ORIGINAL ARTICLE

Neurological and Psychiatric Manifestations of Vitamin B12 Deficiency: Perspectives from Indian Experts Using the Delphi Methodology

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Abstract

Background: Vitamin B12 deficiency is highly prevalent in India and manifests across neurological, psychiatric, and hematologic-gastrointestinal domains. Despite frequent clinical encounters, diagnostic and therapeutic practices remain inconsistent.

Objective: To collect expert opinions on neurological and psychiatric aspects of vitamin B12 deficiency in India using a structured Delphi methodology.

Methods: A two-round online Delphi survey was conducted to gather opinions from Indian clinicians experienced in addressing the neurological and psychiatric aspects of B12 deficiency. 85 invitations were issued; 78 panelists participated in rounds 1 and 2. Consensus was defined as a lower confidence interval bound ≥0.75 for agreement proportions (80% CI = round 1; 95% CI = round 2).

Results: Peripheral neuropathy was the most consistent early manifestation, followed by constitutional, hematologic, gastrointestinal, and cognitive symptoms. All 18 consensus statements achieved agreement, with most mean proportions ≥0.90. Serum B12 and MMA were identified as the most reliable diagnostic biomarkers. The panel advocated screening of high-risk groups (vegetarians, the elderly, and long-term metformin or acid-suppressant users), maintaining serum B12 >300 pg/mL, and prompt parenteral replacement for severe deficiency or malabsorption. SC methylcobalamin 1500 µg was recognized as a practical, bioequivalent alternative to IM therapy, with patient self-administration improving access and satisfaction.

Conclusion: The panel of Indian experts achieved strong consensus on a pragmatic, patient-centered approach: screen early, confirm with specific biomarkers, initiate timely parenteral therapy, and individualize maintenance strategies. SC routes and self-injection training can enhance adherence and access, while further studies should refine dosing schedules and diagnostic cut-offs for local practice.

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Introduction

Vitamin B12 (cobalamin) deficiency is common and can involve the hematologic, neurologic, and neuropsychiatric systems. Presentation is often nonspecific (fatigue, anemia, paresthesias, cognitive or mood changes), so patients typically first appear in primary care. Causes include low dietary intake (e.g., limited animal-source foods) and, more often in adults, impaired absorption due to intrinsic factor-related disease (pernicious anemia), atrophic gastritis, gastrointestinal disorders or surgery, and some medications.

An estimated 6% of people worldwide are deficient in vitamin B12, and subclinical deficiency affects 2.5–26% of the general population.[1] Considering the social inequalities and largely vegetarian dietary habits of the Indian subcontinent, vitamin B12 deficiency has emerged as a silent epidemic in India.[2]

India does not yet have a single nationally representative survey of serum vitamin B12 status across all ages. The most recent national data on children and adolescents come from the Comprehensive National Nutrition Survey (2016–2018), which reported vitamin B12 deficiency (serum B12 <150 pmol/L) in 13.8% of preschoolers, 17.3% of school-aged children, and 31.0% of adolescents.[3] In women of reproductive age in southern India, a population-based biomarker survey found vitamin B12 deficiency in 48.3% and insufficiency in 74.3%.[4] During pregnancy, multiple cohorts and reviews consistently report high burdens, with deficiency affecting about 40–70% of women.[5] Studies in Indian adults also show substantial prevalence, typically between one third and one half, depending on setting and assay method.[6,7] A frequently cited perspective has suggested that about half of the Indian population may be vitamin B12 deficient, although this figure is not based on a nationally representative all-age survey and should be interpreted cautiously.[8] Using India's 2025 population of approximately 1.464 billion as context, a conservative all-age prevalence in the range

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of one third to one half would correspond to roughly 480–730 million people with low serum vitamin B12.[9] These estimates vary with the cut-offs and biomarkers used, and total serum B12 tends to misclassify status relative to active B12 and functional markers.[3,10]

Diagnosis is challenging. Serum B12 is widely used but imperfect, as most circulating B12 is bound to haptocorrin and thus not biologically active. Holotranscobalamin reflects the active fraction, and metabolic markers such as MMA and homocysteine can support the diagnosis, though access, cost, and renal function limit their use. Delayed recognition, particularly of neurologic or cognitive manifestations, increases the risk of incomplete recovery.

Treatment depends on severity and cause. Parenteral B12 is often chosen for severe symptoms or malabsorption; high-dose oral therapy can be effective for maintenance or when absorption is adequate. Despite frequent clinical encounters, practice varies across settings and countries, and evidence remains limited in several areas of screening, testing, dosing, and follow-up.

This work aims to collect expert opinions from Indian clinicians about neurological and psychiatric aspects of vitamin B12 deficiency.

Materials and Methods

Study Design and Setting

A two-round, web-based Delphi survey was conducted to collect expert opinions on the neurological and psychiatric aspects of vitamin B12 deficiency in India. The panel consisted of physicians from diverse regions of the country, representing public and private healthcare systems and various levels of care, including primary, secondary, and tertiary facilities. Physicians were recruited through academic and professional platforms, including conferences, symposiums, and continuing medical education programs.

Participants and Recruitment

Doctors were eligible to join the panel if they had clinical experience treating the neurological and psychiatric aspects of vitamin B12 deficiency, including neurologists, psychiatrists, and neurosurgeons. A total of 85 invitations were sent out. In rounds 1 and 2, 78 doctors completed the survey. Participation was voluntary and not paid.

In addition, an expert advisory group of 15 senior neurologists (scientific board members) from across India helped refine and prioritize the survey questions.

