoms without resolution despite treatment cessation should be evaluated for other possible causes.

The mechanism of neurological side effects due to excessive pyridoxine has not been fully elucidated, although studies have attempted to shed light on possible mechanisms underlying its development.[9,18,22]

1) Dose-dependent pathology: At high doses, pyridoxine saturates pyridoxal kinase and pyridoxine phosphate oxidase, effectively inhibiting these enzymes. Consequently, the pyridoxine vitamer accumulates, leading to paradoxically similar effects as those of Vitamin B6 deficiency.
2) Toxicity to sensory neurons: Pyridoxine disrupts GABA signalling by inhibiting GABA synthesis. As pyridoxine is relatively impermeable to the blood–brain barrier, pyridoxal kinase inhibition would be confined to the peripheral tissues. This may result in disrupted GABA signalling in peripheral tissues such as sensory neurons.
3) Genetic variations: Genes involved in vitamin B6 metabolism (eg pyridoxal kinase gene) have been associated with altered vitamin B6 levels and an increased risk of certain diseases. Genetic variants of the pyridoxine phosphate oxidase (PNPO) locus influence vitamin B6 metabolism and may lead to toxicity.

Statement 5: For patient usage duration of longer than 6 months, and over 50 mg/day vitamin B6, regular monitoring by healthcare professionals is recommended. If patients develop neurological side effects, a washout period of 20 ~ 40 days (3 ~ 6 weeks) is recommended before considering resuming vitamin B6 treatment. For some cases with prolonged symptoms, extend to 3–6 months for recovery depending on patient's neurological side effect.

Strength of Recommendation: 7.3/10

In addition to the suggested dosage and treatment duration for pyridoxine, the panel suggests regular monitoring by healthcare professionals every six months, for patients receiving long-term (>6 months) high-dose (>50mg) vitamin B6. Periodic neurological examinations should assess patients for worsening symptoms of neurological side effects such as numbness, tingling sensation, or weakness in the extremities. Documentation of patients' vitamin B6 intake history, including dosage, duration, and changes over time, is also advised. Periodic laboratory tests, including complete blood counts and metabolic panels, should be conducted to monitor potential haematological or hepatic abnormalities.

In rare cases where patients develop signs or symptoms of vitamin B6 adverse effects such as neurological side effects, the panel suggests a blood test to determine pyridoxine, PLP and pyridoxic acid levels if available. Due to fluctuations in vitamin B6 metabolites level after supplementations, patients are advised to fast for at least 12 hours prior to sample collection.[49] Elevated vitamin B6 levels above the reference value have been noted in patients who

experienced neurological side effects and could be a useful indicator of vitamin B6 toxicity for clinicians.[17,45,47] Hunsel et al investigated the serum pyridoxine levels of patients who developed peripheral neuropathy, and the mean serum level was 907 nmol/l, higher than the reference values of 51–183 nmol/l.[17] PLP and pyridoxic acid have reference values of 5–50 mcg/L and 3–30mcg/L respectively.[49] Different laboratories have differing reference intervals for population normal ranges and clinicians are advised to refer to the reference value fields provided by their respective laboratories. In the absence of vitamin B6 blood tests, clinicians should rely on clinical judgement (ie, signs, symptoms, and differential diagnosis) to determine whether to continue or cease vitamin B6 therapy. If pyridoxine levels are within the normal range, B6 treatment may be continued, while considering alternative causes of adverse effects. However, for patients with pyridoxine levels exceeding the normal range, vitamin B6 usage should be discontinued.

The recovery duration for patients who developed neurological side effects varies in reported studies, with reported recovery durations ranging from 3 months to 2 years after treatment cessation, depending on the dose applied and treatment duration.[44,47,48] Although the duration of recovery remains unclear in the current literature, the panel suggests implementing a washout period for this group of patients. A washout period or drug holiday is a common practice among healthcare professionals, involving deliberate interruption of pharmacotherapy for a defined period of time to alleviate the adverse effects associated with therapy.[50] To the best of our knowledge, no randomized trials have been conducted on practising drug holiday to alleviate adverse effect due to vitamin B6, nor proposed washout period from existing guidelines for the clearance of vitamin B6. However, a recent study conducted on the drug holiday of multiple sclerosis treatment showed non-inferiority compared to a full regimen, demonstrating that drug holidays have the potential to alleviate adverse effects while maintaining a similar level of treatment effectiveness.[51] Based on studies exploring the mechanism of pyridoxine toxicity,[9,18,22] the accumulation of pyridoxine and its metabolites in the body leads to neurological side effects, and cessation of therapy typically results in symptom resolution.

