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Routes of Vitamin B12 Supplementation: Clinical Evidence, Limitations, and Practical Considerations

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Abstract

Introduction and purpose
Vitamin B12 deficiency remains an underdiagnosed condition with significant hematological, neurological, and psychiatric consequences. The aim of this review is to evaluate and compare the efficacy, indications, and clinical applicability of oral, sublingual, intramuscular, and subcutaneous vitamin B12 supplementation routes, and to provide evidence-based recommendations tailored to patient-specific conditions.

Brief description of the state of knowledge
Vitamin B12 is primarily absorbed in the distal ileum via an intrinsic factor-mediated mechanism. Deficiency is commonly caused by malabsorption syndromes, restrictive diets, medication use, and autoimmune disorders such as pernicious anemia. Intramuscular and subcutaneous administration bypass absorption defects and are considered the gold standard, especially in symptomatic patients. Oral and sublingual routes are increasingly used due to ease of use and cost-effectiveness. Sublingual supplementation, in particular, shows comparable biochemical efficacy to intramuscular injection and offers higher patient satisfaction. However, the variability in absorption and the use of surrogate biomarkers limit the consistency of clinical outcomes across studies.

Summary
All forms of vitamin B12 supplementation can be effective when used appropriately. Intramuscular administration remains superior in cases of severe deficiency and neurological involvement. Oral and sublingual supplementation are suitable for long-term maintenance and mild deficiencies, especially in patients with adherence capacity and no profound

malabsorptive conditions. Clinical decision-making should be guided by etiology, severity, patient preference, and logistical feasibility.

Key words : *Vitamin B12 Deficiency, Cobalamin, Dietary Supplements, Intramuscular Injections*

Introduction

Vitamin B12, also known as cobalamin, is a water-soluble vitamin that plays a crucial role in the proper functioning of the human organism. Synthesised by some microorganisms, it is delivered to the human body mostly through foods of animal origin. Sources particularly rich in vitamin B12 include liver, shellfish, red meat of ruminants, eggs, and dairy products. Bound to animal protein, it is released by the action of different gastric enzymes activated in the acidic environment of the stomach. Next, bound by intrinsic factor (IF), the vitamin-B12-IF complex travels to the distal ileum, where it is absorbed. Besides IF, other carrier proteins participating in the process of vitamin B12 absorption include haptocorrin (HC) and transcobalamin (TC). The liver stores substantial amounts of vitamin B12, which are continuously mobilized and reutilized in metabolic processes; thus, the recommended dietary allowance (RDA) for vitamin B12 is the lowest among all vitamins and amounts to approximately 2.5 μg/day [1] Vitamin B12 deficiency results in a complex array of clinical signs and symptoms, primarily stemming from impaired metabolic functions of the two human enzymes: methylmalonic acid (MMA) and homocysteine that depend on vitamin B12 as a cofactor [2]. The clinical manifestations of vitamin B12 deficiency primarily include hematologic, neurologic, and neuropsychiatric symptoms. The prevalence of vitamin B12 deficiency is challenging to assess due to the use of different evaluation methods and diverse underlying etiologies. Globally, the estimated prevalence is approximately 6%, while in Europe it ranges between 1.6% and 10% [3]. Higher rates are observed among individuals over 60 years of age, with prevalence varying from 10% to 19% across different countries. Additionally, deficiency tends to be more common in women compared to men [4]. Given the essential role of vitamin B12 in maintaining proper metabolic function in the human body, it is imperative that healthcare practitioners accurately recognize the clinical signs indicative of its deficiency and implement appropriate supplementation strategies.

Objective

The primary objective of this narrative review is to critically evaluate and compare the clinical efficacy, pharmacokinetics, bioavailability, indications, and limitations of oral, sublingual, intramuscular, and subcutaneous vitamin B12 administration. Special attention is given to the relationship between biochemical outcomes and clinical improvement, the

appropriateness of each route in different patient populations, and the quality of supporting evidence. The review aims to provide clinicians with an evidence-informed framework to guide the selection of the optimal route of cobalamin administration based on individual patient profiles.

