

Vitamin B12

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While some complementary and alternative techniques have been studied scientifically, high-quality data regarding safety, effectiveness, and mechanism of action are limited or controversial for most therapies. Whenever possible, it is recommended that practitioners be licensed by a recognized professional organization that adheres to clearly published standards. In addition, before starting a new technique or engaging a practitioner, it is recommended that patients speak with their primary healthcare provider(s). Potential benefits, risks (including financial costs), and alternatives should be carefully considered. The below monograph is designed to provide historical background and an overview of clinically-oriented research, and neither advocates for or against the use of a particular therapy.

Related Terms:

- B-12, B Complex, B Complex Vitamin, bedumil, cobalamin, cobalamins, cobamin, cyanocobalamin, cyanocobalaminum, cycobemin, hydroxocobalamin, hydroxocobalaminum, hydroxocobemine, idrossocobalamina, methylcobalamin, vitadurin, vitamin B-12.

BACKGROUND

- Vitamin B12 is an essential water-soluble vitamin that is commonly found in a variety of foods such as fish, shellfish, meat, and dairy products. Vitamin B12 is frequently used in combination with other B vitamins in a vitamin B complex formulation. It helps maintain healthy nerve cells and red blood cells and is also needed to make DNA, the genetic material in all cells. Vitamin B12 is bound to the protein in food. Hydrochloric acid in the stomach releases B12 from protein during digestion. Once released, B12 combines with a substance called intrinsic factor (IF) before it is absorbed into the bloodstream.
- The human body stores several years' worth of vitamin B12, so nutritional deficiency of this vitamin is extremely rare. Elderly are the most at risk. However, deficiency can result from being unable to use vitamin B12. Inability to absorb vitamin B12 from the intestinal tract can be caused by a disease known as pernicious anemia. Additionally, strict vegetarians or vegans who are not taking in proper amounts of B12 are also prone to a deficiency state.
- A day's supply of vitamin B12 can be obtained by eating 1 chicken breast plus 1 hard-boiled egg plus 1 cup plain low-fat yogurt, or 1 cup milk plus 1 cup raisin bran.

SCIENTIFIC EVIDENCE

Uses <i>These uses have been tested in humans or animals. Safety and effectiveness have not always been proven. Some of these conditions are potentially serious, and should be evaluated by a qualified healthcare provider.</i>	Grade*
<p><u>Megaloblastic anemia - due to vitamin B12 deficiency</u></p> <p>Vitamin B12 deficiency is a cause of megaloblastic anemia. In this type of anemia, red blood cells are larger than normal and the ratio of nucleus size to cell cytoplasm is increased. There are other potential causes of megaloblastic anemia, including folate deficiency, copper deficiency, and certain metabolic disorders. If the cause is B12</p>	<p>A</p>

<p>folate deficiency or various inborn metabolic disorders. If the cause is B12 deficiency, then treatment with B12 is the standard approach. Patients with anemia should be evaluated by a physician in order to diagnose and address the underlying cause.</p>	
<p><u>Vitamin B12 deficiency</u></p> <p>Studies have shown that a deficiency of vitamin B12 can lead to abnormal neurologic and psychiatric symptoms. These symptoms may include: ataxia (shaky movements and unsteady gait), muscle weakness, spasticity, incontinence, hypotension (low blood pressure), vision problems, dementia, psychoses, and mood disturbances. Researchers report that these symptoms may occur when vitamin B12 levels are just slightly lower than normal and are considerably above the levels normally associated with anemia. People at risk for vitamin B12 deficiency include strict vegetarians, elderly people, and people with increased vitamin B12 requirements associated with pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, liver or kidney disease.</p> <p>Administering vitamin B12 orally, intramuscularly, or intranasally is effective for preventing and treating dietary vitamin B12 deficiency.</p>	<p><u>A</u></p>
<p><u>Pernicious anemia</u></p> <p>Pernicious anemia (blood abnormality) is a form of anemia that occurs when there is an absence of intrinsic factor, a substance normally present in the stomach. Vitamin B12 binds with intrinsic factor before it is absorbed and used by the body. An absence of intrinsic factor prevents normal absorption of B12 and may result in pernicious anemia. Pernicious anemia treatment is usually lifelong; supplemental vitamin B12 given intramuscularly, intranasally, or by mouth.</p>	<p><u>A</u></p>
<p><u>Alzheimer's disease</u></p> <p>Some patients diagnosed with Alzheimer's disease have been found to have abnormally low vitamin B12 levels in their blood. However, vitamin B12 deficiency itself often causes disorientation and confusion and thus mimics some of the prominent symptoms of Alzheimer's disease. Well-designed clinical trials are needed before a strong recommendation can be made.</p>	<p><u>C</u></p>
<p><u>Angioplasty</u></p> <p>Some evidence suggests that folic acid plus vitamin B12 and pyridoxine daily can decrease the rate of restenosis in patients treated with balloon angioplasty. But this combination does not seem to be as effective for reducing restenosis in patients after coronary stenting. Due to the lack of evidence of benefit and potential for harm, this combination of vitamins should not be recommended for patients receiving coronary stents.</p>	<p><u>C</u></p>