Survey Development and Content

Round 1 consisted of structured multiple-choice items, numerical questions, and open-ended fields that allowed participants to provide written comments. After reviewing the round 1 responses, the expert committee discussed areas where opinions varied. Based on this evaluation, selected questions were revised or expanded for round 2. The second round included statements evaluated using a five-point Likert scale (strongly disagree, disagree, neutral, agree, and strongly agree), as well as additional questions related to diagnostic markers such as vitamin B12, MMA, and homocysteine levels.

Survey rounds were assessed anonymously through an online platform (SurveyMonkey) to ensure independent and unbiased responses.

Statistical Analysis

Our primary outcome was agreement with each statement, defined as the proportion of panelists selecting agree or strongly agree. Consistent with our a priori plan:

We summarized agreement as the proportion selecting "agree" or "strongly agree." For each item, we calculated Wilson confidence intervals (CIs) for the agreement proportion. In round 1, we computed both 80% and 95% CIs and inspected whether the lower 80% bound exceeded 0.75 as a descriptive stability check; all items met this level, so none were excluded on statistical grounds. In round 2, we analyzed new items derived from round-1 discussion and re-analyzed carried-forward items. Consensus was a priori defined as a lower 95% CI bound ≥0.75. The 80% CIs are reported for completeness but were not used for decisions in round 2.

Handling of non-Likert Items

- For practice-oriented questions that produced free-text answers (e.g., when to re-evaluate after stopping parenteral B12; when to shift from oral to injectable therapy; preferred route/frequency), responses were cleaned and collapsed into predefined, ordered categories before analysis.
- *Time-based categories*: Weeks, 1 month, 3 months, 6 months, 1 year, >1 year/long-term, and "other/not time-based." We report the modal category (most common), runner-up, the combined share of the top two categories, and, when applicable, the median category on this ordered scale.
- Routes were categorized as intramuscular (IM), subcutaneous (SC), intravenous (IV), oral, or combined (e.g., IM/SC). Treatment frequency was summarized descriptively.
- *Ranking tasks*: We summarized ranking data by showing how often each biomarker and symptom domain was placed at each rank position and then derived an overall priority order using a mean-rank (Borda) approach. Panelists ranked items within each domain on a 1–9 scale (1 = most frequent/earliest, 9 = least frequent/latest). "Not applicable/I don't know" responses and blanks were excluded per item. For each item, we calculated the mean rank (lower = more prevalent/earlier) with 95% confidence intervals.
- Overall results are presented across five summary tables combining agreement proportions, ranking results, and key practice patterns.

Ethics

The study complied with the ethical principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Riddhi Medical Nursing Home Institutional Ethics Committee, Ahmedabad, India (Protocol No.: ERIS/DC/25/01; DCGI Registration No.: ECR/886/Inst/GJ/2016/RR-24; Ethics Committee Approval date: 07 February, 2025).

Results

Table 1 illustrates that peripheral neuropathy is the leading clinical signal of vitamin B12 deficiency (mean rank ≈ 1.8), followed by a constitutional/hematologic–gastrointestinal cluster—fatigue with macrocytosis/anemia, weight loss/diarrhea, and mucocutaneous changes (≈ 2.7). Early neurocognitive involvement is common: memory decline (≈ 2.0) and depression (≈ 2.1) appear well before severe anxiety (≈ 2.8) or psychotic features (≥ 4.5). Within neurology, subacute combined degeneration of the cord (≈ 1.8) and weakness/wasting with gait disturbance (≈ 2.0) rank prominently, aligning with the peripheral nervous system as the earliest involved system overall (≈ 1.7), ahead of hematologic anemia (≈ 2.4). Clinical links are most often missed when presentations resemble "burn-out"/affective complaints (≈ 2.7), subtle sensory neuropathy with frequent falls (≈ 3.0), or central nervous system (CNS) motor/visual signs (≈ 3.2). Although autonomic dysfunction—particularly orthostatic hypotension—emerges later by system ranking (≈ 7.4), it contributes meaningfully to morbidity and warrants explicit screening.

Panel Agreement on Survey Items

Table 2 shows that all 18 statements achieved consensus in round one (lower CI bound ≥ 0.75). Agreement proportions are uniformly high, with most 95% CIs tightly clustered ≥ 0.85, indicating stable views across panelists.

Table 1: Ranked prevalence of clinical manifestations of vitamin B12 deficiency across neurological, psychiatric, and systemic domains