Methods

This study is a structured, narrative review based on a comprehensive literature search of peer-reviewed articles published between 2000 and 2024. Databases searched included PubMed, Scopus, and the Cochrane Library, using combinations of the following keywords: “vitamin B12 deficiency”, “cobalamin supplementation”, “oral vitamin B12”, “intramuscular B12”, “sublingual B12”, “subcutaneous injection”, “bioavailability”, “clinical outcomes”, “pernicious anemia”.
Inclusion criteria were:

- human studies,
- English-language publications,
- randomized controlled trials (RCTs),
- observational studies,
- meta-analyses,
- systematic reviews, and
- relevant clinical guidelines.

Exclusion criteria included case reports, animal studies, non-peer-reviewed literature, and studies focusing solely on pediatric or pregnant populations unless relevant to the general topic. The search strategy was supplemented by manual review of reference lists from key articles.

Key data extracted from each study included:
study design and population, vitamin B12 dosage and route of administration, primary and secondary endpoints (e.g., serum B12, MMA, homocysteine, symptom resolution), duration of follow-up, and main findings.

The strength and limitations of the available evidence were critically assessed with attention to methodological rigor, sample size, clinical relevance, and outcome measures. Where applicable, findings were contextualized based on patient subgroup (e.g., elderly, vegans, post-gastrectomy, neurological symptoms)

Clinical manifestations of vitamin B12 deficiency

The principal clinical features of vitamin B12 deficiency involve disturbances in hematologic, neurologic, and neuropsychiatric systems (Table 1). Clinically, the diagnosis of vitamin B12 deficiency is usually made on discovery of low hemoglobin, increased Mean Corpuscular Volume (MCV) levels, and hypersegmented neutrophils on complete blood count (CBC). More severe hematologic presentations might include cytopenia affecting one, two, or all three blood cell lines (pancytopenia). The spectrum of neurologic complications ranges from mild paresthesia or peripheral neuropathy to severe clinical impairments such as demyelination of the dorsal columns and corticospinal tract. Vitamin B12 deficiency has also

been linked to psychiatric disorders, such as irritability, depression, psychosis, delirium, mania, and cognitive impairment. Moreover, low levels of vitamin B12 may also have indirect cardiovascular complications; vitamin B12 deficiency leads to elevated homocysteine levels (hyperhomocysteinemia), which is recognized as an independent risk factor for the development of atherosclerotic disease [5]. Cutaneous and gastrointestinal symptoms are less common, although they should not be overlooked when encountered in clinical practice. It is important to note that due to liver storage of vitamin B12, which might total up to 3-5mg, signs of deficiency may not appear until up to 10 years of insufficient intake [6].

Table 1. Clinical manifestations of vitamin B12 deficiency.
Hematologic Megaloblastic anemia Pancytopenia
Neurologic Peripheral neuropathy Paresthesias Demyelination of the dorsal columns and corticospinal tract
Neuropsychiatric Irritability Depression Psychosis Delirium Mania Cognitive impairment
Cutaneus Hyperpigmentation Vitiligo
Gastrointestinal Glossitis Jaundice
Cardiovascular Atherosclerotic disease

Diagnosis of Vitamin B12 Deficiency: Current Biomarkers and Limitations

It is important to emphasize that serum vitamin B12 measurements may be significantly influenced by the specific form of cobalamin being assayed. The conventional first-line test for evaluating vitamin B12 status is the measurement of total serum vitamin B12, typically performed using an automated, cost-effective, immune-chemiluminescence-based assay.

However, a critical limitation of this method is its inability to differentiate between biologically active and inactive forms of cobalamin.