<p><u>Breast cancer</u></p> <p>Researchers at Johns Hopkins University report that women with breast cancer tend to have lower vitamin B12 levels in their blood serum than do women without breast cancer. In a subsequent review of these findings, it was hypothesized that vitamin B12 deficiency may lead to breast cancer because it could result in less folate being available to ensure proper DNA replication and repair. Higher dietary folate intake is associated with a reduced risk of breast cancer. The risk may be further reduced in women who also consume high amounts of dietary vitamin B12 in combination with dietary pyridoxine (vitamin B6) and methionine. However, there is no evidence that dietary vitamin B12 alone reduces the risk of breast cancer.</p>	<p><u>C</u></p>
<p><u>Cardiovascular disease/hyperhomocysteinemia</u></p> <p>Hyperhomocysteinemia (high homocysteine levels in the blood) is a risk factor for coronary, cerebral, and peripheral atherosclerosis, recurrent thromboembolism, deep vein thrombosis, myocardial infarction (heart attack), and ischemic stroke. Elevated homocysteine levels may be a marker instead of a cause of vascular disease. However, it is not clear if lowering homocysteine levels results in reduced cardiovascular morbidity and mortality. Folic acid, pyridoxine (vitamin B6), and vitamin B12 supplementation can reduce total homocysteine levels; however, this reduction does not seem to help with secondary prevention of death or cardiovascular events such as stroke or myocardial infarction in people with prior stroke. More evidence is needed to fully explain the association of total homocysteine levels with vascular risk and the potential use of vitamin supplementation.</p>	<p><u>C</u></p>
<p><u>Fatigue</u></p> <p>There is some evidence that intramuscular injections of vitamin B12 given twice per week might improve the general well-being and happiness of patients complaining of tiredness or fatigue. However, fatigue has many potential causes. Well-designed clinical trials are needed before a recommendation can be made.</p>	<p><u>C</u></p>
<p><u>High cholesterol</u></p> <p>Some evidence suggests that vitamin B12 in combination with fish oil might be superior to fish oil alone when used daily to reduce total serum cholesterol and triglycerides. Well-designed clinical trials of vitamin B12 supplementation alone are needed before a conclusion can be drawn.</p>	<p><u>C</u></p>
<p><u>Imlerslund-Grasbeck disease</u></p> <p>Administering vitamin B12 intramuscularly seems to be effective for treating familial selective vitamin B12 malabsorption (Imlerslund-Grasbeck disease). Further research is needed to confirm these results.</p>	<p><u>C</u></p>

<p><u>Shaky-leg syndrome</u></p> <p>Preliminary clinical reports show that cyanocobalamin may help relieve tremor associated with shaky-leg syndrome. Further research is needed to confirm these results.</p>	<p><u>C</u></p>
<p><u>Sickle cell disease</u></p> <p>One study suggests that a practical daily combination may include folic acid, vitamin B12, and vitamin B6. This combination may be a simple and relatively inexpensive way to reduce these patients' inherently high risk of endothelial damage. Further research is needed to confirm these results.</p>	<p><u>C</u></p>
<p><u>Circadian rhythm sleep disorders</u></p> <p>Taking vitamin B12 orally, in methylcobalamin form, does not seem to be effective for treating delayed sleep phase syndrome. Supplemental methylcobalamin, with or without bright light therapy, does not seem to help people with primary circadian rhythm sleep disorders.</p>	<p><u>D</u></p>
<p><u>Lung cancer</u></p> <p>Preliminary evidence suggests that there is no relationship between vitamin B12 status and lung cancer.</p>	<p><u>D</u></p>
<p><u>Stroke</u></p> <p>In people with a history of stroke, neither high dose vitamin B12 combinations containing pyridoxine, vitamin B12, and folic acid nor low dose combinations containing pyridoxine, vitamin B12, and folic acid seem to affect risk of recurring stroke.</p>	<p><u>D</u></p>
<p><u>Leber's disease</u></p> <p>Vitamin B12 is contraindicated in early Leber's disease, which is a hereditary optic nerve atrophy.</p>	<p><u>F</u></p>
<p><i>*Key to grades: A: Strong scientific evidence for this use; B: Good scientific evidence for this use; C: Unclear scientific evidence for this use; D: Fair scientific evidence against this use (it may not work); F: Strong scientific evidence against this use (it likely does not work).</i></p>	