To determine the appropriate washout period for complete clearance of pyridoxine and its metabolites from the body, the pharmacokinetic parameters of pyridoxine and its metabolites were considered based on the following calculation:

$$\text{Washout period} = \text{n} \times \text{Elimination half} - \text{life}(\text{t}1/2)$$

where n refers to the number of half-lives passed before the next treatment phase.

PLP is the predominant metabolite of vitamin B6 and has the longest elimination half-life, ranging from 36–95 hours across pyridoxine metabolites.[6,52] The US FDA and EMA recommend a washout period of five half-lives to ensure complete elimination of the drug before the next treatment phase, whereas Health Canada recommended ten half-lives to determine the washout period.[53–55] Concurrently, the duration for resolution of side effects varies among case reports. Therefore, the panel suggests adopting a conservative approach, allowing complete elimination of pyridoxine when managing patients with side effects, by adopting the longer period of either the time required for full recovery from adverse effects or calculated serum elimination of pyridoxine and its metabolites. For patients indicated for vitamin B6 therapy and requiring treatment, the panel suggests a washout period of 20–40 days before assessing a need for the resumption of vitamin B6.

The panel suggests that the resumption of vitamin B6 treatment be based on the discretion of healthcare professionals, noting the need to maintain a dynamic therapeutic window of pyridoxine for patients and ensuring that patients indicated for vitamin B6 therapy continue to be treated.

Limitations

The limitations of the current body of evidence are evident in the inconclusive data regarding clear well-tolerated dosage and duration of vitamin B6, with concerns from healthcare professionals about a lack of clear guidance on managing patients indicated for vitamin B6 therapy with regard to potential side effects. Additionally, although valuable, post-marketing surveillance data were limited in the comprehensive details required to ascertain the true incidence and causative factors of adverse effects. Concerns of toxicity development have led to regulatory agencies sharing safety concerns with inappropriate usage of vitamin B6-containing products. Finally, the findings and recommendations are solely based on adult patients and do not include children, pregnant women, or lactating women. Hence, the findings and recommendations should not be generalized to these populations.

Despite the stated limitations, the consensus statements developed were grounded in a comprehensive review of the available literature and the extensive experience of the expert panel. The study also acknowledged the limitation of a small group of expert panel sizes in deriving consensus, although the extensive and diverse experience of experts from multiple fields and geographic regions provides a broad range of perspectives. This paper aims to offer healthcare professionals practical guidance on using vitamin B6 in clinical practice. The authors believe a comprehensive review, like the one presented, is the most effective way to achieve this goal and explore the subsequent implications of vitamin B6 usage.

Conclusion

Since its discovery, the critical role of vitamin B6 has been implicated in numerous physiological processes, including neurotransmitter synthesis, metabolism, immune function and treatment of clinical conditions such as peripheral neuropathy. However, the risk of vitamin B6-induced neurological side effects at high doses with long-term usage has been raised over the years and necessitates cautious administration and vigilant monitoring.

This consensus statement publication highlights five key statements which address the dosing, duration, and treatment algorithm for adult patients indicated for vitamin B6 therapy based on the best available evidence to provide guidance for healthcare professionals on the usage of vitamin B6 while minimizing the occurrence of neurological side effects. While current evidence supporting these consensus statements is limited, it is imperative to continue evaluating new and available evidence that supports the safe usage of vitamin B6 to improve patient care. Future research should also aim to address current gaps through large-scale, controlled trials to evaluate the long-term efficacy, safety, and potential risk factors for development of pyridoxine toxicity. Studies investigating underlying mechanisms of pyridoxine-induced neurological side effects will also provide valuable insights.

In conclusion, while vitamin B6 remains a vital nutrient with therapeutic potential, its administration must be carefully managed to mitigate risks and optimize patient outcomes.

Ethics Approval and Informed Consent

All methods in relation to this study were conducted in accordance with the ESOMAR guidelines and the Declaration of Helsinki (1964). This study obtained Exempt status by Pearl IRB (2024-0183) in May 2024. Informed consent was obtained from all experts.

Consent for Publication

Consent for publication was obtained from all authors.

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