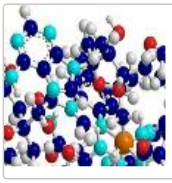

Vitamin B12

SCIENTIFIC NAME
Vitamin B12, Adenosylcobalamin, Cyanocobalamin, Hydroxocobalamin, Methylcobalamin
...read less

FAMILY

Other Common Names

Adénosylcobalamine, B-12, B12, B Complex, B Complex Vitamin, Bedumil, Cobalamin, Cobalamin Enzyme, Cobalamine, Cobamamide, Cobamin, Cobamine, Coenzyme B12, Co-Enzyme B12, Coenzyme B-12, Co-Enzyme B-12, Complexe Vitaminique B, Cyanocobalamine, Cycobemin, Dibencozide, Dibencozida, Hydroxycobalamine, Hydroxocobalaminum, Hydroxocobemine, Hydroxocobémine, Idrossocobalamina, Mecobalamin, Méthylcobalamine, Vitadurin, Vitadurine, Vitamina B12, Vitamine B12.

Overview

Vitamin B12 is an essential water-soluble vitamin that is commonly found in a variety of foods, such as fish, shellfish, meat, eggs, and dairy products (74154). It is frequently used in combination with other B vitamins in vitamin B complex formulations. Methylcobalamin is the active form of vitamin B12. Cyanocobalamin, which must be metabolized to the active form, is the most common form used in supplements (74154,90948). Reportedly, vitamin B12 was discovered by George Whipple while trying to find a cure for pernicious anemia (82798,82828).

Safety

LIKELY SAFE ...when used orally, topically, intravenously, intramuscularly, or intranasally and appropriately. Vitamin B12 is generally considered safe, even in large doses (15,1344,1345,1346,1347,1348,2909,6243,7289,7881) (9414,9416,10126,14392,15765,82832,82949,82860,82864,90386)(111334,111551).

PREGNANCY: **LIKELY SAFE** ...when used orally in amounts that do not exceed the recommended dietary allowance (RDA). The RDA for vitamin B12 during pregnancy is 2.6 mcg daily (6243). There is insufficient reliable information available about the safety of larger amounts of vitamin B12 during pregnancy.

LACTATION: **LIKELY SAFE** ...when used orally in amounts that do not exceed the recommended dietary allowance (RDA). The RDA of vitamin B12 during lactation is 2.8 mcg daily (6243). There is insufficient reliable information available about the safety of larger amounts of vitamin B12 while breastfeeding.

Adverse Effects

General: Orally, intramuscularly, and topically, vitamin B12 is generally well-tolerated.

Most Common Adverse Effects:

Intramuscular: Injection site reactions.

Serious Adverse Effects (Rare):

Intramuscularly: Severe hypokalemia has been rarely linked with correction of megaloblastic anemia with vitamin B12.

Cardiovascular

In human clinical research, an intravenous loading dose of folic acid, vitamin B6, and vitamin B12, followed by daily oral administration after coronary stenting, increased restenosis rates (12150). Hypertension following intravenous administration of hydroxocobalamin has been reported in human research (82870,82864).

Dermatologic

Orally or intramuscularly, vitamin B12 can cause allergic reactions such as rash, pruritus, erythema, and urticaria. Theoretically, allergic reactions might be caused by the cobalt within the vitamin B12 molecule (82864,90373,90381,103974). In one case report, oral methylcobalamin resulted in contact dermatitis in a 59-year-old Japanese female with a cobalt allergy (103974). In another case report, a 69-year-old female developed a symmetrical erythematous-squamous rash for 5 years after oral vitamin B12 supplementation for 10 years. A patch test confirmed that the systemic allergic dermatitis was due to vitamin B12 supplementation, which resolved 3 months after discontinuation (114578).

Vitamin B12 (intramuscular or oral) has also been associated with at least 19 cases of acneiform eruptions which resolved upon discontinuation of vitamin B12 (90365,90369,90388). High-dose vitamin B12 (20 mcg daily) and vitamin B6 (80 mg daily) have been associated with cases of rosacea fulminans characterized by intense erythema with nodules, papules, and pustules. Symptoms may last up to four months after the supplement is stopped and can be treated with systemic corticosteroids and topical therapy (10998,82870,82871).

Gastrointestinal

Intravenously, vitamin B12 (hydroxocobalamin) 2.5-10 grams can cause nausea and dysphagia (82864).

