Lack of sufficient vitamin B₁₂ intake is often associated with the development of vitamin B₁₂ deficiency anemia, which is a medical condition characterized by a low red blood cell count and vitamin B₁₂. Vitamin B₁₂ deficiency anemia has several causes, including pernicious anemia (PA), which results from autoantibodies destroying the cells that make intrinsic factor. Without intrinsic factor, the body is unable to absorb vitamin B₁₂ through the stomach.

Historically, PA was thought to affect the Scandinavian and Celtic-origin populations more than other ethnic groups; however, more recent evidence has shown higher prevalence in the African and Latin American populations.¹,² Understanding the epidemiology of PA is important when discussing patient populations in clinical trials of medications for correcting abnormal vitamin B₁₂ levels. Data indicate that women are almost twice as likely to be affected as men.¹ The median age-group is 40 to 70 years.¹,³ Before treatment can be pursued, the appropriate form of subclinical or clinical vitamin B₁₂ deficiency must be diagnosed.

The early diagnosis of vitamin B₁₂ deficiency is important for preventing anemia, but is challenging because patients may be asymptomatic or have only mild symptoms, such as bowel changes, fatigue, loss of appetite, pale skin, shortness of breath, mild tingling of the extremities, and bleeding gums. These mild symptoms, or lack thereof, are associated with the subclinical form of vitamin B₁₂ deficiency, which is also the most common type of vitamin B₁₂ deficiency. The key diagnostic factor for subclinical vitamin B₁₂ deficiency is a cobalamin level between 200 pg/mL and 350 pg/mL.⁴ The other type of vitamin B₁₂ deficiency is the clinical form, which manifests as anemia or more serious signs and symptoms (e.g., depression, confusion, dementia, and paresthesia in the hands and feet). In this type of vitamin B₁₂ deficiency, the cobalamin level is <200 pg/mL.⁴,⁶ Correcting vitamin B₁₂ levels is especially important in clinically deficient patients, because nerve damage can be permanent if treatment is not initiated within 6 months of symptom onset.⁵ Once the diagnosis is confirmed, the healthcare provider must choose a patient-specific vitamin B₁₂ formulation.

Currently there are myriad formulations of which

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**Cyanocobalamin/Salcaprozate Sodium: A Novel Way to Treat Vitamin B₁₂ Deficiency and Anemia**

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**Background:** Vitamin B₁₂ deficiency anemia is a medical condition characterized by a low red blood cell count and vitamin B₁₂. Various treatment options are available for vitamin B₁₂ deficiency. Cyanocobalamin comes in an array of formulations, including injection, nasal spray, powder, solution, sublingual, and tablets. However, many oral formulations are considered supplements, which are not regulated by the US Food and Drug Administration.

**Objective:** The purpose of this review is to compare cyanocobalamin/salcaprozate sodium (SNAC) with other available cyanocobalamin formulations based on pharmacokinetics and efficacy.

**Discussion:** Injections of vitamin B₁₂ typically have been the predominant method for treating patients who require a fast or highly bioavailable response. However, the pharmacokinetic profile of cyanocobalamin/SNAC was shown to be more favorable than that of another oral formulation of cyanocobalamin (not containing SNAC), because it reached a higher peak plasma concentration than the other oral formulation.

**Conclusion:** Cyanocobalamin/SNAC is a major advancement in the treatment of hypocobalaminemia because it is the first formulation to include the absorption promoter SNAC. Cyanocobalamin/SNAC was shown to be as effective as intramuscular cyanocobalamin in restoring normal levels of serum cobalamin, which makes this drug an attractive option for the treatment of patients with vitamin B₁₂ deficiency.

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treatment of vitamin B₁₂ deficiency can consist. The purpose of this review is to compare cyanocobalamin/salcaprozate sodium (SNAC) with other available vitamin B₁₂ formulations based on their pharmacokinetics, efficacy, and cost.