Total serum vitamin B12 assays detect both inactive cobalamin forms bound to transcobalamin I and III—collectively known as holo-haptocorrin—and the active form bound to transcobalamin II, known as holo-transcobalamin (holoTC), which is responsible for cellular uptake of vitamin B12 [7]. This lack of specificity is clinically significant, as holo-haptocorrin-bound cobalamin is not bioavailable for metabolic functions. As approximately 80% of circulating cobalamin is bound to haptocorrin, total serum B12 levels may appear normal even in patients with clinically evident cobalamin deficiency [8].

Therefore, total serum vitamin B12 alone is not a reliable biomarker for assessing true vitamin B12 status. In search of more accurate indicators of functional or biochemical deficiency, alternative tests such as plasma homocysteine, plasma methylmalonic acid (MMA), and serum holo-transcobalamin (holoTC) have been proposed. Despite their clinical utility, these assays are not yet routinely used in standard diagnostic practice [9]

A study by Heil et al., which validated the diagnostic accuracy of total serum vitamin B12 and holoTC on 360 patient samples, confirmed that holoTC is a more accurate marker and can effectively replace total serum B12 in screening for deficiency. The study established a clinical decision threshold for holoTC at 32 pmol/L [10].

Causes of vitamin B12 deficiency

Following the diagnosis of vitamin B12 deficiency, a thorough investigation should be undertaken to identify its etiology. Causes of vitamin B12 deficiency can be roughly divided into three categories: nutritional deficits, malabsorption due to different causes, and others. These potential etiological causes define groups of patients that are particularly susceptible to developing vitamin B12 deficiency (Table 2). Since plant-based foods generally do not contain active forms of B12 vitamin, vegans and vegetarians are at risk of developing a deficiency. Several studies suggest that certain types of nori seaweed, mushrooms, and fish sauce may contain trace amounts of vitamin B12; however, the bioavailability of these sources remains uncertain [11]. Another groups at risk include patients with low appetite and poorly balanced diet, such as the elderly and chronic alcohol users.

A classic example of malabsorption syndrome is pernicious anemia. It is an autoimmune disease in which parietal cells of the stomach are targeted and damaged, resulting in an IF deficit. Additional causes of malabsorption encompass different conditions that interfere with gastric acid production and the subsequent release of vitamin B12 from food proteins. These include inflammatory diseases of the gastric and intestinal mucous membrane, post-surgical reduction of functioning cells in the gastrointestinal tract, and long-term use of acid-suppressing medications, such as metformin, proton pump inhibitors, and antihistamines, or gynecological medications such as oral contraceptives and hormonal replacement therapy. Moreover, some patients have genetic disorders that impair vitamin B12 metabolism at various stages, ultimately leading to its deficiency. For example, transcobalamin II deficiency is a rare autosomal recessive disorder leading to a lack of transcobalamin II, the protein

responsible for transporting vitamin B12 into cells. In Imerslund-Gräsbeck Disease, due to mutations in CUBN or AMN genes, vitamin B12 absorption in the ileum is impaired, even with adequate dietary intake [12].

Table 2. Causes of low vitamin B12 levels and the associated groups at risk of deficiency.

Cause	**Group at risk**
Low vitamin B12 intake	Vegans, strict vegetarians, chronic alcohol users, and the geriatric population
Food-bound cobalamin malabsorption	Patients with Helicobacter pylori-associated gastritis, atrophic gastritis
Malabsorption	Patients with chronic inflammatory bowel disease, celiac disease, small intestine bacterial overgrowth, and parasitic infection
Drug-related malabsorption	Patients taking medications such as metformin, proton pump inhibitors, and antihistamines
Post-surgery malabsorption	Patients post-gastrectomy and post-ileal resection
Genetic - defective transport	Patients with transcobalamine II deficiency, Imerslund-Gräsbeck Disease (IGS)
Autoimmune	Patients with Sjögren's syndrome, pernicious anaemia
Obstetric/gynaecological	Pregnant women, women taking oral contraceptives, or hormonal replacement therapy

Oral and Sublingual Supplementation

Absorption, Bioavailability, and Dosing

Vitamin B12 is primarily absorbed in the terminal ileum via an intrinsic factor (IF)-dependent mechanism. In patients with IF deficiency or intestinal malabsorption, passive diffusion provides an alternative, though inefficient, absorption pathway, accounting for approximately 1–2% of an oral dose [13]. Consequently, high-dose oral supplementation (1000–2000 µg/day) may result in 10–20 µg absorbed daily, sufficient to normalise serum levels in many individuals.

