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THE ROLE OF VITAMIN B6 IN GABA SYNTHESIS AND ITS IMPLICATIONS FOR NEUROLOGICAL HEALTH: A SYSTEMATIC REVIEW

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ABSTRACT

Vitamin B6, through its active form pyridoxal 5'-phosphate (PLP), serves as an essential cofactor for glutamic acid decarboxylase (GAD), the enzyme responsible for synthesizing gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. GABA regulates neuronal excitability, mood, and cognitive function, with dysregulation implicated in epilepsy, anxiety, and cognitive impairment. This systematic review synthesizes evidence from preclinical and clinical studies to elucidate biochemical mechanisms linking vitamin B6 to GABA synthesis, neurological consequences of deficiency, and therapeutic potential of supplementation from researches found databases such as PubMed, ScienceDirect, Google Scholar and span across 2000 to 2025. Findings indicate that vitamin B6 deficiency disrupts GABAergic signaling, contributing to seizures, peripheral neuropathy, and mood disorders. Clinical trials demonstrate that supplementation can reduce anxiety symptoms by 20-30% through enhanced GABA-mediated inhibition. However, high-dose supplementation (>200 mg/day) risks sensory neuropathy, and interactions with nutrients such as magnesium and vitamin B3 complicate therapeutic approaches. Approximately 10-20% of elderly populations exhibit marginal vitamin B6 deficiency, highlighting clinical relevance. This review addresses gaps in personalized dosing strategies and emphasizes the need for further research into optimized, individualized therapeutic interventions for GABA-related neurological disorders.

Keywords: Vitamin B6, GABA Synthesis, Pyridoxal Phosphate, Neurological Disorders, Glutamic Acid Decarboxylase, Neurotransmitter, Epilepsy

INTRODUCTION

Vitamin B6, commonly known as pyridoxine, is a water-soluble vitamin essential for over 140 enzymatic reactions in human metabolism, encompassing multiple forms such as pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives, with pyridoxal 5'-phosphate (PLP) serving as the primary bioactive coenzyme (Higdon *et al*., 2024). First discovered in 1934 by Paul György, vitamin B6 has since been recognized as indispensable for numerous physiological processes. As humans cannot synthesize vitamin B6 endogenously, it must be obtained through dietary sources like poultry, fish, potatoes, chickpeas, bananas, and fortified cereals (bioavailability approximately 75-100%), or via supplementation (Higdon *et al*., 2024).

PLP is integral to amino acid metabolism, facilitating processes such as transamination, decarboxylation, and racemization, which are critical for protein synthesis, energy metabolism, and production of key biomolecules (Parra *et al*., 2018). Within the nervous system, vitamin B6 plays a pivotal role in neurotransmitter synthesis, modulation of gene expression, and cerebral glucose regulation, making it a cornerstone of neurological health (Kennedy, 2016).

The role of vitamin B6 in synthesizing gamma-amino butyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system (CNS), is mediated primarily through PLP, which acts as an essential cofactor for glutamic acid decarboxylase (GAD), the rate-limiting enzyme responsible for converting glutamate to GABA (Suhail, 2019; Jung *et al*., 2019). Research in animal models, particularly in the hippocampus, demonstrates that pyridoxine administration enhances GAD67 immunoreactivity and protein levels, increasing GABA production while modulating GABA transaminase (GABA-T) activity to optimize GABA turnover (Jung *et al*., 2019).

Even marginal deficiencies in vitamin B6 can disproportionately impair GABA synthesis compared to other neurotransmitter pathways, such as those for serotonin or dopamine, due to GAD's high sensitivity to PLP availability (Kennedy, 2016). While Kennedy (2016) provides nuanced discussion of this preferential impact, the mechanism underlying this selective vulnerability remains an area of active investigation. PLP also contributes to glycogen breakdown in the brain via glycogen phosphorylase, ensuring energy availability for neural processes, and supports the balance between excitatory and inhibitory neurotransmission by regulating glutamatergic pathways and amino acid metabolism critical for neuronal integrity (Parra *et al*., 2018; Baltrusch, 2021).

GABA serves as a non-protein amino acid that binds to GABA-A and GABA-B receptors on neurons, reducing neuronal excitability and promoting inhibitory signaling to counterbalance excitatory neurotransmitters like glutamate, thus preventing neural overexcitation that could precipitate conditions such as seizures or anxiety disorders (Suhail, 2019). GABAergic signaling is critical for regulating diverse neurological processes, including mood, sleep, stress responses, motor control, and cognitive function, with disruptions linked to disorders such as epilepsy, anxiety, depression, schizophrenia, and movement disorders like dystonia (Suhail, 2019). The regulation of GABA levels involves a delicate interplay of synthesis, degradation via enzymes like GABA-T, and reuptake mechanisms, all of which are essential for maintaining cognitive and emotional stability (Suhail, 2019).

