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Sublingual and intranasal vitamin B12: Emerging non-invasive approaches for cobalamin deficiency in adults and elderlies

Emmanuel Andrès[1,2]*; Noel Lorenzo-Villalba[1]

[1]Department of Internal Medicine, Hautepierre Hospital, University Hospitals of Strasbourg, Strasbourg, France.

[2]Mitochondria and Oxidative Stress, Faculty of Medicine, University of Strasbourg, Strasbourg, France.

***Corresponding Author: Emmanuel Andrès**
Department of Internal Medicine, Hautepierre Hospital, University Hospitals of Strasbourg, Strasbourg, France.
Tel: 333-88-11-50-66, Fax: 333-88-11-62-62;
Email: emmanuel.andres@chru–strasbourg.fr

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Abstract

Vitamin B12 (cobalamin) deficiency can lead to hematological, neurological, and cognitive complications, particularly in elderly patients and those with malabsorption. While traditional supplementation relies on oral or intramuscular routes, sublingual and intranasal administration have emerged as non-invasive alternatives. Clinical evidence shows that intranasal and sublingual vitamin B12 effectively normalize serum levels, improve hematological and biochemical parameters, and maintain adequate concentrations over time. Both routes are generally well tolerated, with mild adverse effects such as transient nasal irritation or oral discomfort. Limitations include small sample sizes, heterogeneous dosing, and limited long-term data. Future research should focus on standardized protocols, pharmacokinetics, long-term safety, and patient-centered outcomes. Intranasal and sublingual vitamin B12 offer safe, effective, and patient-friendly alternatives to conventional oral or intramuscular supplementation.

Keywords: Vitamin B12; Cobalamin; Vitamin B12 deficiency; Intranasal administration; Sublingual administration; Efficacy; Safety; Elderly; Malabsorption; Food-cobalamin malabsorption; Clinical review.

Introduction

Vitamin B12 (cobalamin) is a crucial water-soluble vitamin involved in DNA synthesis, red blood cell formation, and neurological function [1]. Deficiency can result in megaloblastic anemia, neuropathy, cognitive decline, and increased morbidity, particularly in older adults, chronically ill patients, and individuals with malabsorption syndromes [2]. Beyond hematological and neurological consequences, low vitamin B12 status is linked to elevated homocysteine levels, increasing cardiovascular risk, and may exacerbate neuropsychiatric symptoms, including depression and memory impairment. Early detection and effective supplementation are therefore critical to prevent irreversible complications.

Traditionally, vitamin B12 supplementation has relied on oral administration, which requires adequate gastric acid, intrinsic factor, and ileal absorption, or intramuscular injections, which bypass gastrointestinal barriers but are invasive, can cause injection-site discomfort, and may reduce adherence [3]. In response to these limitations, non-invasive alternatives-notably sublingual and intranasal routes-have gained increasing attention. Sublingual administration leverages the vascularized mucosa under the tongue to achieve serum vitamin B12 levels comparable to injections, while intranasal delivery enables rapid systemic absorption with enhanced patient convenience and acceptability, particularly for those with malabsorption or needle aversion [4].

This review provides a comprehensive overview of sublingual and intranasal vitamin B12 supplementation, examining absorption physiology, clinical efficacy, safety, and patient-centered outcomes, and discusses future directions for optimizing vitamin B12 therapy in diverse at-risk populations. By highlighting these non-invasive strategies, we aim to inform clinical practice and expand therapeutic options beyond traditional oral and intramuscular supplementation.

Usual routes of vitamin B12 administration

Vitamin B12 is most commonly administered intramuscularly or orally. Intramuscular injections deliver vitamin B12 directly into systemic circulation, bypassing gastrointestinal barriers. Standard regimens include daily injections for one-week, weekly injections for one month, followed by monthly maintenance [2,3]. While highly effective, this route is invasive, may cause local pain, hematoma, or infection, and often requires healthcare visits, which can reduce long-term adherence.

Oral administration depends on gastric acid and intrinsic factor to facilitate absorption in the terminal ileum via the Cubilin-Amnionless complex (CUBAM) [5]. In healthy individuals, only 1-2% of a large oral dose is absorbed, which may be insufficient for patients with documented malabsorption [6]. Nevertheless, high-dose oral supplementation (1000-2000 µg daily) can partially overcome these limitations.