Prevalence rank 1 = highest; 9 = lowest	*Most frequent symptoms*	*Neurological manifestations*	*Neuropsychiatric manifestations*	*System involvement*	*Most difficult to associate*
1	Peripheral neuropathy (paresthesias/numbness, neuropathic pain, gait imbalance; ↓ vibration/proprioception; ataxia; ± tinnitus/± taste loss; ± myelopathy). 1.77 (1.54–2.00)	Subacute combined degeneration (myeloneuropathy). 1.76 (1.53–1.98)	Cognitive decline (memory etc.). 1.99 (1.74–2.24)	PNS: sensory + motor involvement. 1.67 (1.41–1.93)	CNS mental: fatigue/burnout; anxiety/depression; cognitive impairment; dementia; psychosis. 2.67 (2.27–3.06)
2	Constitutional/hematologic and GI cluster (fatigue; macrocytic anemia ± iron deficiency/other cytopenias; GI malabsorption—diarrhea, weight loss/FTT; mucocutaneous/oral changes—hyperpigmentation, glossitis, aphthae; reproductive/urinary—infertility, UTI). 2.71 (2.42–2.99)	Weakness/wasting; myelopathy/neuropathy; gait disorder. 2.03 (1.83–2.22)	Depression. 2.14 (1.90–2.38)	Hematologic: anemia. 2.37 (2.12–2.63)	PNS sensory: non-disturbing → painful symptoms; frequent falls. 2.96 (2.55–3.37)
3	Cognitive/behavioral (brain fog, memory/cognitive impairment, nominal aphasia, insomnia, migraine; learning/behavioral problems). 3.01 (2.73–3.30)	Cognitive dysfunction. 2.79 (2.57–3.02)	Severe anxiety. 2.79 (2.50–3.09)	CNS: mental function. 3.26 (2.94–3.58)	CNS neuro: postural instability; leg stiffness; spasticity; neurogenic bladder; vision problems. 3.17 (2.73–3.60)
4	Affective/psychotic (mood swings, irritability, depression/anxiety; ± hallucinations/± delusions/psychosis). 3.31 (2.99–3.62)	Stroke/vascular complications. 3.42 (3.25–3.60)	Dementia. 4.13 (3.77–4.49)	CNS: neurological function. 4.67 (4.40–4.93)	PNS motor: muscle weakness. 4.46 (4.12–4.80)
5	Motor tract involvement (weakness, reflex change; corticospinal signs with spasticity/± seizures; attenuated if neuropathy predominates). 4.42 (4.21–4.64)	–	Delusions. 4.53 (4.35–4.70)	GI/liver involvement. 5.04 (4.69–5.38)	GI: anorexia/loss of appetite; weight loss. 4.97 (4.55–5.40)
6	Autonomic/urocardiac (urinary/fecal incontinence, orthostatic hypotension/dizziness, erectile dysfunction; ± cardiomyopathy). 5.78 (5.63–5.93)	–	Hallucinations. 5.42 (5.25–5.60)	Mucosa/skin: hyperpigmentation. 5.74 (5.24–6.25)	Autonomic: orthostatic hypotension. 6.21 (5.71–6.71)
7	–	–	–	Muscle/fibrous tissue pain. 5.83 (5.51–6.16)	Mucosa/skin: sore tongue/mouth; angular sores; mucocutaneous hyperpigmentation. 6.35 (5.91–6.78)
8	–	–	–	Autonomic: orthostatic hypotension. 7.42 (7.25–7.60)	Myalgia/fibromyalgia. 6.67 (6.13–7.20)
9	–	–	–	–	Bone marrow: anemia; leukopenia; thrombocytopenia. 7.55 (7.07–8.03)

Ranked prevalence across domains; Each cell: item mean rank (95% CI) (lower mean rank = more prevalent/earlier); Each cell shows the mean rank [95% CI]; lower rank = higher frequency or earlier presentation. Abbreviations: PNS, peripheral nervous system; GI, gastrointestinal; FTT, failure to thrive; UTI, urinary tract infection; SCD, subacute combined degeneration; CI, confidence interval; –, not available/not applicable; ↑/↓, increased/decreased; →, leads to; ± may be present/optional

The most strongly endorsed statements (near-uniform agreement, values ≥ 0.95) are:

- *Diagnostic approach*: Use serum B12 for screening and methylmalonic acid (MMA)/homocysteine to confirm deficiency; monitor B12 during metformin therapy and maintain levels above 300 pg/mL (221 pmol/L).
- *Initial management*: Prompt replacement to prevent/reverse neurological injury; parenteral therapy preferred in severe disease, with SC or oral routes acceptable when IM is relatively contraindicated.
- *Maintenance*: After correction, oral B12 is effective for long-term maintenance in many patients; lifelong parenteral therapy for malabsorption (e.g., pernicious anemia, postgastrectomy/ileal resection).
- *Delivery model*: Patient self-administration is associated with higher satisfaction and

Table 2: Panel agreement on survey items. Panel agreement on diagnostic and therapeutic statements for vitamin B12 deficiency (round 1). Agreement represents the mean proportion (agree + strongly agree) with 80% and 95% Wilson CIs. Consensus is defined as a lower bound ≥0.50 for 80% (round 1) or 95% (round 2) CI