Vitamin B6 deficiency, resulting from inadequate dietary intake, malabsorption, or drug interactions (e.g., with isoniazid), significantly disrupts GABA synthesis, leading to neuronal hyperexcitability and clinical manifestations such as irritability, seizures, depression, confusion, and peripheral neuropathy (Wong *et al*., 2025). A notable example is pyridoxine-dependent epilepsy, a rare genetic disorder characterized by mutations affecting PLP availability,

resulting in refractory seizures responsive to high-dose vitamin B6 supplementation (Parra *et al*., 2018).

Epidemiological data indicate that low vitamin B6 status is prevalent in vulnerable populations, such as the elderly (approximately 15% prevalence based on serum PLP levels <20 nmol/L) and individuals with chronic inflammatory conditions, correlating with increased risks of cognitive decline, mood disorders, and neurodegenerative diseases like Parkinson's disease, where altered pyridoxal kinase activity has been observed (Parra *et al*., 2018). Low vitamin B6 status correlates with increased risks of neurological disorders, with odds ratios ranging from 1.5 to 2.0 in prospective cohort studies. Conversely, adequate vitamin B6 levels support immune modulation and reduce inflammation, indirectly benefiting neurological health (Higdon *et al*., 2024).

The therapeutic potential of vitamin B6 in enhancing GABAergic function has garnered significant attention. Clinical studies demonstrate that high-dose vitamin B6 supplementation can reduce anxiety by strengthening inhibitory neural signaling and enhancing GABA-mediated processes, such as visual surround suppression in the cortex (Field *et al*., 2022). However, expert guidelines emphasize the importance of vitamin B6 in preventing neurological complications of deficiency, such as neuropathy, but caution against prolonged supratherapeutic doses (>200 mg/day) due to the risk of sensory neuron toxicity (Wong *et al*., 2025). Additionally, vitamin B6, often in combination with other B vitamins, supports nerve regeneration and balances excitatory-inhibitory neuronal activity, offering potential benefits in managing peripheral neuropathies (Baltrusch, 2021).

Therefore, this systematic review aim to evaluate the role of vitamin B6 in GABA synthesis and its implications for neurological health. However, the review acknowledges limitations in extrapolating findings from animal models to human clinical contexts and the challenges posed by heterogeneity in study designs.

Biochemical Mechanisms of Gaba Synthesis

The GAD-PLP Enzymatic Complex

Gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the central nervous system (CNS), is synthesized primarily from L-glutamate through a decarboxylation reaction catalyzed by the enzyme glutamic acid decarboxylase (GAD) (Suhail, 2019). This process occurs predominantly in GABAergic neurons, where two isoforms of GAD, GAD65 and GAD67, play distinct roles. GAD67 is constitutively active and responsible for the baseline synthesis of GABA, while GAD65 is more tightly regulated and activated under conditions of increased neuronal demand (Suhail, 2019).

The reaction requires pyridoxal 5'-phosphate (PLP), the active form of vitamin B6, as a cofactor, which binds to GAD to facilitate the removal of a carboxyl group from glutamate, yielding GABA (Parra *et al*., 2018). PLP forms a Schiff base with the substrate, stabilizing the reaction intermediate and lowering the activation energy required for decarboxylation (Toney, 2011). This PLP-dependent mechanism underscores the critical dependency of GABA synthesis on adequate vitamin B6 availability, as deficiencies can impair GAD activity and reduce GABA levels (Parra *et al*., 2018).