Genitourinary

Intravenously, vitamin B12 (hydroxocobalamin) 5-15 grams has been associated with chromaturia in clinical research (82870,82871,112282,112264).

Hematologic

According to case report data, the correction of megaloblastic anemia with vitamin B12 may result in fatal hypokalemia (82914).

Musculoskeletal

According to case report data, correction of megaloblastic anemia with vitamin B12 has precipitated gout in susceptible individuals (82879).

Neurologic/CNS

Treatment with vitamin B12 has been rarely associated with involuntary movements in infants with vitamin B12 deficiency (90370,90385,90397). In some cases these adverse reactions were misdiagnosed as seizures or infantile tremor syndrome (90370,90385). These adverse reactions presented 2-5 days after treatment with vitamin B12 and resolved once vitamin B12 was discontinued (90370,90385,90397).

Oncologic

Although some epidemiological research disagrees (9454), most research has found that elevated plasma levels of vitamin B12 are associated with an increased risk of various types of cancer, including lung and prostate cancers and solid tumors (50411,102383,107743). One study found, when compared with blood levels of vitamin B12 less than 1000 ng/mL, plasma vitamin B12 levels of at least 1000 ng/mL was strongly associated with the occurrence of solid cancer (107743). It is unclear if increased intake of vitamin B12, either through the diet or supplementation, directly affects the risk of cancer. It is possible that having cancer increases the risk of vitamin B12 elevation. However, one observational study has found that the highest quintile of dietary intake of vitamin B12 is associated with a 75% increased incidence of developing esophageal cancer when compared with the lowest quintile in never drinkers, but not drinkers (107147).

Renal

There is a case report of oxalate nephropathy in a 54-year-old male which was determined to be related to the use of intravenous hydroxocobalamin as treatment for cyanide poisoning. Intermittent hemodialysis was started 5 days after admission, along with a low-oxalate diet, oral calcium acetate, and pyridoxine 5 mg/kg daily (107148). A review of the use of intravenous hydroxocobalamin for suspected cyanide poisoning in 21 intensive care units in France between 2011 and 2017 resulted in a 60% increased odds of acute kidney injury and a 77% increased odds of severe acute kidney injury in the first week. However, biopsies were not conducted and a direct link with use of hydroxocobalamin could not be made (107139).

Other

Several studies have found that higher vitamin B12 levels may be associated with increased mortality or decreased survival rates in hospitalized elderly patients (82889,82812,82857,82895). Human research has also found a positive correlation between vitamin B12 status and all-cause mortality in Pima Indians with diabetes (82863).

Effectiveness

EFFECTIVE

Imerslund-Grasbeck disease. Intramuscular vitamin B12 is effective for patients with this condition.

Details: Administering intramuscular vitamin B12 (hydroxocobalamin) 1 mg daily for 10 days, followed by monthly injections for the remainder of a patient's life, is effective for treating familial selective vitamin B12 malabsorption (Imerslund-Grasbeck disease) (15,82862).

Vitamin B12 deficiency. Administering vitamin B12 orally, intramuscularly, or intranasally is effective for preventing and treating vitamin B12 deficiency.

Details: Vitamin B12 deficiency has varying definitions but is often defined as vitamin B12 (cobalamin) levels less than 180-200 pmol/L (or 240 pg/mL). Some believe that only intramuscular vitamin B12 is effective for treating vitamin B12 deficiency. However, clinical research shows that oral therapy increases cobalamin levels similarly to intramuscular administration, even in patients with pernicious anemia or malabsorption, if a high enough dose is given (2909,2911,2915,9335,82832) (82836,82949,82860,103976,103972,107141,107144). Some evidence suggests that the most effective oral dose is between 647-1032 mcg daily (13106). However, in certain situations, intramuscular treatment might be more appropriate. Guidelines by the British Committee for Standards in Hematology recommend only intramuscular vitamin B12 for initial treatment of severe vitamin B12 deficiency in patients with pernicious anemia, malabsorption disorders, or neurological involvement (94722). Intramuscular vitamin B12 is also appropriate in patients with diarrhea or vomiting and those likely to be nonadherent (103972).