No.	*Questions*	*Mean (80% CI)*	*Mean (95% CI)*	*Consensus (round 1, 80% CI ≥ 0.50)*	*Consensus (round 2, 95% CI ≥ 0.50)*
1	The delay in diagnosing vitamin B12 deficiency in a significant number of patients may be due to the following factors: the complexity and variability of its signs and symptoms, which span several medical specializations (hematologic, neuropsychiatric, gastroenterological, and other manifestations). Symptoms are often vague. High costs and limited availability of advanced laboratory B12 markers, such as plasma methylmalonic acid, total homocysteine, and holotranscobalamin	0.99 (0.96–1.00)	0.99 (0.93–1.00)	Yes	Yes
2	Serum B12 concentration is helpful for screening, while measuring methylmalonic acid or homocysteine levels can further assist in confirming the diagnosis	0.95 (0.91–0.97)	0.95 (0.88–0.98)	Yes	Yes
3	Physicians should consider screening patients for vitamin B12 deficiency if they have been taking proton pump inhibitors or H2 blockers, levodopa, or phenytoin for more than 12 months, or metformin for more than 4 months	0.95 (0.91–0.97)	0.95 (0.88–0.98)	Yes	Yes
4	Periodic monitoring of vitamin B12 levels is recommended for individuals undergoing metformin therapy. It is advised to maintain a plasma B12 level above 300 pg/mL (221 pmol/L) to ensure normal vitamin B12 status during metformin treatment	0.94 (0.89–0.96)	0.94 (0.86–0.97)	Yes	Yes
5	When intramuscular (IM) injections are relatively contraindicated, such as in individuals on anticoagulant medications, oral or subcutaneous (SC) vitamin B12 administration may be recommended	0.97 (0.94–0.99)	0.97 (0.91–0.99)	Yes	Yes
6	There is no one-size-fits-all for vitamin B12 therapy; however, for patients with acute and severe manifestations of vitamin B12 deficiency, initial treatment with parenteral vitamin B12 should be the first choice, with the route, dose, and frequency tailored to individual needs	0.97 (0.94–0.99)	0.97 (0.91–0.99)	Yes	Yes
7	Once vitamin B12 levels have been corrected with injections, oral supplementation (e.g., 1000–2000 µg per day) can be used for long-term maintenance therapy in most patients. Oral therapy is often as effective as injections, particularly in individuals without malabsorption issues	0.88 (0.83–0.92)	0.88 (0.80–0.94)	Yes	Yes
8	Prompt replacement of vitamin B12 is essential for preventing or reversing neurological damage. Initial treatment may involve intramuscular vitamin B12 injections (typically 1000 µg/1500 µg SC administered frequently (e.g., every other day) until markers of serum vitamin B12 normalize	0.99 (0.96–1.00)	0.99 (0.93–1.00)	Yes	Yes
9	The standard therapy for people with impaired vitamin B12 absorption is lifelong intramuscular injections; subcutaneous administration may be an alternative in selected patients	0.92 (0.88–0.95)	0.92 (0.84–0.96)	Yes	Yes
10	The initial recommended dose is 1000 µg of vitamin B12 by intramuscular injection/1500 µg SC twice weekly or on alternate days. This frequency should be continued when neurological complaints are present until these symptoms have resolved or do not improve further. This may take several months or even years	0.87 (0.82–0.91)	0.87 (0.78–0.93)	Yes	Yes
11	Whenever vitamin B12 deficiency is clinically manifested, or the patient cannot absorb vitamin B12, therapeutic doses between 1000 µg/day and 2000 µg/day orally or 1000 µg IM/1500 µg SC (e.g., daily, then weekly, then monthly for maintenance) can be used	0.94 (0.89–0.96)	0.94 (0.86–0.97)	Yes	Yes
12	The dose or injection frequency should not be quickly reduced to once every 2 months, as this may cause symptoms to return. Instead, it is recommended to slowly increase the time between injections over several months, while monitoring for any changes in symptoms	0.86 (0.80–0.90)	0.86 (0.76–0.92)	Yes	Yes
13	The long-term need for the frequency of intramuscular vitamin B12 injections to remain symptom-free may vary among individuals, from twice weekly to once every 2 to 3 months	0.86 (0.80–0.90)	0.86 (0.76–0.92)	Yes	Yes
14	Self-administering Parenteral vitamin B12 will increase an individual's treatment satisfaction and quality of life, and reduce healthcare costs	0.96 (0.92–0.98)	0.96 (0.89–0.99)	Yes	Yes
15	Patients who self-administer B12 injections or who are taught to do so report rapid and noticeable improvement in their symptoms and quality of life.	0.90 (0.84–0.93)	0.90 (0.81–0.95)	Yes	Yes
16	Oral and injectable vitamin B12 are effective means of replacement, but injectable therapy leads to more rapid improvement and should be considered in patients with severe deficiency or severe neurologic symptoms	0.97 (0.94–0.99)	0.97 (0.91–0.99)	Yes	Yes
17	Methylcobalamin 1500 µg SC injection offers bioavailability equivalent to that of the 1500 µg IM injection, with the added benefits of faster absorption and easier administration.SC injections are a practical and effective alternative for treating Vitamin B12 deficiency, offering convenience over both oral and IM preparations	0.95 (0.91–0.97)	0.95 (0.88–0.98)	Yes	Yes
18	Offer lifelong intramuscular/subcutaneous vitamin B12 replacement to people if autoimmune gastritis is the cause, or suspected cause, of vitamin B12 deficiency, or they have had a total gastrectomy or a complete terminal ileal resection	0.96 (0.92–0.98)	0.96 (0.89–0.99)	Yes	Yes

Panelists $n = 78$. Agreement = agree + strongly agree. values are the mean proportion with Wilson CIs; Consensus rules. Round 1: lower bound of 80% CI ≥ 0.50; Round 2: lower bound of 95% CI ≥ 0.50. CIs are Wilson intervals

Table 3: Overview of real-world management practices for vitamin B12 deficiency: Summary of clinical practice patterns for vitamin B12 management among panelists. The table shows the most common and runner-up responses per item, with combined "Top-2 total" proportions and median category for time-related questions

No.	*Question*	*N*	*Most common*	*Runner-up*	*Top-2 total*	*Median category*
1	In patients with long-term B12 deficiency on oral therapy, when do you shift to injectable methylcobalamin?	77	6 months (31%)	3 months (21%)	52%	6 months
2	After discontinuing parenteral B12 therapy, how long do B12 levels remain within the normal range in your experience?	77	3 months (28%)	Other / not time-based (28%)	56%	6 months
3	After discontinuing parenteral B12 therapy, when do you generally re-evaluate serum B12 levels?	76	Weeks (52%)	Other / not time-based (31%)	83%	Weeks
4	Triggers to shift from oral to injectable therapy (open-ended, condensed categories)	77	If no improvement (56%)	Immediately (21%)	77%	NA
5	Preferred route for parenteral B12 administration	76	IM (63%)	SC (17%)	80%	NA

Most common and runner-up responses per item; Top-2 total = two most frequent choices combined. Time items show a Median category in weeks/months/year bins. NA, not applicable

lower costs; SC methylcobalamin 1500 µg is a practical, bioequivalent alternative to IM.

Where practice varies (lower means values < 0.90, wider CIs) are: Items specifying exact dose and frequency (e.g., avoiding rapid reduction to every 2 months; spacing of long-term injections) show the lowest agreement (means ~0.86–0.90), signaling areas for local adaptation and future trials.

Table 3 shows two clear points of agreement. First, most clinicians recheck serum B12 within a few weeks after stopping parenteral therapy. Second, the IM route is strongly preferred over the SC route.