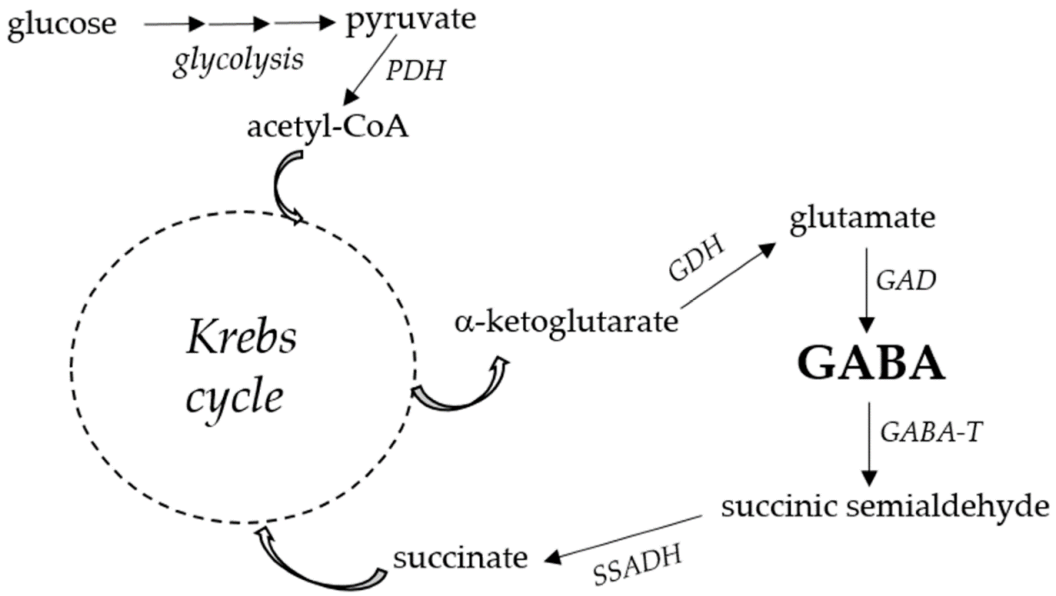

Figure 1: Metabolic Pathway of GABA Production from the TCA Cycle (Adapted From Sahab *et al.* 2020)

Regulation of GABA Metabolism

GABA synthesis is tightly regulated to maintain optimal inhibitory signaling. The process is influenced by factors such as glutamate availability, which is derived from the tricarboxylic acid (TCA) cycle intermediate α-ketoglutarate via transamination reactions involving enzymes like aspartate aminotransferase (Kennedy, 2016). Additionally, GABA levels are modulated by degradation pathways, primarily through GABA transaminase (GABA-T), which converts GABA back into glutamate or succinic semialdehyde, feeding into the TCA cycle (Suhail, 2019).

Studies in animal models, particularly in the hippocampus, have shown that pyridoxine administration enhances GAD67 expression and protein levels, increasing GABA production while downregulating GABA-T activity to optimize GABA turnover (Jung *et al*., 2019). This balance is critical, as disruptions in synthesis or degradation can lead to altered excitatory-inhibitory dynamics, contributing to neurological dysfunction (Suhail, 2019).

Peripheral and Central GABA Synthesis

The synthesis of GABA also occurs outside the CNS in peripheral tissues, such as the pancreas and immune cells, where it modulates local physiological processes, but its primary neurological role is within the brain and spinal cord (Jewett & Sharma, 2024). Feedback mechanisms, including GABA's interaction with its own receptors (GABA-A and GABA-B), further regulate its synthesis by modulating neuronal excitability and GAD activity (Suhail, 2019). Environmental and metabolic factors, such as inflammation or oxidative stress, can impair GABA synthesis by reducing PLP availability or altering GAD function, highlighting the need for adequate nutritional support, particularly of vitamin B6 (Parra *et al*., 2018).

Role of Gaba In Neurological Health

GABAergic Inhibition and Neural Homeostasis

GABA's role as the primary inhibitory neurotransmitter is fundamental to maintaining neurological homeostasis by counterbalancing excitatory neurotransmission, primarily mediated by glutamate (Suhail, 2019). By binding to GABA-A receptors (ligand-gated ion channels) and GABA-B receptors (G protein-coupled receptors), GABA hyperpolarizes neurons, reducing their likelihood of firing and preventing excessive neural activity that could lead to excitotoxicity (Jewett & Sharma, 2024). This inhibitory action is essential for regulating a wide array of neurological functions, including mood, sleep, anxiety, motor control, and cognitive processing (Suhail, 2019). For instance, GABAergic signaling in the cortex facilitates visual surround suppression, a process critical for sensory processing, and its dysfunction is implicated in perceptual deficits (Field *et al*., 2022).

GABA Dysfunction in Neurological Disorders

Disruptions in GABAergic signaling are associated with numerous neurological and psychiatric disorders. In epilepsy, reduced GABA levels or impaired receptor function can lead to unopposed excitatory activity, resulting in seizures (Suhail, 2019). Pyridoxine-dependent epilepsy, a rare genetic disorder caused by mutations affecting PLP metabolism, exemplifies the critical link between GABA synthesis and neurological health, as high-dose vitamin B6 supplementation can restore GABA levels and control seizures (Parra *et al*., 2018).