Alternative routes, including high-dose oral and sublingual administration, have been proposed, particularly for food-cobalamin malabsorption, as well as for pernicious anemia (Biermer's disease) and following surgical resection [3]. Evidence suggests that sublingual vitamin B12 can achieve serum levels comparable to intramuscular injections, although absorption variability remains a concern [2,3]. More recently, the intranasal route has emerged as a promising option, offering convenience, rapid absorption, and improved patient compliance [7].

Mechanisms of sublingual and intranasal absorption

The sublingual and nasal mucosae provide highly vascularized surfaces that allow rapid systemic absorption of small molecules and certain hydrophilic vitamins, including vitamin B12 (Figure 1) [4]. In both routes, absorption occurs through two main pathways: transcellular transport, in which molecules pass directly through epithelial cells, and paracellular transport, involving movement between cells via tight junctions [2,4]. The rich blood supply and thin epithelial barriers of these mucosae facilitate rapid entry into the systemic circulation.

Intranasal delivery bypasses the gastrointestinal tract and avoids first-pass hepatic metabolism, which can limit oral bioavailability [3,7]. Pharmacokinetic studies show that intranasal vitamin B12 reaches peak serum concentrations within 1-2 hours after administration, demonstrating rapid systemic availability [3]. Sublingual administration similarly allows direct absorption into the bloodstream via the lingual veins, providing a convenient alternative to oral tablets or injections, particularly in individuals with impaired gastrointestinal absorption.

Both routes are minimally invasive, easy to self-administer, and generally well tolerated, making them suitable for chronic supplementation [3]. Formulation strategies, including the use of mucoadhesive carriers and pH optimization, further enhance absorption efficiency. Overall, sublingual and intranasal routes provide reliable and rapid pathways for systemic delivery of vitamin B12, supporting their clinical use in populations at risk of deficiency or with malabsorption.

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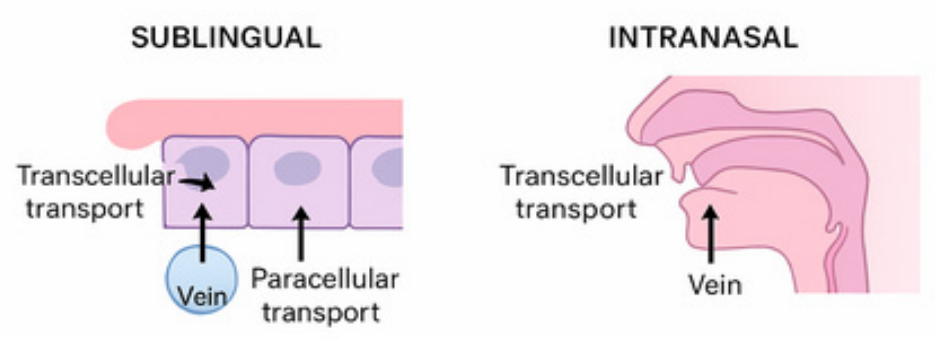

Figure 1: Mechanisms of sublingual and intranasal absorption.

Clinical studies and efficacy in adults and elderlies

Intranasal vitamin B12 supplementation has demonstrated consistent efficacy in correcting deficiency and maintaining adequate serum levels across a variety of patient populations. Sharabi et al. [4] conducted a randomized study in 18 elderly patients with documented deficiency, administering 500 µg cyanocobalamin sublingual tablets once weekly for 8 weeks. Serum vitamin B12 normalized in 90% of participants, treatment was well tolerated, and most patients expressed a preference for the nasal route over oral or intramuscular administration. Slot et al. [8] evaluated 60 adults receiving 500 µg cyanocobalamin via nasal spray 1-2 times weekly, observing normalization of serum vitamin B12 and improvement of clinical symptoms, demonstrating efficacy equivalent to oral supplementation.

Table 1: Intranasal and sublingual vitamin B12: Clinical studies, formulations, and recommendations.