Sublingual (SL) supplementation bypasses the gastrointestinal tract entirely, allowing direct systemic absorption through the richly vascularized sublingual mucosa. This avoids dependence on IF and hepatic first-pass metabolism, and may enhance bioavailability [7].

Oral Supplementation: Advantages and Limitations

Oral vitamin B12 supplementation is widely utilised due to its non-invasive administration, low cost, and broad accessibility. It is most commonly indicated in individuals with dietary insufficiency (e.g., vegans, vegetarians), age-related hypochlorhydria, or chronic use of medications that impair cobalamin absorption, such as metformin or proton pump inhibitors. It is also appropriate for patients without significant malabsorptive conditions.

Despite its widespread use, the clinical efficacy of oral vitamin B12 supplementation remains a topic of debate. While normalisation of serum cobalamin levels is frequently observed, studies have consistently demonstrated a weak correlation between biochemical correction and the resolution of clinical symptoms. Furthermore, passive diffusion—the primary mechanism by which high-dose oral B12 is absorbed in the absence of intrinsic factor—exhibits substantial interindividual variability. In some individuals, absorption may be as low as 0.1–0.5% of the administered dose [13]. At present, no practical clinical method exists to assess individual absorption efficiency reliably.

Most trials evaluating oral B12 therapy emphasise surrogate endpoints, such as total serum cobalamin, rather than functional biomarkers like methylmalonic acid or homocysteine, or patient-reported symptom improvement [4; 8]. Consequently, the therapeutic relevance of biochemical normalisation alone remains uncertain.

A recent Cochrane review concluded that the quality of evidence supporting the equivalence of oral and intramuscular (IM) B12 supplementation in terms of clinical outcomes is very low, primarily due to methodological shortcomings, small sample sizes, and inconsistent outcome measures [14]. Additionally, patient-reported outcomes suggest that oral therapy may be less effective in alleviating symptoms compared to parenteral administration [15]. As noted by Seage et al. , predicting which patients can be safely transitioned from IM to oral therapy remains challenging, and in some cases, such a switch may result in symptom recurrence or clinical deterioration. [16].

Sublingual Supplementation: Evidence and Clinical Application

Sublingual vitamin B12 supplementation is increasingly favoured due to its simplicity, tolerability, and ability to bypass gastrointestinal limitations. It is particularly beneficial in individuals with IF deficiency, altered gut anatomy (e.g., post-bariatric surgery), or those on long-term medications interfering with B12 absorption [17].

In a large retrospective study involving 4,281 patients, sublingual vitamin B12 supplementation resulted in a significantly greater increase in serum B12 levels compared to intramuscular administration, with a mean rise of 252 ± 223 ng/L versus 218 ± 184 ng/L, respectively [18]. Similarly, Strong et al. found SL B12 equally effective as IM over 6 months in diabetic patients with low serum B12 [19]. A randomised trial by Del Bo et al.

(2019) demonstrated that both low daily (50 µg) and high weekly (2000 µg) sublingual doses effectively improved B12 status in vegans and vegetarians with marginal deficiency. [20]

Ongoing Italian multicenter research using a once-weekly 1000 µg SL formulation (750 µg cyanocobalamin + 250 µg methylcobalamin) in bariatric and malnourished patients has shown promising early results: a 17.8% increase in serum B12 levels and a halving of severe deficiency cases after 6 months of therapy [7].

A recent systematic review and network meta-analysis concluded that sublingual B12 is as effective as oral and IM routes in correcting serum levels, with higher patient satisfaction and lower cost, supporting its use in long-term maintenance therapy [17].