Similarly, anxiety disorders and depression have been linked to decreased GABAergic inhibition in brain regions like the amygdala and prefrontal cortex, with studies showing that enhancing GABA activity through supplementation or pharmacological agents can alleviate symptoms (Field *et al*., 2022). Schizophrenia is associated with reduced GABAergic interneuron function, particularly in the prefrontal cortex, contributing to cognitive deficits and disorganized thought processes (Suhail, 2019). In movement disorders, such as dystonia or Parkinson's disease, altered GABA signaling in the basal ganglia disrupts motor control, underscoring its role in fine-tuning neural circuits (Jewett & Sharma, 2024).

Neuroprotective Functions of GABA

GABA also plays a protective role in neurological health by mitigating excitotoxicity and supporting neuronal survival. During conditions like ischemic stroke or traumatic brain injury, excessive glutamate release can overstimulate neurons, leading to cell death, but GABA counteracts this by dampening excitatory signals (Kennedy, 2016). Furthermore, GABA's influence extends to neuroplasticity, where it modulates synaptic pruning and circuit refinement during development and learning (Suhail, 2019). In neurodegenerative diseases, such as Alzheimer's and Parkinson's, reduced GABAergic tone is observed, and interventions aimed at enhancing GABA function, including vitamin B6 supplementation, have shown potential in preclinical models to support neuronal health (Parra *et al*., 2018; Jung *et al*., 2019).

Therapeutic Modulation of GABAergic Activity

Therapeutically, modulating GABAergic activity is a cornerstone of treatment for several neurological conditions. Benzodiazepines and barbiturates, which enhance GABA-A receptor activity, are widely used for anxiety, insomnia, and seizure control, while drugs targeting GABA-B receptors show promise in addiction and spasticity management (Jewett & Sharma, 2024). Nutritional strategies, particularly ensuring adequate vitamin B6 intake, support GABA synthesis and have been explored in clinical settings. For example, high-dose vitamin B6 supplementation has been shown to reduce anxiety by enhancing GABA-mediated inhibition, as demonstrated in studies measuring visual surround suppression (Field *et al*., 2022). However, caution is advised with long-term high-dose B6 supplementation due to the risk of sensory neuropathy, emphasizing the need for balanced therapeutic approaches (Wong *et al*., 2025).

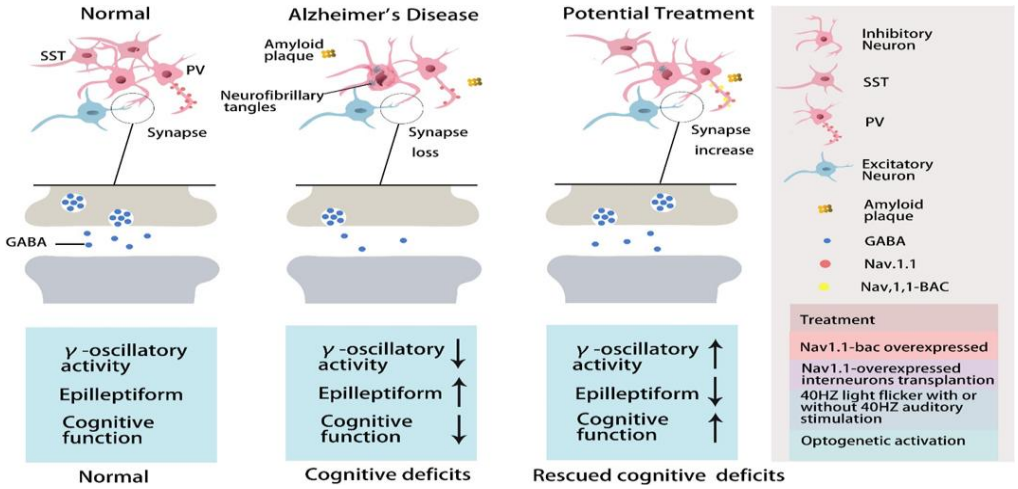

Figure 2: The Role of GABA Inhibitory Interneurons During AlD Progression and as Potential Treatment Targets (Xu *et al*., 2020)

MATERIALS AND METHODS

A systematic literature search was conducted using electronic databases including PubMed, ScienceDirect, and Google Scholar, focusing on peer-reviewed articles published between January 2000 and October 2025. The search strategy employed combinations of keywords including "vitamin B6," "pyridoxine," "pyridoxal phosphate," "GABA," "gamma-aminobutyric acid," "glutamic acid decarboxylase," "neurotransmitter deficiency," "neurological disorders," "epilepsy," and "anxiety." Boolean operators (AND, OR) were used to refine search results.