Study	Population	Route & dose	Duration	Key outcomes
Sharabi et al. 2003	18 elderly patients with vitamin B12 deficiency	Sublingual 500 µg once weekly	8 weeks	Serum vitamin B12 normalized in 90%; treatment well tolerated; most preferred sublingual route
Slot et al. 2006	60 adults	Nasal spray 500 µg 1-2 times weekly	–	Serum vitamin B12 normalized; clinical symptoms improved; efficacy equivalent to oral supplementation
Tillemans et al. 2024	60 elderly ≥65 yrs	Nasal 1000 µg: daily 14 days + weekly (loading) or every 3 days 90 days (no-loading)	14–90 days	Both regimens increased serum vitamin B12 & holotranscobalamin; normalized methylmalonic acid & homocysteine; loading gave rapid rise
Bensky et al. 2019	Adults post-bariatric surgery	Nasal 1000 µg weekly	–	Serum vitamin B12 maintained >200 pg/mL; effective in malabsorptive populations
Wang et al. 2021 (review)	Various	Nasal 500-1000 µg 1-2 times weekly	–	Clinically significant absorption; highlights need for standardized protocols
Del Bo' et al. 2019	40 vegans/vegetarians with marginal B12 deficiency	Sublingual 350 µg/week vs 2000 µg/week	12 weeks	Both doses increased serum vitamin B12, holotranscobalamin, methionine, succinic acid; reduced methylmalonic acid, homocysteine, folate; no difference between doses
Jacobson Bensky et al. 2019	4281 adults with vitamin B12 deficiency	Sublingual 500–2000 µg daily vs Intramuscular standard regimen	Retrospective	Mean increase in serum vitamin B12 higher in sublingual group (252 ± 223 ng/L) vs intramuscular (218 ± 184 ng/L $p < 0.001$); OR 1.85 (95% CI 1.5-2.3 $p < 0.001$); sublingual as effective or superior to intramuscular; improved patient adherence

Table 2: Results of commercial intranasal vitamin B12 products.

Study/Reference	Population	Formulation/Dose	Duration/Frequency	Main results	Comments
Nascobal® (USA)	Patients with Biermer's disease	Cyanocobalamin gel 500 µg / dose	Once weekly	Sustained increase in serum vitamin B12	FDA-approved; not available in all countries
Vibispray® (Europe)	Patients with mild/moderate deficiency	Cyanocobalamin nasal spray 500 µg	Twice weekly in loading phase	Corrected deficiency within 1 month in >80% of patients	Easy to use; good patient adherence

FDA: Food and Drug Administration; normal serum B12 = generally >200-300 pg/mL; gels adhere longer to the nasal mucosa but are less commonly used than sprays.

In a prospective randomized study, Tillemans et al. [9] administered 1000 µg intranasally to elderly patients aged ≥65 years using two regimens: a loading regimen (daily for 14 days followed by weekly doses) and a no-loading regimen (every 3 days for 90 days). Both approaches produced significant increases in serum vitamin B12 and holotranscobalamin (holoTC) levels, with normalization of Methylmalonic Acid (MMA) and total Homocysteine (tHcy). The loading regimen achieved a rapid rise to a median serum B12 of 1090 pmol/L at 14 days, whereas the no-loading regimen reached 717 pmol/L at 90 days, demonstrating that both regimens are effective for restoring adequate B12 status.

In the post-bariatric surgery population, Bensky et al. [10] studied 60 patients who had undergone Roux-en-Y gastric bypass or sleeve gastrectomy, comparing weekly intranasal cyanocobalamin (500 µg) with intramuscular injections (1000 µg) over 12 weeks. Both routes produced comparable and significant increases in serum B12, were well tolerated, and showed high patient adherence, supporting the use of intranasal supplementation in malabsorptive populations. Similarly, Rozgony et al. [11] demonstrated that 8 weeks of intranasal cyanocobalamin significantly improved serum B12 in elderly nursing home residents, including long-term users of proton pump inhibitors.

In this context, Wang et al. [7] reviewed 12 studies and reported variable but clinically significant absorption with 500-1000 µg per spray, 1-2 times weekly, highlighting the need for standardized protocols.