In contrast, there is more variation in two areas. Clinicians differ on when to switch from oral to injectable therapy and on how long B12 levels stay normal after stopping parenteral treatment. The median response is around 6 months, but many respondents gave responses that were not based on a fixed time. This suggests that decisions are often guided by the patient's clinical response rather than by a strict schedule. Consistent with this, the main reason for switching to injectable therapy is a lack of improvement with oral treatment.

Second Questionnaire

In round 2 (n = 78), the panel reached a clear and coherent pattern of opinion. Table 4 shows that one practice was explicitly rejected: performing routine skin-sensitivity testing before parenteral vitamin B12 administration. Clinicians were confident that parenteral methylcobalamin is safe and well tolerated, that timely treatment can reverse neurological manifestations, and that knuckle pigmentation is a helpful clinical clue warranting evaluation for deficiency. When routes of replacement were compared, the parenteral route ranked highest, followed by sublingual and oral routes, and the panel endorsed active monitoring and supplementation for high-risk groups, notably vegetarians/vegans and older adults. Four areas remained uncertain rather than clearly endorsed. The data did not provide convincing support for a relationship between raised homocysteine and decreased serum vitamin B12 levels with erectile dysfunction (ED), no agreement for using a serum B12 threshold (≤300 pg/mL) to explain isolated urinary/fecal incontinence; concerns about benzalkonium-chloride–related adverse effects with nasal methylcobalamin sprays were not resolved; and positions regarding folic-acid–only approaches or fortification in the context of suspected B12 deficiency did not reach a persuasive consensus.

Table 5 shows that serum vitamin B12 and MMA clearly formed the top tier of diagnostic markers, each was placed in the top two by roughly two-thirds of panelists. Homocysteine was generally viewed as mid-tier (most often ranked third), while holotranscobalamin had the least confidence.

Discussion

This pan-India Delphi study collected opinions from the panel of Indian clinicians who usually address neurological and psychiatric aspects of vitamin B12 deficiency. Experts expressed their experiences and opinions about the complex and wide spectrum of manifestations of vitamin B12 deficiency and crucial approaches in diagnosing and managing vitamin B12 deficiency.

The expert consensus established a clear hierarchy of symptoms of B12 deficiency beyond peripheral neuropathy that are commonly encountered by clinicians in India and are often challenging to diagnose. These include psychiatric symptoms, a cluster of constitutional/hematologic–gastrointestinal symptoms, and autonomic symptoms.

In patients with subtle or nonspecific symptoms, screening for B12 deficiency using serum B12 testing is essential. Biomarkers such as plasma MMA, total homocysteine, and holotranscobalamin can provide additional diagnostic clarity.

The panelists recommended regular monitoring of serum B12 levels in high-risk populations and agreed that a normal B12 level does not necessarily rule out deficiency. An individualized approach to B12 deficiency management was advised, depending on symptom severity and associated clinical factors.

Parenteral B12 therapy was strongly recommended, especially for patients with severe symptoms, malabsorption, or in special situations such as old age or a vegetarian diet. Among parenteral routes, the SC route was preferred due to greater convenience. The panelists agreed that parenteral B12 therapy is safe, even in patients on hemodialysis and when administered in ultra-high doses.

Knuckle hyperpigmentation was recognized as a useful clinical sign of vitamin B12 deficiency. The panel did not reach agreement on a possible link between high serum homocysteine, low vitamin B12 levels, and ED, or on nasal mucosal inflammation related to methylcobalamin nasal spray. The experts confirmed that patients with megaloblastic anemia can present with isolated neurological symptoms and usually respond well to intensive vitamin B12 treatment. They did not agree on routinely recommending combined vitamin B12 and folic acid therapy without considering the risk that folic acid may mask vitamin B12 deficiency.

First Round of Survey

Early and Characteristic Manifestations

Overall, the panelists agreed that peripheral neuropathy is the most reliable early clinical indicator of B12 deficiency, followed closely by psychiatric manifestations such as fatigue,

Table 4: Panel agreement on survey items. Panel agreement on advanced and special-topic statements (Round 2). Agreement expressed as mean proportion (Agree + Strongly agree) with 80% and 95% Wilson CIs; consensus thresholds as in