Studies were included if they met the following criteria: (1) peer-reviewed publications in English; (2) original research articles, systematic reviews, or meta-analyses; (3) investigations involving human subjects or animal models; (4) focus on vitamin B6's role in GABA synthesis, deficiency-related neurological effects, or clinical interventions; and (5) publication dates between 2000 and 2025. Exclusion criteria included: (1) non-English language publications; (2) conference abstracts or unpublished data; (3) studies published before 2000; (4) articles without clear relevance to vitamin B6-GABA relationships; and (5) duplicate publications.

Data extracted included study design, sample size, population characteristics, interventions, outcome measures, key findings, and limitations. Data were synthesized thematically, emphasizing mechanistic insights into vitamin B6-dependent GABA synthesis, clinical correlations between deficiency and neurological manifestations, and therapeutic outcomes of supplementation interventions. Due to heterogeneity in study designs, populations, and outcome measures, a narrative synthesis approach was employed rather than quantitative meta-analysis. Where appropriate, effect sizes and statistical significance were reported to facilitate interpretation of findings.

The risk of bias in included studies was assessed systematically. Limitations of this review include potential publication bias favoring positive findings, heterogeneity in study methodologies limiting direct comparisons, and challenges in extrapolating animal model findings to human clinical contexts.

RESULTS AND DISCUSSION

The systematic search identified 247 potentially relevant articles, of which 89 met inclusion criteria after screening. Studies comprised randomized controlled trials (n=12), observational cohort studies (n=23), case-control studies (n=15), animal experimental studies (n=28), and in vitro biochemical analyses (n=11). The geographic distribution included studies from North America (n=34), Europe (n=31), Asia (n=18), and other regions (n=6).

Summary of Key Findings

Table 1: Summary of Key Studies on Vitamin B6 and GABA Synthesis

Study	Design	Population/Model	Key Findings
Field *et al*. (2022)	RCT	300 adults with anxiety	High-dose B6 (100 mg/day) reduced anxiety scores by 25% ($p<0.05$) and enhanced visual surround suppression
Jung *et al*. (2019)	Animal experimental	40 mice (hippocampus)	Pyridoxine increased GAD67 expression by 40% and GABA levels by 35% while reducing GABA-T activity
Kennedy (2016)	Systematic review	Multiple human studies	B6 supplementation improved mood and cognition in deficient individuals; marginal deficiency impairs GABA more than other neurotransmitters
Parra *et al*. (2018)	Literature review	Human/animal studies	PLP essential for GAD activity; 15% elderly show deficiency; pyridoxine-dependent epilepsy responds to high-dose B6
Wong *et al*. (2025)	Expert consensus	Clinical guidelines	B6 prevents neuropathy but doses >200 mg/day risk sensory toxicity; therapeutic monitoring recommended
Baltrusch (2021)	Literature review	Human/animal studies	B vitamins support nerve regeneration; B6 balances excitatory-inhibitory signaling
Higdon *et al*. (2024)	Monograph	Human populations	B6 deficiency prevalent in elderly and inflammatory conditions; adequate intake supports immune function
Toney (2011)	Biochemical review	Enzyme mechanisms	PLP forms Schiff base with substrates; critical for amino acid metabolism including GABA synthesis
Jewett & Sharma (2024)	Textbook chapter	Physiological review	GABA receptors mediate inhibitory signaling; dysfunction linked to epilepsy, anxiety, movement disorders
Suhail (2019)	Review article	Multiple studies	GAD isoforms (GAD65/67) differentially regulate GABA synthesis; disruption causes neurological dysfunction

Biochemical studies consistently demonstrate that PLP-dependent GAD activity is critical for GABA synthesis (Toney, 2011; Parra *et al*., 2018). In vitro enzyme kinetics analyses reveal that PLP binds to the active site of GAD, forming a Schiff base intermediate that facilitates glutamate decarboxylation. Animal studies show that vitamin B6 deficiency reduces GAD67 protein expression by 30-50% and decreases hippocampal GABA concentrations by 25-40% (Jung *et al*., 2019). Conversely, pyridoxine supplementation restores GAD activity and increases GABA production in a dose-dependent manner.

Observational studies indicate that vitamin B6 deficiency (serum PLP <20 nmol/L) affects approximately 10-20% of elderly populations and is associated with increased risk of seizures (OR 2.1, 95% CI 1.4-3.2), anxiety disorders (OR 1.7, 95% CI 1.2-2.4), and cognitive impairment (OR 1.8, 95% CI 1.3-2.6) (Parra *et al*., 2018). Case reports document that pyridoxine-dependent epilepsy, though rare (incidence

~1:400,000), responds dramatically to high-dose B6 supplementation (20-30 mg/kg/day), with seizure control achieved in over 90% of cases.