Additionally, evidence indicates that sublingual administration effectively restores vitamin B12 levels in vulnerable groups (Table 1). Del Bo' et al. [12] conducted a 12-week randomized, double-blind, controlled trial in 40 vegans and vegetarians with marginal vitamin B12 deficiency, comparing a low dose (350 µg/week) to a high dose (2000 µg/week). Both regimens significantly increased serum vitamin B12, holoTC, methionine, and succinic acid levels, while reducing MMA, tHcy, and folate levels. No significant differences were observed between the two dosing strategies, indicating that a lower weekly dose of 350 µg was sufficient to restore adequate vitamin B12 status. These results highlight that both sublingual and intranasal routes are effective strategies to correct deficiency, improve metabolic markers, and support nutritional adequacy in at-risk populations. Jacobson Bensky et al. [13] conducted a large retrospective study comparing Sublingual (SL) versus Intramuscular (IM) administration in 4281 adults. The mean increase in serum vitamin B12 was higher in the SL group (252±223 ng/L) compared to the IM group (218±184 ng/L, $p<0.001$), with an odds ratio of

Table 3: Potential indications of intranasal vitamin B12 therapy in adult and elderly population.

Population/Condition	Risk of vitamin B12 deficiency	Advantages of intranasal and sublingual administration	Limitations/Considerations
Strict vegans / vegetarians	No dietary intake; limited body stores	Sublingual supplementation shown effective in Del Bo' et al. [12]; well tolerated and easy to use	Requires biological monitoring (e.g., holotranscobalamin, methymalonic acid) and dose adjustment
Food-cobalamin malabsorption (Helicobacter pylori, protons pump inhibitors, metformin)	Reduced intestinal absorption; progressive deficiency	Intranasal and sublingual routes bypass gastrointestinal tract and restore serum levels [4,8]	Long-term data limited; dosing regimens not yet standardized
Bariatric surgery / gastric bypass	Impaired absorption in stomach and ileum	Intranasal 1000 µg/week effective post-surgery [10]; better adherence than intramuscular injections	Maintenance dosing may need to be more frequent depending on surgery type
Pernicious anemia (Biermer's disease)	Lack of intrinsic factor → severely impaired oral absorption	Intranasal products (e.g., Nascobal®) maintain adequate levels without injections; good tolerability	Requires close monitoring to prevent relapse
Intestinal resection (terminal ileum or small bowel)	Markedly reduced or absent B12 absorption	Sublingual and intranasal routes provide non-digestive absorption	Effectiveness may vary by extent of resection; follow-up is essential
Elderly patients (≥65 years)	Multifactorial malabsorption, hypochlorhydria, reduced intake	Sharabi et al. [4] and Tillemans et al. [9] showed effective correction and good acceptability	Limited long-term (>1 year) outcome data
Chronic use of protons pump inhibitors or metformin	Gradual impairment of cobalamin assimilation	Nasal spray shown effective even in protons pump inhibitor users [11]	Optimal protocols still need clarification
Patients with poor adherence to intramuscular injections	Risk of undertreatment and relapse	Sublingual [13] and intranasal routes offer equal or superior efficacy with higher adherence	Requires patient education and regular monitoring

1.85 (95% CI 1.5-2.3, p<0.001) for achieving increased B12 levels. This study highlights that sublingual supplementation can be as effective-or even superior-to intramuscular injections in restoring adequate B12 status, while improving patient adherence.

Commercial products such as Nascobal® (USA) and Vibispray® (Europe) have demonstrated sustained increases in serum vitamin B12 with good tolerability and patient adherence (Table 2) [14]. Nascobal®, a 500 µg cyanocobalamin nasal gel approved by the U.S. FDA, has been shown in clinical studies to produce a rapid rise in serum vitamin B12, reaching a mean peak concentration of 1021 pg/mL within 1.5 hours after a single dose, with serum levels elevated by 46% above baseline at 72 hours. Weekly administration maintains these elevated levels over time, offering an effective maintenance therapy for patients with pernicious anemia or other causes of B12 deficiency. Vibispray®, a 500 µg cyanocobalamin nasal spray available in Europe, has been reported to normalize serum vitamin B12 levels within 1 month in over 80% of patients with mild to moderate deficiency. The treatment was well tolerated, easy to administer, and associated with high patient compliance, making it a convenient alternative to intramuscular injections.