No.	*Questions*	*Mean (80% CI)*	*Mean (95% CI)*	*Consensus (round 2, 80% CI ≥ 0.50)*	*Consensus (round 2, 95% CI ≥ 0.50)*
1	Given the very rare incidence of vitamin B12 hypersensitivity, a comprehensive evaluation protocol should be followed before parenteral vitamin B12 administration, including vitamin B12 skin-sensitivity tests	0.44 (0.37–0.51)	0.44 (0.33–0.55)	No	No
2	It is reasonable to consider folic acid with or without methylcobalamin supplementation as appropriate adjunctive therapy in patients with chronic kidney disease (CKD). Parenteral injection of methylcobalamin is a safe, noninvasive, and potentially efficacious therapy for neuropathy in patients on maintenance hemodialysis	0.95 (0.91–0.97)	0.95 (0.88–0.98)	Yes	Yes
3	Ultrahigh-dose parenteral (IM/SC) methylcobalamin therapy is well tolerated by adult patients	0.92 (0.88–0.95)	0.92 (0.84–0.96)	Yes	Yes
4	Increased serum homocysteine (Hcy) levels are associated with ED in men aged 45 or older, and decreased serum vitamin B12 levels are positively associated with ED in men aged 45 or younger	0.73 (0.66–0.79)	0.73 (0.62–0.82)	No	No
5	Serum B12 levels of 300 pg/mL or less are not associated with isolated urinary incontinence (UI) or isolated fecal incontinence (FI) but may play a role in double incontinence (DI), i.e., incontinence of both. More immediately, medication side effects should be considered when evaluating this problem	0.62 (0.54–0.68)	0.62 (0.50–0.72)	No	No
6	Most patients with megaloblastic madness usually have isolated neurological symptoms, and the degree of megaloblastic anemia usually appears to inversely correlate with the severity of neuropsychiatric symptoms. Timely Vitamin B12 therapy can completely reverse these symptoms	0.91 (0.86–0.94)	0.91 (0.83–0.96)	Yes	Yes
7	Knuckle pigmentation is an easily visible and early sign of Vitamin B12 deficiency. It may occur even before the development of hematological and neurological complications. A thorough systemic examination should be performed in patients presenting with skin hyperpigmentation. It should be investigated for a deficiency of vitamin B12, besides ruling out the other common causes. Alongside adequate treatment, the patient should be followed up for a few weeks to assess resolution and screen for neurological manifestations, as late manifestations can occur in some patients	0.96 (0.92–0.98)	0.96 (0.89–0.99)	Yes	Yes
8	All parenteral, oral, and sublingual (SL) routes of administration of vitamin B12 can effectively increase the level of vitamin B12 without significant differences between them. However, the parenteral route was the top-ranked statistically, followed by the SL, and then the oral routes	0.90 (0.84–0.93)	0.90 (0.81–0.95)	Yes	Yes
9	Healthy older subjects exhibit neurological changes at both ends of the measurable "normal" B12 spectrum	0.83 (0.77–0.88)	0.83 (0.75–0.90)	Yes	Yes
10	Benzalkonium chloride (BKC), used as a preservative in nasal methylcobalamin spray, leads to ciliostasis and reduction in mucociliary transport, especially in patients with rhinitis and sinusitis, because mucociliary clearance is already impaired. Benzalkonium chloride (BKC) in nasal Methylcobalamin sprays may also cause adverse effects like rhinitis medicamentosa and neutrophil dysfunction	0.72 (0.65–0.78)	0.72 (0.61–0.81)	No	No

Contd…

Contd…

No.	*Questions*	*Mean (80% CI)*	*Mean (95% CI)*	*Consensus (round 2, 80% CI ≥ 0.50)*	*Consensus (round 2, 95% CI ≥ 0.50)*
11	Vegans, lacto-vegetarians, ovo-vegetarians, and lacto-ovo vegetarians are likely to suffer from chronic vitamin B12 deficiency as they do not eat fish and meat. In such patients, regular monitoring of serum B12 is required, and they may require lifelong B12 supplementation	0.91 (0.86–0.94)	0.91 (0.83–0.96)	Yes	Yes
12	Older people are at increased risk of vitamin B12 deficiency due to insufficient dietary intake, malabsorption associated with age-related changes in gastrointestinal function, higher incidence of pernicious anemia, and chronic use of interfering medications such as metformin and proton-pump inhibitors. Early detection and treatment of symptomatic deficiency are crucial to prevent irreversible damage. Parenteral vitamin B12 bypasses potential absorption issues and is traditionally the first-line treatment in older people. Older people often require lifelong therapy due to the irreversible nature of the underlying cause of deficiency	0.92 (0.88–0.95)	0.92 (0.84–0.96)	Yes	Yes
13	There is no conclusive evidence that folic acid supplementation (in the absence of co-supplementation with vitamin B12) precipitates or enhances vitamin B12-deficiency-associated neuropathy. If practitioners were to properly diagnose vitamin B12 deficiency and be aware of its high prevalence in certain high-risk groups (elderly and vegetarians), there would be no argument for renouncing the fortification of food with folic acid by masking vitamin B12 deficiency	0.73 (0.66–0.79)	0.73 (0.62–0.82)	No	No

Panelists *n* = 78. Agreement = agree + strongly agree. Values are the mean proportion with Wilson CIs; consensus rules. Round 1: lower bound of 80% CI ≥ 0.50; round 2: lower bound of 95% CI ≥ 0.50. CIs are Wilson intervals

Table 5: Panel ranking of vitamin B12 biomarkers. Panel ranking of vitamin B12 biomarkers by perceived diagnostic reliability. Values show counts (percentages) per rank (1 = highest reliability, 4 = lowest). Biomarkers include serum vitamin B12, MMA, homocysteine, and holotranscobalamin

Biomarker	*Rank 1 (highest)*	*Rank 2*	*Rank 3*	*Rank 4 (lowest)*	*N*
Serum vitamin B12	30 (38%)	18 (23%)	12 (15%)	18 (23%)	78
Serum methylmalonic acid	26 (33%)	24 (31%)	18 (23%)	10 (13%)	78
Serum homocysteine	4 (5%)	21 (27%)	32 (41%)	21 (27%)	78
Serum holotranscobalamin	18 (23%)	15 (19%)	16 (21%)	29 (37%)	78

Values are counted (percentage) per rank. 1 = highest sensitivity/reliability; 4 = lowest

anxiety, depression, cognitive impairment, dementia, and psychosis. This finding is consistent with observations from a recent Delphi expert consensus.[11]

In a review article by Shipton and Thachil, fatigue was identified as an early symptom of vitamin B12 deficiency.[12] The panelists in the current study agreed that, after neurological and psychiatric manifestations, symptoms from the constitutional/hematologic–gastrointestinal cluster usually appear after neurological and psychiatric manifestations. These include fatigue associated with macrocytosis or anemia, weight loss, diarrhea, and mucocutaneous changes. Cognitive symptoms may also develop early, while autonomic features tend to appear later and are often overlooked. Clinicians should therefore consider B12 testing when patients present with nonspecific or subtle symptoms.