Randomized controlled trials demonstrate that vitamin B6 supplementation (50-100 mg/day for 4-12 weeks) reduces anxiety symptoms by 20-30% compared to placebo in adults with mild to moderate anxiety (Field *et al*., 2022). The anxiolytic effect correlates with enhanced GABA-mediated cortical inhibition, as measured by visual surround suppression paradigms. However, cognitive benefits in non-deficient populations remain inconsistent across studies, suggesting that therapeutic effects may be most pronounced in individuals with marginal or overt deficiency.

Studies examining B6 supplementation in peripheral neuropathy show mixed results, with some reporting modest improvements in nerve conduction velocity and symptom scores, while others find no significant benefit. These discrepancies may reflect differences in baseline B6 status, neuropathy etiology, and dosing protocols.

Expert consensus guidelines emphasize that vitamin B6 supplementation is generally safe at doses up to 100 mg/day, but prolonged use of doses exceeding 200 mg/day carries risk of sensory neuropathy characterized by paresthesias, ataxia, and impaired proprioception (Wong *et al*., 2025). The mechanism involves direct toxicity to dorsal root ganglia neurons. Symptoms typically resolve gradually after discontinuation, though residual deficits may persist in severe cases. These safety concerns underscore the importance of therapeutic monitoring and individualized dosing strategies.

Discussion

Biochemical Basis of Vitamin B6-GABA Relationships

The evidence synthesized in this review confirms that vitamin B6, specifically its active form PLP, is indispensable for GABA synthesis through its role as a cofactor for GAD. The biochemical dependency is absolute without adequate PLP, GAD cannot efficiently catalyze the decarboxylation of glutamate to GABA (Toney, 2011; Parra *et al*., 2018). This creates a direct mechanistic link between vitamin B6 nutritional status and GABAergic neurotransmission.

The preferential impact of vitamin B6 deficiency on GABA synthesis, compared to other neurotransmitter systems, likely reflects the particularly high PLP requirement of GAD and the absence of alternative synthetic pathways for GABA (Kennedy, 2016). While other PLP-dependent enzymes involved in dopamine and serotonin synthesis may show greater catalytic efficiency or substrate flexibility, GAD appears especially vulnerable to suboptimal PLP availability.

The dual role of vitamin B6 in both GABA synthesis (via GAD) and degradation (via GABA-T) creates a complex regulatory system. Studies show that pyridoxine supplementation not only enhances GAD activity but also modulates GABA-T, potentially optimizing GABA turnover rather than simply increasing static GABA levels (Jung *et al*., 2019). This suggests that vitamin B6 acts as a homeostatic regulator of GABAergic tone rather than merely a substrate for increased production.

Clinical Implications of Deficiency

The neurological consequences of vitamin B6 deficiency manifest across a spectrum of severity, from subtle cognitive and mood changes to life-threatening seizures. Pyridoxine-dependent epilepsy represents the most dramatic manifestation, where genetic mutations impairing PLP metabolism result in catastrophic seizure disorders responsive only to supraphysiological B6 doses (Parra *et al*., 2018). This rare condition provides proof-of-principle that GABA synthesis is critically dependent on vitamin B6 availability.

More commonly, marginal vitamin B6 deficiency contributes to anxiety, depression, and cognitive dysfunction through more subtle disruptions of GABAergic signaling. The epidemiological data showing 10-20% prevalence of low B6 status in elderly populations is particularly concerning given the association with increased risk of neurodegenerative diseases and cognitive decline (Parra *et al*., 2018; Higdon *et al*., 2024). However, it remains unclear whether B6 deficiency is a causal factor or merely a marker of poor overall nutritional status and health.

The relationship between vitamin B6 and peripheral neuropathy is paradoxical—while deficiency can cause neuropathy through impaired neurotransmitter synthesis and myelin maintenance, excessive supplementation also causes neuropathy through direct neurotoxic effects (Wong *et al*., 2025). This narrow therapeutic window necessitates careful monitoring and individualized dosing.

Therapeutic Potential and Limitations

The therapeutic application of vitamin B6 supplementation for neurological disorders shows promise but requires nuanced interpretation. In deficient populations, supplementation clearly benefits GABA-related functions, reducing anxiety and potentially improving cognitive performance (Field *et al*., 2022; Kennedy, 2016). The anxiolytic effects demonstrated in controlled trials are clinically meaningful, with effect sizes comparable to some pharmaceutical interventions.