Vitamin B12 deficiency is especially common in older adults, primarily due to lack of intrinsic factor and malabsorption (2915,2919,9335). Daily supplementation with vitamin B12 50-100 mcg might be needed to correct deficiency (10126), while daily doses of 25-37.5 mcg help to maintain normal levels over time (9335). In addition to supplements, foods such as milk and bread fortified with vitamin B12 can be used and are approximately 55% to 60% absorbed by people over 60 years of age (10124).

Vitamin B12 deficiency is also common in patients that have had gastric surgery, including gastrectomy and bariatric surgery (107144,107145). Taking vitamin B12 in the doses found in multivitamins or generic vitamin B supplements does not seem to prevent vitamin B12 deficiency following bariatric surgery (107145). However, taking methylcobalamin 500 mcg daily is beneficial for treating vitamin B12 deficiency associated with a total gastrectomy and taking cyanocobalamin 5000 mcg daily is beneficial for preventing vitamin B12 deficiency following gastric bypass (107144).

Other people at risk for vitamin B12 deficiency include strict vegetarians who eat no animal products (vegans) and people with increased vitamin B12 requirements associated with pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, and hepatic and kidney disease. Moderate consumption of animal products may not be sufficient to restore and maintain vitamin B12 levels, especially in adolescents who had consumed macrobiotic (vegan type) diets for the first 6 years of life. High dietary intake of vitamin B12 or supplements is usually needed in order to restore and maintain optimal vitamin B12 levels in these adolescents (10125).

LIKELY EFFECTIVE

Cyanide poisoning. Intravenous hydroxocobalamin (Cyanokit) is likely effective as an antidote for patients with suspected or known cyanide toxicity due to inhalation, ingestion, or skin exposure.

^ Details: Treatment of cyanide poisoning with hydroxocobalamin (Cyanokit) up to 10 grams has been approved by the US Food and Drug Administration (FDA) and recommended by the Australian Resuscitation Council (82870,82905,82906). Hydroxocobalamin is also FDA-approved for treating cyanide toxicity during pregnancy (82904).

POSSIBLY EFFECTIVE

Canker sores. Sublingual or topical vitamin B12 seems to reduce canker sore symptoms.

^ Details: Clinical research in patients with canker sores shows that applying a topical ointment containing vitamin B12 500 mcg in four divided doses daily for 2 days reduces pain levels by 80% when compared with a control ointment not containing vitamin B12 (96176). Other preliminary clinical research shows that taking vitamin B12 1000 mcg sublingually daily for 6 months reduces the duration of canker sore outbreaks, the number of ulcers, and level of pain when compared with placebo in patients with normal vitamin B12 levels (17242).

Hyperhomocysteinemia. Oral vitamin B12 in combination with folic acid, and sometimes with vitamin B6, reduces homocysteine levels.

^ Details: While folic acid 0.5-5 mg daily lowers fasting homocysteine levels by an average of 25%, adding vitamin B12 0.5 mg daily produces an additional decrease of about 7% on average (6883,9400,9401,9405,9409,50145,107136). Vitamin B12 in combination with folic acid and other vitamins also reduces homocysteine levels in patients with kidney failure, sickle cell disease, and those receiving nitrous oxide general anesthesia (1489,6883,6884,7289,7881,9324,9414,9415,9416,9481,82941). Some researchers recommend routine use of vitamin B12 with homocysteine-lowering regimens to avoid the risk of neuropathy in people with undetected vitamin B12 deficiency (9405). Using vitamin B12 alone has a limited effect on homocysteine levels, and probably only in those people with vitamin B12 deficiency (2147,9410,9512).

Hyperhomocysteinemia is considered by some to be an independent risk factor for atherosclerosis, recurrent thromboembolism, deep vein thrombosis, myocardial infarction, and ischemic stroke (1899,2147,3323,9402,9405,9408,9409). Clinical research suggests that supplementation with folic acid, pyridoxine, and vitamin B12 decreases homocysteine levels and reduces the atherosclerosis progression in patients at risk for atherosclerosis when compared with placebo (50133,50056,82806). However, other research suggests that elevated homocysteine levels may be a marker, as opposed to a cause, of vascular disease (11387,11388). A 5 µmol/L increase in plasma homocysteine increases the risk of cerebrovascular disease by 50%, and the odds of coronary heart disease by 60% and 80% in males and females, respectively (9407,9411). However, it is not clear if reducing homocysteine levels results in reduced cardiovascular morbidity and mortality (1489,6883,6884,9400,9405,9409,96417). Folic acid, vitamin B6, and vitamin B12 supplementation can reduce total homocysteine from 13.4 to 11 µmol/L. However, this reduction does not seem improve endothelial function or help with secondary prevention of death or myocardial infarction, and some research even suggests an increase in cardiovascular disease (CVD) risk (11387,13482,50373,50314,97619).