Safety and tolerability

Intranasal and sublingual vitamin B12 have consistently demonstrated a favorable safety and tolerability profile. Across multiple studies, adverse effects were generally mild and infrequent. Sharabi et al. [4] reported no serious events in 18 elderly patients receiving 500 µg sublingual weekly for 8 weeks, with only minor gastrointestinal discomfort in one patient. Similarly, Slot et al. [8] observed transient nasal discomfort in less than 5% of 60 patients receiving intranasal cyanocobalamin, without systemic effects. In a prospective randomized trial, Tillemans et al. [9] reported mild local irritation and transient rhinorrhea in approximately 10% of elderly patients receiving intranasal 1000 µg vitamin B12, which resolved spontaneously, with no systemic reactions. In a large retrospective study of 4281 adults, Jacobson Bensky et al. [13] found that sublingual supplementation was well tolerated, with no serious adverse events reported and high patient adherence. Furthermore, studies in special populations, including post-bariatric surgery patients, demonstrated that intranasal administration is safe, well tolerated, and associated with good adherence [10]. Overall, both intranasal and sublingual vitamin B12 offer non-invasive, safe, and patient-friendly alternatives to oral or intramuscular supplementation, with minimal local or systemic side effects.

Limitations and future perspectives

Although both intranasal and sublingual vitamin B12 supplementation have demonstrated efficacy and safety across different populations, several limitations must be acknowledged. Most available studies remain small, single-center trials with heterogeneous dosing regimens and formulations, thereby limiting generalizability [7]. For intranasal therapy, evidence from elderly patients, post-bariatric cohorts, and those with mild to moderate deficiency [4,8-10] consistently shows normalization of serum vitamin B12 and improvement in metabolic markers. Likewise, sublingual supplementation has been supported by prospective trials [4,12] and large retrospective data [13], confirming that this route can be as effective as, or even superior to, intramuscular administration. However, long-term outcomes on adherence, neurological improvement, and standardized dosing strategies remain insufficiently studied.

Another challenge is the lack of harmonized international guidelines and the variability among commercial formulations. Intranasal preparations such as Nascobal® (USA) and Vibispray®

(Europe) have proven efficacy and good tolerability, but access and approved dosing regimens differ between countries. Similarly, sublingual formulations range widely from low weekly doses (350 µg) to high daily intakes (2000 µg), without consensus on optimal protocols. Moreover, long-term safety data remain scarce, particularly in elderly individuals and patients with chronic malabsorptive conditions.

In clinical practice, intranasal and sublingual routes represent valuable alternatives when gastrointestinal absorption is impaired or when intramuscular injections compromise adherence. These approaches are particularly suitable for adults and elderly patients with confirmed vitamin B12 deficiency who do not present with severe neurological involvement. Common etiologies in these populations include atrophic gastritis (often linked to Helicobacter pylori infection or autoimmune gastritis), previous gastric or intestinal surgery, chronic diseases such as celiac disease or Crohn's disease, long-term use of proton pump inhibitors or metformin, and strict vegetarian or vegan diets [15]. In the elderly, deficiency is frequently multifactorial, combining reduced intake, hypochlorhydria, and autoimmune mechanisms. In such contexts, sublingual and intranasal administration provide effective, safe, and patient-friendly options, supporting the maintenance of adequate vitamin B12 status and preventing hematological and neurological complications.

Conclusion

Intranasal and sublingual vitamin B12 supplementation represent safe, effective, and patient-centered alternatives to traditional oral and intramuscular routes. Across diverse populations-including older adults, post-bariatric patients, individuals with pernicious anemia, vegans, and those with food-cobalamin malabsorption-these non-invasive methods have demonstrated the ability to rapidly correct deficiency, normalize biochemical markers, and maintain adequate serum levels over time. Both routes are well tolerated, with adverse effects largely limited to mild, transient local irritation.

Despite their demonstrated efficacy, current evidence is limited by small samples, heterogeneous dosing regimens, and variable follow-up durations. Long-term data on safety, adherence, and optimal maintenance strategies remain insufficient, particularly in elderly or malabsorptive patients. Further research should focus on standardized dosing protocols, real-world effectiveness, patient-reported outcomes, and pharmacokinetic comparisons between delivery routes.

From a clinical perspective, the intranasal and sublingual routes offer valuable alternatives for patients who poorly tolerate injections, have limited venous access, demonstrate low adherence to intramuscular regimens, or present with gastrointestinal malabsorption. Their simplicity of use and favorable tolerability support integration into personalized supplementation plans, allowing clinicians to tailor therapy to individual metabolic needs, lifestyle preferences, and comorbidities.

Declarations

Conflicts of interest: The authors declare no conflicts of interest.

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