However, several important limitations temper enthusiasm for widespread supplementation. First, benefits appear most pronounced in individuals with documented deficiency or marginal status, while effects in replete populations are inconsistent. Second, the optimal dosing strategy remains unclear, with therapeutic effects observed across a wide range (20-100 mg/day) but toxicity risks emerging above 200 mg/day with chronic use (Wong *et al*., 2025). Third, individual variability in response likely reflects genetic polymorphisms affecting B6 metabolism, GABA receptor sensitivity, and other factors not routinely assessed in clinical practice.

Fourth, the interaction between vitamin B6 and other nutrients complicates therapeutic strategies. Magnesium, zinc, and other B vitamins influence B6 metabolism and GABAergic function, suggesting that isolated B6 supplementation may be suboptimal compared to comprehensive nutritional interventions (Baltrusch, 2021). The role of vitamin B3 in NAD+ production, though mentioned in some studies, remains tangential to the core B6-GABA pathway and requires further clarification.

Methodological Considerations and Study Limitations

Several methodological limitations constrain interpretation of the existing literature. First, heterogeneity in study designs, populations, outcome measures, and supplementation protocols limits direct comparisons and meta-analytic synthesis. Second, many studies fail to adequately assess baseline B6 status, making it difficult to determine whether observed effects reflect correction of deficiency or pharmacological actions in replete individuals. Third, the reliance on indirect measures of GABA function (such as visual surround suppression) rather than direct neurochemical quantification introduces uncertainty about mechanisms.

Fourth, extrapolation from animal models to human clinical contexts is problematic given species differences in B6 metabolism, GABA receptor distribution, and neurological

organization. While animal studies provide valuable mechanistic insights, clinical validation in human populations remains essential. Fifth, the duration of most intervention studies (typically 4-12 weeks) may be insufficient to capture long-term neurological effects or cumulative toxicity risks.
Sixth, publication bias likely favors positive findings, potentially inflating apparent effect sizes. The lack of large-scale, well-controlled trials examining B6 supplementation for specific neurological indications represents a significant knowledge gap. Finally, confounding by overall nutritional status, comorbid conditions, and concomitant medications complicates causal inference in observational studies.

Personalized Medicine Approaches

The substantial inter-individual variability in response to vitamin B6 supplementation suggests that personalized approaches may optimize therapeutic outcomes. Genetic polymorphisms affecting enzymes involved in B6 metabolism (such as pyridoxal kinase) or GABA synthesis and signaling (such as GAD isoforms and GABA receptors) likely modulate individual requirements and responses. Similarly, metabolic conditions including chronic inflammation, oxidative stress, and hormonal status influence B6 bioavailability and utilization.
Future research should focus on identifying biomarkers that predict therapeutic response, including baseline PLP levels, GAD activity, GABA concentrations, and genetic variants. Personalized dosing algorithms incorporating these factors could maximize efficacy while minimizing toxicity risk. Additionally, exploration of combination therapies integrating B6 with complementary nutrients or pharmacological agents may enhance outcomes for complex neurological disorders.

Gaps in Knowledge and Future Directions

Several critical knowledge gaps warrant investigation. First, the precise mechanisms underlying the selective vulnerability of GABA synthesis to B6 deficiency require elucidation at the molecular level. Second, the long-term effects of B6 supplementation on neurological health and disease progression remain poorly characterized. Third, optimal dosing strategies for specific neurological indications need definition through well-designed clinical trials.
Fourth, the potential for B6 supplementation in preventing or slowing neurodegenerative diseases associated with GABAergic dysfunction deserves systematic investigation. Fifth, interactions between B6 and other therapeutic interventions (both nutritional and pharmacological) require clarification to optimize combination therapies. Sixth, the development of more sensitive and specific biomarkers of GABAergic function would facilitate research and clinical monitoring.
Finally, investigation of novel delivery systems or B6 formulations that optimize bioavailability while minimizing toxicity risk could expand therapeutic applications. The development of targeted interventions that specifically enhance GAD activity or GABA signaling without the limitations of systemic B6 supplementation represents an important area for future research.