Formulations

Cyanocobalamin is the most common commercially available form of vitamin B₁₂. It comes in an array of formulations, including intramuscular (IM) injection, nasal spray, powder, solution, sublingual, and tablet form. Although various treatment options exist, many oral formulations are considered dietary supplements, which are not regulated by the US Food and Drug Administration (FDA), and little clinical data exist to support their use. The current FDA-approved formulations of cyanocobalamin are IM injection, subcutaneous (SC) injection, intravenous (IV) infusion, and nasal spray. IV infusion is not frequently used because cyanocobalamin is lost more rapidly via the urine than with the other parenteral formulations, leaving little time for liver storage and use, and causing less of a therapeutic response.⁸

Cyanocobalamin is converted to methylcobalamin in vivo by removal of a cyanide group and subsequent methylation. As a result, supplemental methylcobalamin is often presumed to have improved bioavailability and clinical efficacy compared with cyanocobalamin; however, there is insufficient evidence to indicate its superiority.⁹ Methylcobalamin is available only as a dietary supplement, while cyanocobalamin is available as dietary supplements, FDA-approved medications, and now as a medical food. Also, cyanocobalamin is more stable and less expensive to produce.⁹

Cyanocobalamin/salcaprozate sodium (Eligen B₁₂; Emisphere Technologies, Roseland, NJ), the newest tablet formulation, differs from other medications and supplements for vitamin B₁₂ deficiency because it contains an oral absorption promoter, known as salcaprozate sodium (SNAC). SNAC chaperones vitamin B₁₂ through the gastric lining into the bloodstream. This added constituent gives cyanocobalamin/SNAC a drug-absorption profile similar to that of injectable vitamin B₁₂, as was shown in a small clinical trial.¹⁰ As a result, cyanocobalamin/SNAC has been classified as a medical food.

Medical foods are intended for the nutritional support of patients with a specific disease or condition. Because they are classified as food, they are not subject to drug regulations. For example, medical foods do not have to undergo premarket review or approval, making them similar to dietary supplements. However, unlike supplements, medical foods must comply with all applicable FDA requirements for food, such as regulations of the Current Good Manufacturing Practice and the Registration of Food Facilities. In addition, medical foods can be labeled for medical conditions, as long as the label is not misleading and based on clinical data. A prescription may also be required for their use. All ingredients contained in medical foods must be generally recognized as safe or approved food additives.¹¹,¹² Therefore, it is more difficult to produce and market a product as a medical food than as a dietary supplement.

Comparison of Cyanocobalamin Formulations

Oral Tablet

Studies of cyanocobalamin have demonstrated differences in pharmacokinetics depending on the formulation examined. Berlin and colleagues conducted a long-term study in which the absorption of oral vitamin B₁₂ was evaluated for up to 5 years among 64 patients.¹³ They found that approximately 56% of a 1-μg dose of oral cyanocobalamin was absorbed; however, absorption decreased dramatically when the intrinsic factor capacity was exceeded (approximately 1-2 μg of vitamin B₁₂).¹³,¹⁴ The authors of the study demonstrated intrinsic factor–unrelated diffusion of 1.2% of any oral dose, and concluded that oral administration delivers much less cobalamin per dose if the intrinsic factor saturation point is exceeded, or if the patient has PA.¹³ Therefore, as a result of wide individual variation, ≥1000 μg must be taken daily to treat a vitamin B₁₂ deficiency if malabsorption is the leading cause. Moreover, Berlin and colleagues concluded that absorption is decreased if oral cyanocobalamin is taken with a meal as opposed to fasting, with absorption rates of 1.8 μg to 7.5 μg versus 2.8 μg to 13.4 μg, respectively, for a 500-μg dose.¹³,¹⁴ Overall, this study illustrates some of the key absorptive issues related to dietary supplements of vitamin B₁₂.¹³,¹⁴

Sublingual Tablets and Lozenges

Although sublingual tablets and lozenges are often touted as having superior efficacy and bioavailability than other oral formulations, clinical evidence supporting this claim is lacking. However, studies have shown that the efficacy of both methylcobalamin and cyanocobalamin sublingual formulations is equal to that of oral tablets.¹⁵,¹⁶