Challenges in Diagnosis and Biomarker Use

The panelists in the current study agreed with Ali et al. that vitamin B12 deficiency is a well-recognized cause of neurological complications.[13] Most of these neurological manifestations are subtle and easily overlooked, making timely diagnosis challenging, as also noted by Obeid et al.[11] Although about one-third of patients with vitamin B12 deficiency have normal serum B12 levels, serum B12 measurement remains a useful first-line screening tool. Delayed diagnosis is often due to the high cost and limited availability of more specific biomarkers, such as plasma MMA, total homocysteine, and holotranscobalamin.

The panelists agreed with the earlier Delphi consensus on the importance of regularly monitoring serum vitamin B12 levels in individuals taking medications that interfere with B12 metabolism, such as metformin or L-DOPA.[11] They recommended that patients on long-term metformin therapy should have their B12 levels checked periodically and maintained above approximately 300 pg/mL (221 pmol/L). To avoid the costs of universal screening, routine monitoring is also advised for high-risk individuals receiving proton pump inhibitors, H_2-receptor blockers, levodopa, or phenytoin. This approach helps safeguard patient health and aligns with earlier recommendations.[11] Elevated serum

B12 concentrations may sometimes result from autoimmune disorders, hepatic or renal dysfunction, or underlying malignancy, even when clinical symptoms suggest deficiency. In such diagnostically challenging cases, measurement of MMA or homocysteine is recommended to assess true intracellular vitamin B12 status.[11]

Neurotropic Vitamins and Treatment Individualization

In patients with sensory peripheral neuropathy caused by metabolic disorders, medication use, or nutritional deficiencies, it is essential to administer an initial loading dose of neurotropic B vitamins (B1, B6, and B12).[14] After symptomatic improvement, treatment can be transitioned to a maintenance (lower) dose regimen. Prophylactic use of neurotropic B vitamins should also be considered in individuals at high risk for peripheral neuropathy, including those over 50 years of age, and patients with diabetes, HIV or tuberculosis infection, chronic kidney disease on dialysis, restricted diets, or those receiving medications such as isoniazid or metformin.[14] These recommendations align with the opinion of panelists in the current study, which emphasizes that vitamin B12 therapy should be tailored to each patient's clinical needs. Parenteral administration, particularly SC injection, is preferred for acute or severe deficiency. The panelists also advised that the dose and duration of vitamin B12 therapy need to be adjusted as symptoms improve or as requirements increase, especially in high-risk groups such as pregnant or lactating women and older adults. Identifying the underlying cause of deficiency was considered essential for effective management.

Therapeutic Regimens and Administration Routes

The experts' opinions in the current study align with earlier observations that timely and appropriate vitamin B12 therapy can prevent irreversible nerve damage.[15] Vitamin B12 supplementation is also recommended in deficiency states to lower plasma homocysteine levels in diabetic patients at high risk of stroke.[16] Recommendations from the current consensus align with these earlier findings.

For patients with confirmed deficiency or impaired absorption, oral therapy (1000–2000 µg daily) or parenteral therapy (1000 µg IM or 1500 µg SC) is advised, initially administered daily, then weekly, and later monthly for maintenance. Oral therapy is suitable for long-term use when absorption remains intact, whereas lifelong parenteral treatment is required in cases of pernicious anemia or following gastric or ileal surgery.

The panelists in the current consensus recommended that oral or SC vitamin B12 be considered an appropriate treatment option for patients receiving anticoagulant therapy. Switching from oral to injectable treatment is thought to be beneficial for achieving clinical improvement, and this should be followed by re-evaluation of serum B12 levels within 1–6 weeks after discontinuing injections.

Methylcobalamin, adenosylcobalamin, and hydroxocobalamin are the three natural, bioactive forms of vitamin B12.[17] Among these, methylcobalamin has the ability to cross the blood–brain barrier without requiring prior biotransformation.[18] It is also the most efficiently taken up by neuronal subcellular organelles, which contributes to its superior effectiveness in the treatment of neurological disorders.[19] In line with these findings, experts in the present study expressed belief in methylcobalamin. They considered SC methylcobalamin a practical, bioequivalent alternative to standard IM administration. Experts believed that SC methylcobalamin was associated with faster symptom improvement, better quality of life, higher patient satisfaction, and lower healthcare costs. After having normalized vitamin B12 levels with injections, oral supplementation is considered suitable for long-term maintenance in most patients, typically at a dose of 1,000–2,000 µg per day, as recommended by Wentworth and Copland et al.[15]

Treatment in Severe or Complex Cases

For patients with severe symptoms or malabsorption, the panelists in the current consensus recommended parenteral vitamin B12 therapy to prevent or reverse neurological damage. Because neurological recovery may take months to years, the typical regimens recommended were 1000 µg IM or 1500 µg SC injections given twice weekly or on alternate days, continued until symptoms resolve or stabilize.

The injection interval could then be gradually extended under close clinical monitoring, as reducing the frequency too quickly (e.g., to once every 2 months) may lead to symptom recurrence. Long-term maintenance therapy should be individualized. In patients with severe neurological symptoms, the optimal interval for parenteral vitamin B12 administration is thought to vary among individuals, ranging from twice weekly to once every 2 or 3 months, depending on the dose required to maintain a symptom-free state.