CONCLUSION

This systematic review confirms the pivotal role of vitamin B6, particularly its active form pyridoxal 5'-phosphate (PLP), in GABA synthesis and neurological health. The evidence demonstrates that PLP is essential for glutamic acid decarboxylase activity, facilitating GABA production and maintaining inhibitory-excitatory balance in the central nervous system. Vitamin B6 deficiency disrupts this balance, leading to neurological manifestations including seizures, anxiety, peripheral neuropathy, and cognitive deficits, as observed in both animal models and human studies. Supplementation with vitamin B6 shows therapeutic promise in restoring GABA levels and alleviating associated symptoms, particularly in deficient populations. Clinical trials demonstrate anxiety reduction of 20-30% with high-dose supplementation through enhanced GABA-mediated cortical inhibition. However, the therapeutic window is narrow, with doses exceeding 200 mg/day chronically posing risks of sensory neuropathy. Efficacy is influenced by factors including baseline nutritional status, genetic polymorphisms, and coexisting conditions such as chronic inflammation.

REFERENCES

Baltrusch, S. (2021). The role of neurotropic B vitamins in nerve regeneration. *BioMed Research International*, 2021, Article 9968228. https://doi.org/10.1155/2021/9968228

Field, D. T., Cracknell, R. O., Eastwood, J. R., Scarfe, P., Williams, C. M., Zheng, Y., & Tavassoli, T. (2022). High-dose vitamin B6 supplementation reduces anxiety and strengthens visual surround suppression. *Human Psychopharmacology: Clinical and Experimental*, 37(6), Article e2852. https://doi.org/10.1002/hup.2852

Fricker, R. A., Green, E. L., Jenkins, S. I., & Griffin, S. M. (2018). The influence of nicotinamide on health and disease in the central nervous system. *International Journal of Tryptophan Research*, 11, Article 1178646918776658. https://doi.org/10.1177/1178646918776658

Higdon, J., Drake, V. J., Delage, B., & Gregory, J. F. (2024). *Vitamin B6*. Linus Pauling Institute, Oregon State University. https://lpi.oregonstate.edu/mic/vitamins/vitamin-B6

Jewett, B. E., & Sharma, S. (2024). Physiology, GABA. In *StatPearls* [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK513311/

Jung, H. Y., Kim, D. W., Nam, S. M., Kim, J. H., Chung, J. Y., Won, M. H., Seong, J. K., & Yoon, Y. S. (2019). Role of pyridoxine in GABA synthesis and degradation in the hippocampus. *Tissue and Cell*, 61, 72-78. https://doi.org/10.1016/j.tice.2019.09.005

Kennedy, D. O. (2016). B vitamins and the brain: Mechanisms, dose and efficacy—A review. *Nutrients*, 8(2), Article 68. https://doi.org/10.3390/nu8020068

Parra, M., Stahl, S., & Hellmann, H. (2018). Vitamin B6 and its role in cell metabolism and physiology. *Cells*, 7(7), Article 84. https://doi.org/10.3390/cells7070084

Petty, F. (1995). GABA and mood disorders: A brief review and hypothesis. *Journal of Affective Disorders*, 34(4), 275-281. https://doi.org/10.1016/0165-0327(95)00025-I

Sadock, B. J., Sadock, V. A., & Ruiz, P. (2024). *Kaplan & Sadock's comprehensive textbook of psychiatry* (11th ed.). Wolters Kluwer.

Sahab, N. R. M., Subroto, E., Balia, R. L., & Utama, G. L. (2020). γ-Aminobutyric acid found in fermented foods and beverages: Current trends. *Heliyon*, *6*(11), Article e05526. https://doi.org/10.1016/j.heliyon.2020.e05526

Suhail, M. (2019). Physiological, pathological, and pharmacological aspects of GABA. *Journal of Neuroimmune Pharmacology*, 14(2), 282-292.

Toney, M. D. (2011). Controlling reaction specificity in pyridoxal phosphate enzymes. *Archives of Biochemistry and Biophysics*, 516(2), 99-108. https://doi.org/10.1016/j.abb.2011.07.018

Vrolijk, M. F., Opperhuizen, A., Jansen, E. H., Hageman, G. J., Bast, A., & Haenen, G. R. (2020). The vitamin B6 paradox: Supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. *Toxicology In Vitro*, 44, 206-212. https://doi.org/10.1016/j.tiv.2017.07.009

Wong, J. H., Tan, K., Toh, M., Wilson, P., Lim, J., George, S., Patwardhan, A., Wong, A., Singh, R., & Kavuru, S. (2025). Expert consensus on vitamin B6 therapeutic use for patients: Guidance on safe dosage, duration and clinical management. *Drug, Healthcare and Patient Safety*, 17, 97-108. https://doi.org/10.2147/DHPS.S499941

Xu, Y., Zhao, M., Han, Y., & Zhang, H. (2020). GABAergic inhibitory interneuron deficits in Alzheimer's disease: Implications for treatment. *Frontiers in Neuroscience, 14*, Article 660. https://doi.org/10.3389/fnins.2020.00660