Parenteral Formulations

The pharmacokinetics of cyanocobalamin in IM, IV, and SC dosages has been examined in clinical trials. Studies have shown that between 50% and 98% of an IM or SC dose of 100 μg to 1000 μg of cyanocobalamin is excreted unchanged in the urine, with the majority appearing within 8 hours after injection.⁸ Doses that exceed 100 μg will not result in significantly greater vita-
min B₁₂ retention. However, liver stores may be replenished more quickly with a lower dose. In addition, parenteral administration of cyanocobalamin at doses of 100 μg and 1000 μg are associated with a total body retention of 55% and 15%, respectively. The remaining 45% to 85% is excreted unchanged in the urine. The time to peak concentration (T_max) for the IM injection is 1 hour. Specific data are not available for the T_max of the SC injection, but are thought to be comparable to the IM injection.

**Nasal Spray**

Cyanocobalamin nasal spray, marketed as Nascobal (Endo Pharmaceuticals, Malvern, PA), is the only FDA-approved nasal spray to increase and maintain healthy levels of vitamin B₁₂. It is administered once weekly. When studied in 25 healthy patients, peak concentrations occurred at 1.25 ± 1.9 hours. The bioavailability of the nasal spray relative to IM injection was found to be 6.1%. Therefore, the intranasal medication peaks quickly, but its overall efficacy compared with IM injection is questionable based on the low relative bioavailability.

**Cyanocobalamin/SNAC Oral Tablet**

The FDA designation of cyanocobalamin/SNAC as a medical food was based on 2 limited drug trials, including a pharmacokinetics study of oral formulations in 20 healthy men, and an efficacy and tolerability comparison of cyanocobalamin/SNAC with the current FDA-approved IM formulation.

**Study 1: Pharmacokinetics.** In this study of 20 healthy men aged 20 to 45 years, cyanocobalamin/SNAC had a more favorable pharmacokinetic profile than oral cyanocobalamin without SNAC. The 5-mg dose of cyanocobalamin/SNAC had a mean absolute bioavailability of 75.6%, whereas the 5-mg commercial oral formulation had a bioavailability of 21.7%. In addition, cyanocobalamin/SNAC reached a peak plasma concentration (C_max) of 12,847 pg/mL, whereas the C_max for the commercial oral product was 239 pg/mL. The T_max was also lower for cyanocobalamin/SNAC (0.5 hours vs 6.83 hours for the commercial formulation). The elimination half-life was similar: 30.06 hours for cyanocobalamin/SNAC versus 25.95 hours for the commercial formulation.

**Study 2: Efficacy and tolerability.** The same investigators conducted a 3-month, randomized, multicenter trial in which 48 patients with vitamin B₁₂ deficiency were randomly assigned to receive 1000 μg of oral cyanocobalamin/SNAC daily or 1000 μg of IM cyanocobalamin on study days 1, 3, 7, 10, 14, 21, 30, 60, and 90.

The participants were required to be aged ≥60 years, or ≥18 years with gastrointestinal abnormalities or with a restricted diet. The participants aged ≥60 years were not required to have gastrointestinal abnormalities or a restricted diet. The primary efficacy outcome was normalization of cobalamin levels (≥350 ng/mL) following 60 days of treatment, maintained through day 91 (the day following the last treatment). Both formulations were effective in restoring normal levels of serum cobalamin in all patients studied.

The observed adverse effects were mild or moderate in intensity. Overall, 56.0% of study participants reported ≥1 adverse effects, all of which were transient. Among patients who received cyanocobalamin/SNAC, 54.2% reported ≥1 adverse effects. Of those who received IM cyanocobalamin, 57.7% reported ≥1 adverse effects. These mild and moderate effects included constipation, diarrhea, nausea, fatigue, headache, back pain, and respiratory tract infection. Any adverse effects considered severe were deemed unrelated to the study medications. This study demonstrated that oral vitamin B₁₂ formulated with SNAC is as safe and effective as IM injections of this vitamin.