Intramuscular and Subcutaneous Vitamin B12 Supplementation

Mechanism of Action
Parenteral administration of vitamin B12 (intramuscularly or subcutaneously) bypasses the intrinsic-factor-dependent gastrointestinal absorption step. Approximately 10–20% of the injected dose binds to transcobalamin II and is distributed to proliferating tissues, while the rest circulates bound to haptocorrin as a mobilisable reserve [21 ,22]. Hydroxocobalamin (OH-Cbl) is strongly protein-bound (>90%) and creates a local reservoir at the injection site, allowing for prolonged release over up to two days, with an elimination half-life of 24–48 hours. In contrast, cyanocobalamin binds plasma proteins more loosely and is cleared within 6–24 hours [22].

Human pharmacokinetic data show that subcutaneous methylcobalamin achieves a slightly slower Tmax (1.38 h vs. 1.49 h) but a higher Cmax (57.01 vs. 45.82 pg/mL) compared to the intramuscular route, with overall systemic exposure being nearly identical (SC/IM AUC ratio ~104%) [23].

Bioavailability
More than 90% of an intramuscular dose enters systemic circulation, compared to only 1–5% of oral B12 that diffuses passively across the gut wall [17, 24]. In the OB12 trial, a single 1 mg IM dose increased serum B12 nearly fourfold over eight weeks, while the oral group achieved similar levels with a step-down regimen (1 mg/day for one week, then 1 mg/week) [25]. Similar findings were reported in patients following Roux-en-Y gastric bypass surgery, where high-dose oral therapy proved non-inferior to IM supplementation over six months [26,27].

Evidence
Once malabsorption is excluded and the dosage is adequate, adherence becomes the primary determinant of therapeutic success. In older adults treated in primary care, an oral step-down regimen proved equally effective as a single IM dose in correcting biomarkers of deficiency within eight weeks [25]. Observational studies in real-world settings have demonstrated that sublingual and intramuscular B12 supplementation provide equivalent biochemical and clinical outcomes in patients with asymptomatic deficiency [18]. High-dose methylcobalamin has been evaluated in early-stage amyotrophic lateral sclerosis (ALS), although its use remains investigational [28].

Indications and Limitations
Parenteral B12 is indicated when intrinsic-factor-mediated absorption is absent or impaired (e.g., pernicious anaemia, total gastrectomy) or when rapid repletion is required, such as in neuropsychiatric presentations, nitrous oxide-induced myelopathy, or inherited remethylation disorders [29-31]. Hydroxocobalamin is the standard parenteral treatment for symptomatic B12 deficiency in both adults and children. Initial doses of 1 mg IM or SC are given every other day for 1–2 weeks, followed by maintenance every 2–3 months [29].

IM and SC injections are generally well tolerated but may cause local pain, bruising, lipoatrophy, or superficial cellulitis. Rarely, anaphylaxis occurs (<1:50,000) [21, 22]. Transient polycythaemia and pink discoloration of urine may be observed with over-supplementation but are benign [22]. Given the costs and need for healthcare personnel, oral or sublingual B12 (1–2 mg/day) is typically preferred in asymptomatic cases [32].

Parenteral vitamin B12 remains the gold standard in cases of impaired absorption or urgent neurological symptoms. However, for long-term care, well-dosed oral or sublingual therapy can achieve similar outcomes with fewer logistical burdens. The administration route should be tailored to the patient's clinical status, preferences, and healthcare context.

Discussion

This review provides a comprehensive and comparative analysis of oral, sublingual, intramuscular, and subcutaneous routes of vitamin B12 administration, integrating pharmacokinetic data, biochemical efficacy, clinical outcomes, and patient-centered considerations. The findings underscore the complexity of vitamin B12 supplementation and the need for individualized therapeutic approaches.