TRADITION/THEORY

The below uses are based on tradition, scientific theories, or limited research. They often have not been thoroughly tested in humans, and safety and effectiveness have not always been proven. Some of these conditions are

potentially serious, and should be evaluated by a qualified healthcare provider. There may be other proposed uses that are not listed below.

- Aging, AIDS, allergies, amyotrophic lateral sclerosis, asthma, chronic fatigue syndrome, depression, depressive disorder (major), diabetes, diabetic peripheral neuropathy, energy level enhancement, growth disorders (failure to thrive), hemorrhage, immunosuppression, improving concentration, inflammatory bowel disease, kidney disease, liver disease, male infertility, malignant tumors, memory loss, mood (elevate), mouth and throat inflammation (atrophic glossitis), multiple sclerosis, myoclonic disorders (spinal myoclonus), osteoporosis, periodontal disease, protection from tobacco smoke, psychiatric disorders, seborrheic dermatitis, seizure disorders (West syndrome), tendonitis, thyrotoxicosis / Thyroid storm (adjunct iodides), tinnitus, tremor, vitiligo.

DOSING

The below doses are based on scientific research, publications, traditional use, or expert opinion. Many herbs and supplements have not been thoroughly tested, and safety and effectiveness may not be proven. Brands may be made differently, with variable ingredients, even within the same brand. The below doses may not apply to all products. You should read product labels, and discuss doses with a qualified healthcare provider before starting therapy.

Adults (over 18 years old)

- Recommended dietary allowances (RDAs) are 2.4 micrograms per day for adults and adolescents aged 14 years and older, 2.6 micrograms per day for adult and adolescent pregnant females, and 2.8 micrograms per day for adult and adolescent lactating females. Because 10-30% of older people do not absorb food-bound vitamin B12 efficiently, those over 50 years of age should meet the RDA by eating foods fortified with B12 or by taking a vitamin B12 supplement. Supplementation of 25-100 micrograms per day has been used to maintain vitamin B12 levels in older people. A doctor and pharmacist should be consulted for use in other indications. Vitamin B12 has been taken by mouth and given by intramuscular (IM) injection by healthcare professionals. One clinical trial tested patients' acceptance of intranasal vitamin B12 replacement therapy (500 micrograms per week).

Children (under 18 years old)

- Recommended dietary allowances (RDAs) have not been established for all pediatric age groups; therefore Adequate Intake (AI) levels have been used instead. The RDA and AI of vitamin B12 are: infants 0-6 months, 0.4 micrograms (AI); infants 7-12 months, 0.5 micrograms (AI); children 1-3 years, 0.9 micrograms; children 4-8 years, 1.2 micrograms; and children 9-13 years, 1.8 micrograms.

SAFETY

The U.S. Food and Drug Administration does not strictly regulate herbs and supplements. There is no guarantee of strength, purity or safety of products, and effects may vary. You should always read product labels. If you have a medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy. Consult a healthcare provider immediately if you experience side effects.

Allergies

- Vitamin B12 supplements should be avoided in people sensitive or allergic to cobalamin, cobalt, or any other product ingredients.

Side Effects and Warnings

- Caution should be used in patients undergoing angioplasty since an intravenous loading dose of folic acid, vitamin B6, and vitamin B12 followed by oral administration taken daily after coronary stenting might actually increase restenosis rates. Due to the potential for harm, this combination of vitamins should not be recommended for patients receiving coronary stents.
- Itching, rash, transitory exanthema, and urticaria have been reported. Vitamin B12 and pyridoxine has been associated with cases of rosacea fulminans, characterized by intense erythema with nodules, papules, and pustules. Symptoms may persist for up to four months after the supplement is stopped, and may require treatment with systemic corticosteroids and topical therapy.
- Diarrhea has been reported.
- Peripheral vascular thrombosis has been reported. Treatment of vitamin B12 deficiency can unmask polycythemia vera, which is characterized by an increase in blood volume and the number of red blood cells. The correction of megaloblastic anemia with vitamin B12 can result in fatal hypokalemia and gout in susceptible individuals, and it can obscure folate deficiency in megaloblastic anemia. Caution is warranted.
- Vitamin B12 is contraindicated in early Leber's disease, which is hereditary optic nerve atrophy. Vitamin B12 can cause severe and swift optic atrophy.