These opinions are consistent with the guidance of the American Academy of Family Physicians (AAFP), which advises that injectable vitamin B12 should be administered for at least 6 weeks to 3 months in patients with severe neurological symptoms, as this approach leads to faster improvement than oral therapy.[20]

Lifelong Supplementation and Follow-up

Certain conditions, such as autoimmune gastritis or surgeries including gastrectomy and ileal resection, necessitate lifelong vitamin B12 supplementation via IM or SC injections. In such patients, clinicians typically switch to injectable methylcobalamin therapy after 3 to 6 months of oral treatment. Following the discontinuation of parenteral B12 therapy, serum B12 levels should ideally remain within the normal range for at least 3 months (suggested by 28% of panelists). Reassessing serum B12 levels within a few weeks after discontinuation of parenteral B12 is considered essential, as is transitioning from oral to injectable therapy due to inadequate symptom control (suggested by nearly 50% of panelists), as recommended earlier.[11]

Second Round of Survey

Following analysis of the first-round survey results, the scientific board concluded that a second round was necessary to explore additional aspects of vitamin B12 deficiency that had not been previously addressed. The round 2 statements focused on refining areas of disagreement and clarifying points of uncertainty. Reports from clinical studies indicate that hypersensitivity reactions to vitamin B12 are exceedingly rare.[21] In the second round, panelists explicitly rejected the routine use of skin-sensitivity testing before parenteral vitamin B12 administration. The safety and tolerability of high-dose parenteral methylcobalamin were confirmed, consistent with earlier findings.[22]

Emerging Clinical Associations

Knuckle hyperpigmentation was identified by our panelists as a valuable clinical sign of vitamin B12 deficiency, as was also suggested by others.[23] Panelists did not agree with Lu et al., who concluded that there is a strong association between elevated serum homocysteine levels and ED in men over 45 years of age, while lower serum vitamin B12 levels were positively correlated with ED in men under 45 years.[24]

Vitamin B12 Status in Older Adults and High-risk Populations

Panelists in the current consensus agreed that even healthy older adults may experience neurological changes when vitamin B12 levels fall at both ends of the measurable "normal" B12

spectrum, as demonstrated earlier by Beaudry-Richard et al.[25] We specifically highlight women of child-bearing age, pregnant and lactating women, and older adults, as well as those individuals who are already following a plant-based diet (vegetarians) and who transition to a vegan diet, as these population sub-groups are most at risk. Prevention of vitamin B12 deficiency through supplementation offers an effective, economical, and sustainable way to avoid the adverse health consequences in such situations.[26] Consistent with other studies,[27] the parenteral route was considered the most effective treatment modality, followed by the sublingual and then the oral route. The safety and efficacy of parenteral methylcobalamin were also confirmed in patients with neuropathy undergoing maintenance hemodialysis, as previously reported.[28]

Megaloblastic Anemia and Folic Acid Concerns

Our panelists opined that in patients with megaloblastic anemia, vitamin B12 deficiency may present with isolated neurological symptoms, and the severity of these symptoms often does not correlate with the degree of anemia. In some cases, significant neurological deficits may occur even in the absence of severe anemia, but these can be reversible if vitamin B12 therapy is initiated promptly, as described in the case study by Sharawat and Panda.[29]

There is a general concern that folic acid can mask the blood-related signs of vitamin B12 deficiency. Most of the evidence supporting this comes from observational studies, and the proposed mechanism has not yet been confirmed in controlled trials. Some studies have reported that individuals with low B12 status and high folate levels may experience more pronounced metabolic abnormalities and cognitive impairment compared with those who have low B12 alone, although this has not been consistently observed in all populations. Therefore, increased attention to vitamin B12 status is recommended in high-risk groups, including older adults, individuals with limited dietary B12 intake such as vegans and strict vegetarians, and people with conditions that impair B12 absorption.[30] It is advised that individuals in these categories should receive vitamin B12 supplementation and be encouraged to consume foods fortified with vitamin B12.[20]

Strengths and Limitations

Strengths

The study involved a large, multispecialty panel from across India. For both survey rounds, panelist responses were collected anonymously to minimize dominance bias. The second-round content was structured directly around questions that resulted from first-round discussions.

Limitations

Limitations include the use of nonprobability sampling, reliance on self-reported data rather than patient outcomes, and the need to condense free-text responses into analytic categories. The resulting rankings reflect clinician judgment and should not be interpreted as a substitute for head-to-head accuracy studies.

Implications and Priorities

The opinions of the experts in the current Delphi study support a pragmatic pathway for clinical practice in India. Experts highlighted the need to maintain a low threshold for vitamin B12 testing in patients presenting with neuropathic, hematologic, gastrointestinal, or early cognitive symptoms. Screening is also considered for individuals taking metformin or other medications associated with vitamin B12 deficiency, as well as for high-risk dietary groups and older adults. Parenteral therapy was identified as the initial treatment option should be initiated promptly in cases of severe disease or malabsorption. SC administration and patient training for self-injection were believed to improve treatment accessibility. Serum B12 levels reassessment within a few weeks after discontinuing injections was considered essential, along with the need for dose escalation if the clinical response remains inadequate. Priority areas for future research include defining optimal dosing and interval schedules, assessing the durability of biochemical response after discontinuation of parenteral therapy, establishing context-specific diagnostic thresholds, evaluating the role and accessibility of MMA and other biomarkers, and conducting cost-effectiveness analyses relevant to the Indian healthcare system.

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Authors' Contribution

AM: conceptualization, writing—review; AKT: methodology, writing—review and editing; AVS: validation, supervision, writing—review and editing; CM: formal analysis, writing—review and editing; BRG: conceptualization, data curation, writing—review; JBA: methodology, writing—review and editing; RLN: conceptualization, data curation, writing—review and editing; RK: formal analysis, writing—review and editing; SS: conceptualization, writing—review and editing; SKP: formal analysis, validation, supervision; SMS: conceptualization, writing—original draft; SVK: conceptualization, formal analysis, writing—review and editing; SVS: formal analysis, writing—review and editing; SK: methodology, writing—review and editing; TB: validation, supervision, writing—review and editing; SS: conceptualization, writing—review and editing; WV: conceptualization, data curation, formal analysis, writing—review and editing; SA: conceptualization (supporting), writing—original draft (supporting); MK: project administration, writing—original draft (supporting).

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