While intramuscular (IM) injection remains the gold standard for patients with severe deficiency or malabsorption syndromes, emerging evidence suggests that both oral and sublingual (SL) administration may offer comparable efficacy in selected populations, particularly those with mild to moderate deficiency or dietary insufficiency. High-dose oral regimens (≥1000 μg/day) are sufficient to achieve repletion through passive diffusion, although individual variability in absorption and symptom resolution remains a concern.

Sublingual B12 supplementation demonstrates promising results, particularly for patients with impaired gastrointestinal absorption or those preferring non-invasive alternatives. Several studies have shown SL administration to be as effective as IM injections in raising serum cobalamin levels, with high patient satisfaction and improved adherence. However, the relative scarcity of long-term and large-scale trials precludes definitive conclusions regarding its clinical superiority or equivalence to parenteral therapy.

It is noteworthy that many studies rely heavily on biochemical markers (e.g., total serum B12) rather than functional biomarkers (MMA, homocysteine) or clinical symptom resolution. This reliance limits the interpretability of the data in terms of true clinical benefit. Furthermore, the heterogeneity of study populations, dosing regimens, and outcome measures complicates direct comparisons across trials.

Another key issue is the lack of standardized criteria for treatment response and failure, particularly when considering switching routes (e.g., from IM to oral). Some patients

experience symptomatic relapse despite biochemical normalization, indicating a potential disconnect between surrogate endpoints and actual clinical benefit.

Ultimately, the choice of route should be guided by the underlying etiology of deficiency, urgency of correction, patient adherence, and access to care. In the context of long-term maintenance, SL and oral routes offer attractive, cost-effective alternatives that merit broader adoption—provided appropriate monitoring is in place.

Conclusion

Summarizing vitamin B12 supplementation, it is important to mention the differences in their bioavailability, mechanism, primary indications, key advantages and disadvantages. Each method of cobalamin delivery should be precisely analyzed so that the patient ensures optimum clinical results. The table below shows the main differences between various type of vitamin B12 supplementation.

Table 3. Comparative Overview of Vitamin B12 Supplementation Routes: Mechanisms, Bioavailability, and Clinical Application

Parameter	Oral	Sublingual	Intramuscular / Subcutaneous
Route of Absorption	Gastrointestinal tract; intrinsic factor (IF)-dependent and passive diffusion at high doses	Direct mucosal absorption into systemic circulation	Direct injection into muscle or subcutaneous tissue
Bioavailability	Low (1–5%); variable with passive diffusion	Moderate to high; bypasses gastrointestinal limitations	Very high (>90%)
Onset of Action	Slow (weeks to months)	Moderate (1–2 weeks)	Rapid (days to weeks)
Key Advantages	Non-invasive, low cost, widely accessible	Non-invasive, IF-independent, well tolerated	Rapid effect, reliable in malabsorption and severe cases
Key Limitations	Variable absorption, limited efficacy in malabsorption	Fewer long-term studies; absorption may vary between patients	Invasive, requires trained personnel, higher cost
Clinical Indications	Mild deficiency, dietary insufficiency (e.g., vegans)	Functional deficiency, malabsorption, post-bariatric surgery	Pernicious anemia, neurologic symptoms, severe depletion
Monitoring Requirements	Regular monitoring of serum B12, MMA/homocysteine	Similar to oral; follow-up recommended	Less frequent after stabilization (e.g., every 2–3 months)

Current evidence suggests that all routes of vitamin B12 administration can be clinically effective.. The optimal route of vitamin B12 supplementation depends on the pathophysiology and severity of the deficiency. Intramuscular or subcutaneous administration remains the "gold standard" for chronic and severe malabsorption. Oral supplementation is the most appropriate method for correcting dietary deficiency. In addition, sublingual administration is a highly effective alternative that bypasses the gastrointestinal tract and is comparable, if not superior, to the efficacy of intramuscular therapy for the treatment of vitamin B12 deficiency. Individual treatment decisions guided by the clinical context, not just serum levels, are essential to achieve optimal therapeutic outcomes.

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