Pregnancy and Breastfeeding

- Vitamin B12 is likely safe when used orally in amounts that do not exceed the recommended dietary allowance (RDA).
- There is insufficient reliable information available about the safety of larger amounts of vitamin B12 during pregnancy.

INTERACTIONS

Most herbs and supplements have not been thoroughly tested for interactions with other herbs, supplements, drugs, or foods. The interactions listed below are based on reports in scientific publications, laboratory experiments, or traditional use. You should always read product labels. If you have a medical condition, or are taking other drugs, herbs, or supplements, you should speak with a qualified healthcare provider before starting a new therapy.

Interactions with Drugs

- Excessive alcohol intake lasting longer than two weeks can decrease vitamin B12 absorption from the gastrointestinal tract.
- Aminosalicic acid can reduce oral vitamin B12 absorption, possibly by as much as 55%, as part of a general malabsorption syndrome. Megaloblastic changes, and occasional cases of symptomatic anemia, have occurred. Vitamin B12 levels should be monitored in people taking aminosalicic acid for more than one month.
- An increased bacterial load can bind significant amounts of vitamin B12 in the gut, preventing its absorption. In people with bacterial overgrowth of the small bowel, antibiotics such as metronidazole (Flagyl®) can actually improve vitamin B12 status. The effects of most antibiotics on gastrointestinal bacteria are unlikely to have clinically significant effects on vitamin B12 levels.
- The data regarding the effects of oral contraceptives on vitamin B12 serum levels are conflicting. Some studies have found reduced serum levels in birth control pill users, but

others have found no effect despite the use of birth control pills for up to six months. When birth control pill use is stopped, normalization of vitamin B12 levels usually occurs. Lower vitamin B12 serum levels seen with birth control pills probably are not clinically significant.

- Limited case reports suggest that chloramphenicol can delay or interrupt the reticulocyte response to supplemental vitamin B12 in some patients. Blood counts should be monitored closely if this combination cannot be avoided.
- Cobalt irradiation of the small bowel can decrease gastrointestinal (GI) absorption of vitamin B12.
- Colchicine can disrupt normal intestinal mucosal function, leading to malabsorption of several nutrients, including vitamin B12. Lower doses do not seem to have a significant effect on vitamin B12 absorption after three years of colchicine therapy. The significance of this interaction is unclear. Vitamin B12 levels should be monitored in people taking large doses of colchicine for prolonged periods.
- Colestipol (Colestid®) and Cholestyramine (Questran®) resins can decrease gastrointestinal (GI) absorption of vitamin B12. It is unlikely that this interaction will deplete body stores of vitamin B12 unless there are other factors contributing to deficiency. In a group of children treated with cholestyramine for up to 2.5 years, there was not any change in serum vitamin B12 levels. Routine supplements are not necessary.
- H2-blockers include cimetidine (Tagamet®), famotidine (Pepcid®), nizatidine (Axid®), and ranitidine (Zantac®). Reduced secretion of gastric acid and pepsin produced by H2-blockers can reduce absorption of protein-bound (dietary) vitamin B12, but not of supplemental vitamin B12. Gastric acid is needed to release vitamin B12 from protein for absorption. Clinically significant vitamin B12 deficiency and megaloblastic anemia are unlikely, unless H2-blocker therapy is prolonged (two years or more) or the person's diet is poor. It is also more likely if the person is rendered achlorhydric (lacking hydrochloric stomach acid), which occurs more frequently with proton pump inhibitors than H2-blockers. Vitamin B12 levels should be monitored in people taking high doses of H2 blockers for prolonged periods.
- Metformin may reduce serum folic acid and vitamin B12 levels. These changes can lead to hyperhomocysteinemia (abnormally large levels of homocysteine in the blood), adding to the risk of cardiovascular disease in people with diabetes. There are also rare reports of megaloblastic anemia in people who have taken metformin for five years or more. Reduced serum levels of vitamin B12 occur in up to 30% of people taking metformin chronically. However, clinically significant deficiency is not likely to develop if dietary intake of vitamin B12 is adequate. Deficiency can be corrected with vitamin B12 supplements even if metformin is continued. The metformin-induced malabsorption of vitamin B12 is reversible by oral calcium supplementation. A multivitamin preparation may also be valuable for some patients. Patients should be monitored for signs and symptoms of vitamin B12 and folic acid deficiency. People taking metformin chronically should be advised to include adequate amounts of vitamin B12 in their diet, and have their serum vitamin B12 and homocysteine levels checked annually.
- Absorption of vitamin B12 can be reduced by neomycin, but prolonged use of large doses is needed to induce pernicious anemia. Supplements are not usually needed with normal doses.
- Nicotine can reduce serum vitamin B12 levels. The need for vitamin B12 supplementation has not been adequately studied.
- Nitrous oxide inactivates the cobalamin form of vitamin B12 by oxidation. Symptoms of vitamin B12 deficiency, including sensory neuropathy, myelopathy, and encephalopathy can occur within days or weeks of exposure to nitrous oxide anesthesia in people with subclinical vitamin B12 deficiency. Symptoms are treated with high doses of vitamin B12, but recovery can be