There is also some debate about whether supplementation with homocysteine-lowering B vitamins can reduce the risk of stroke. A number of large clinical studies and meta-analyses show that supplementation with folic acid, vitamin B6, and vitamin B12, alone or in combination, does not reduce the risk of stroke in patients with CVD or impaired kidney function (11387,13482,50423,83050,96150). However, a more recent meta-analysis of 10 clinical trials including over 44,000 patients shows that B vitamin supplementation reduces the relative risk of stroke by 10% when compared with placebo in patients at risk or with a history of CVD (97619). Also, a meta-analysis in adults with a history of stroke shows that B vitamin supplementation modestly reduces the relative risk of stroke recurrence by 13% and vascular death by 11% when compared with placebo (107136).

Postherpetic neuralgia. Subcutaneous injections of vitamin B12 seem to reduce postherpetic neuralgia symptoms.

^ Details: Clinical research in patients with subacute herpetic neuralgia shows that subcutaneous injection of vitamin B12 (methylcobalamin) 1000 mcg six times weekly for 4 weeks reduces pain when compared with oral vitamin B12 or subcutaneous lidocaine (90394). Another clinical study shows that administering local subcutaneous injections of methylcobalamin 1000 mcg plus lidocaine up to 20 mg daily for 12 injections over 14 days, starting within 7 days of the onset of subacute ophthalmic herpetic neuralgia, decreases the mean pain score by 63% to 79% when compared with intravenous lidocaine and intramuscular methylcobalamin. Less than 2 patients need to be treated to achieve a pain reduction to ≤3 out of 10. Healing of rash, itching, numbness, and tingling were also improved (96175). Additional clinical research in patients with postherpetic pain and itching shows that this same dosing regimen of subcutaneous vitamin B12 reduces pain and analgesic requirements when compared to baseline (90396).

POSSIBLY INEFFECTIVE

Age-related cognitive decline. Oral vitamin B12 does not seem to improve cognitive function in older adults when used alone or in combination with other B vitamins.

^ Details: Taking vitamin B12 100-1000 mcg plus folic acid 400-2000 mcg, with or without vitamin B6 3-50 mg, daily for up to about 2 years does not seem to improve tests of cognitive function in adults aged 65 or older, most of whom do not report cognitive impairment at baseline (14392,50225,50510,90392,107140). Also, supplementation with vitamin B12 does not seem to improve cognitive function in elderly individuals with low vitamin B12 levels (12305).

Alzheimer disease. Oral vitamin B12, when used in combination with other B vitamins, does not seem to improve cognitive function in patients with Alzheimer disease.

^ Details: Clinical research in patients with probable Alzheimer disease using routine medication shows that taking vitamin B12 1 mg, folic acid 5 mg, and vitamin B6 25 mg daily for 18 months does not have a beneficial effect on cognitive function or the severity of disease when compared with placebo. In this study, all patients were consuming a folate-fortified diet (50319). Also, a meta-analysis of clinical research in elderly adults with mild cognitive impairment or dementia shows that taking vitamin B12, usually with other B vitamins, does not improve cognitive function (50510). Observational research has also found that higher vitamin B12 intake over 3 years in a population consuming a folate-fortified diet is not associated with a decreased risk of

developing Alzheimer disease (15270). In contrast, preliminary clinical research in patients with probable Alzheimer disease who are not consuming a folate-fortified diet shows that taking vitamin B12 50 mcg daily plus folic acid 1.2 mg daily for 6 months modestly improves some measures of cognitive performance and decreases levels of homocysteine when compared with placebo (107150). More research is needed to determine if any changes in this latter study are clinically relevant.

Cataracts. Oral vitamin B12 does not seem to reduce cataract development.
^ Details: Clinical research in women with existing cardiovascular disease (CVD) or at increased risk of CVD shows that ta a combination of folic acid 2.5 mg daily, vitamin B6 50 mg daily, and vitamin B12 1 mg daily for an average of 7.3 years does r reduce the risk of cataracts and seems to increase the risk of cataract extraction by 28% when compared with placebo (96149).