**Discussion**

Many formulations are available for treating vitamin B₁₂ deficiency, each with the common goal of increasing the levels of vitamin B₁₂ in the bloodstream. IM injections of vitamin B₁₂ typically have been the predominant delivery method for treating patients who require a rapid or highly bioavailable response. With cyanocobalamin/SNAC, patients can receive a concentration level similar to that of injectable vitamin B₁₂ without having to undergo injection. Cyanocobalamin/SNAC is the only once-daily oral prescription medical food tablet that has been shown to normalize vitamin B₁₂ levels without the need for injection.

Cyanocobalamin/SNAC was not shown to offer greater efficacy than IM vitamin B₁₂, which is the current standard of care for hypocobalaminemia. However, cyanocobalamin/SNAC reached a higher C_max than oral formulations of cyanocobalamin that do not contain SNAC, and its T_max was only 30 minutes. Another oral formulation took almost 7 hours to reach a lower C_max. C_max represents the peak concentration that a substance attains in the body and is reflective of systemic exposure.

The pharmacokinetics study was conducted exclusively in healthy men, which is problematic because women are twice as likely as men to develop vitamin B₁₂ deficiency. Vitamin B₁₂ deficiency can result from an abnormally functioning gastrointestinal tract. Patients aged between 40 and 70 years are often affected by vitamin B₁₂ deficiency as normal aging occurs, and this population is likely to have a decrease in kidney function.
compared with younger adults (aged 20-45 years), who also participated in the 2 aforementioned studies. Furthermore, 15 of the 20 participants were African American; Caucasian and Latin American patients were poorly represented. As a result, this study may not be applicable to other races. Although few studies exist on this medical food, it will be interesting to see what the future holds for cyanocobalamin/SNAC and other novel medications that may include absorption promoters to increase mean concentration levels. In addition, more head-to-head trials should be conducted to compare the currently available cyanocobalamin medications with dietary supplements and with the medical food.

As is often true of new medications or medical foods, associated costs may be higher than those of existing treatments. Patients who receive injectable vitamin B₁₂ can purchase a vial of cyanocobalamin for approximately $10, whereas the cost of cyanocobalamin/SNAC is approximately $45 for a 30-day supply. Moreover, there is a compliance concern regarding cyanocobalamin/SNAC. Patients would be required to remember to take it daily, whereas IM maintenance injections are administered monthly, and the only FDA-approved nasal spray (Nascobal) is administered weekly. The cost of the cyanocobalamin nasal spray for patients who have commercial insurance is ≤$25 with a copay card from the manufacturer’s website. The price of the nasal spray for patients ineligible to receive the copay card exceeds $100 for a 1-month supply. Even though the price of the nasal spray with a copay card is cheaper than the price of cyanocobalamin/SNAC, studies have not shown that the bioavailability of the nasal spray is equivalent to that of the IM injection. Injection of cyanocobalamin is currently the most cost-effective treatment for patients with vitamin B₁₂ deficiency, but cyanocobalamin/SNAC provides an oral option for patients who are not comfortable receiving injections.

Conclusion

Cyanocobalamin/SNAC is a major advancement in the treatment of vitamin B₁₂ deficiency, because it is the first product to include the absorption promoter SNAC. Cyanocobalamin/SNAC has been shown to have an absorption profile similar to that of injectable solutions of vitamin B₁₂. Oral cyanocobalamin/SNAC and IM injections have been effective in restoring normal levels of serum cobalamin in all patients studied thus far.

In general, vitamin B₁₂ deficiency is mild when discovered, and the etiology varies greatly. If untreated, serious conditions can occur, such as permanent nerve damage and anemia. Therefore, it is important to correct vitamin B₁₂ levels as early as possible in patients with subclinical deficiency so that clinical deficiency can be averted. The absorption of oral vitamin B₁₂ dietary supplements and the nasal spray is not adequate to supply the amount of vitamin B₁₂ needed to correct the deficiency, and IM or IV injection of cyanocobalamin can be painful and undesirable for certain patients. Cyanocobalamin/SNAC represents a new treatment option that may be attractive for patients with vitamin B₁₂ deficiency.

Author Disclosure Statement
The authors have no conflicts of interest to report.

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