slow and incomplete. People with normal vitamin B12 levels have sufficient vitamin B12 stores to make the effects of nitrous oxide insignificant, unless exposure is repeated and prolonged (nitrous oxide abuse). Vitamin B12 levels should be checked in people with risk factors for vitamin B12 deficiency prior to using nitrous oxide anesthesia.

- Phenytoin (Dilantin®), phenobarbital, and primidone (Mysoline®) anticonvulsants have been associated with reduced vitamin B12 absorption and reduced serum and cerebrospinal fluid levels in some patients. This may contribute to the megaloblastic anemia, primarily caused by folate deficiency, associated with these drugs. It has also been suggested that reduced vitamin B12 levels may contribute to the neuropsychiatric side effects of these drugs. Patients should be encouraged to maintain adequate dietary vitamin B12 intake. Folate and vitamin B12 status should be checked if symptoms of anemia develop.
- Proton pump inhibitors (PPIs) include omeprazole (Prilosec®, Losec®), lansoprazole (Prevacid®), rabeprazole (Aciphex®), pantoprazole (Protonix®, Pantoloc®), and esomeprazole (Nexium®). The reduced secretion of gastric acid and pepsin produced by PPIs can reduce absorption of protein-bound (dietary) vitamin B12, but not supplemental vitamin B12. Gastric acid is needed to release vitamin B12 from protein for absorption. Reduced vitamin B12 levels may be more common with PPIs than with H2-blockers, because they are more likely to produce achlorhydria (complete absence of gastric acid secretion). However, clinically significant vitamin B12 deficiency is unlikely, unless PPI therapy is prolonged (two years or more) or dietary vitamin intake is low. Vitamin B12 levels should be monitored in people taking high doses of PPIs for prolonged periods.
- Reduced serum vitamin B12 levels may occur when zidovudine (AZT, Combivir®, Retrovir®) therapy is started. This adds to other factors that cause low vitamin B12 levels in people with HIV and might contribute to the hematological toxicity associated with zidovudine. However, data suggests vitamin B12 supplements are not helpful for people taking zidovudine.

Interactions with Herbs and Dietary Supplements

- Folic acid, particularly in large doses, can mask vitamin B12 deficiency. In vitamin B12 deficiency, folic acid can produce hematologic improvement in megaloblastic anemia, while allowing potentially irreversible neurological damage to progress. Vitamin B12 status should be determined before folic acid is given as a monotherapy.
- Potassium supplements can reduce absorption of vitamin B12 in some people. This effect has been reported with potassium chloride and, to a lesser extent, with potassium citrate. Potassium might contribute to vitamin B12 deficiency in some people with other risk factors, but routine supplements are not necessary.
- Preliminary evidence suggests that vitamin C supplements can destroy dietary vitamin B12. However, other components of food, such as iron and nitrates, might counteract this effect. Clinical significance is unknown, and it can likely be avoided if vitamin C supplements are taken at least two hours after meals.

AUTHOR INFORMATION

- This information is based on a systematic review of scientific literature edited and peer-reviewed by contributors to the Natural Standard Research Collaboration (www.naturalstandard.com).

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Natural Standard developed the above evidence-based information based on a thorough systematic review of the available scientific articles. For comprehensive information about alternative and complementary therapies on the professional level, go to www.naturalstandard.com. Selected references are listed below.

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