Circadian rhythm sleep disorders. Oral vitamin B12 does not seem to improve sleep disorders.
^ Details: Oral vitamin B12 (methylcobalamin) does not seem to be effective for treating delayed sleep phase syndrome. Methylcobalamin 0.5-1 mg three times daily, with or without bright light therapy, also does not seem to help people with primary circadian rhythm sleep disorders (1344,1345,1346,1347,1348).

Cognitive impairment. Oral vitamin B12 does not seem to be beneficial for older adults with cognitive impairment.
^ Details: A meta-analysis of clinical research in elderly adults with mild cognitive impairment or dementia shows that taking vitamin B12, usually with other B vitamins, does not improve cognitive function (50510). One clinical trial in elderly people with memory complaints shows that taking a combination of B vitamins, including folic acid 0.8 mg, vitamin B12 0.5 mg, and vitamin B6 (form not specified) 20 mg daily for 24 months reduces cerebral atrophy in the gray matter regions associated with Alzheimer disease by up to seven-fold when compared with placebo. However, this protection does not occur in patients with the lowest average blood levels of homocysteine (90374).

Fall prevention. Oral vitamin B12 does not seem to reduce the risk of falls.
^ Details: Clinical research shows that taking B vitamins, including folic acid 400 mcg and vitamin B12 500 mcg, daily for 2 years does not prevent falls when compared with placebo in elderly individuals also taking vitamin D (96148).

Osteoporosis. Oral vitamin B12 does not seem to reduce the risk of osteoporotic fractures.
^ Details: Clinical research in elderly patients or patients with a history of cerebrovascular disease shows that taking vitamin B12 500 mcg and folic acid 0.4-2 mg, with or without vitamin B6 25 mg, daily for 2-3 years does not seem to reduce the risk for osteoporotic fractures when compared with placebo (90377,90393). A 5-7 year follow-up of this research has also found no benefit (103981).

Physical performance. Oral vitamin B12 does not seem to improve physical performance in older adults.
^ Details: Clinical research shows that taking B vitamins, including folic acid 400 mcg and vitamin B12 500 mcg, daily for 2 years does not increase hand strength or improve performance such as walking when compared with placebo in elderly individuals also taking vitamin D (96148).

INSUFFICIENT RELIABLE EVIDENCE to RATE
Age-related macular degeneration (AMD). Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A large-scale clinical study shows that taking vitamin B12 1000 mcg, folic acid 2.5 mg, and vitamin B6 50 mg daily, reduces the risk of developing AMD in females over 40 years of age with a history of cardiovascular disease (CVD) or at least three risk factors for CVD. Those who took this combination for an average of 7.3 years had a 34% reduced risk of developing AMD and a 41% reduced risk of visually significant AMD when compared with placebo (14620). It is unclear if this effect is due to vitamin B12, other ingredients, or the combination.

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). It is unclear if high-dose intramuscular vitamin B12 improves the prognosis of ALS.
^ Details: A clinical study in patients with ALS symptoms for 3 years or less shows that intramuscular vitamin B12 (methylcobalamin) 25-50 mg twice weekly for 3.5 years does not slow functional decline or increase the time until ventilation or death when compared with placebo. However, other clinical research in patients with early-stage ALS shows that intramuscular methylcobalamin 50 mg twice weekly for 16 weeks is associated with slower functional decline and a longer period of time until death or full ventilation when compared with placebo (104947,111556). These effects seem to be particularly notable in fine and gross motor skills, but not bulbar or respiratory functions. Furthermore, vitamin B12 and riluzole slowed clinical progression of ALS more than riluzole alone (111556).

Angioplasty. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Some evidence suggests that vitamin B12 400 mcg, folic acid 1 mg, and vitamin B6 10 mg daily can decrease the rate of restenosis in patients treated with balloon angioplasty (8009,9412,34540). However, this combination does not seem to be as effective for reducing restenosis in patients after coronary stenting (8009). An intravenous loading dose of folic acid, pyridoxine, and vitamin B12 followed by oral administration of folic acid 1.2 mg, pyridoxine 48 mg, and vitamin B12 60 mcg daily after bare metal coronary stenting also does not seem to reduce restenosis and might actually increase restenosis (12150,12151,34540). 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 (12151). It is unclear if any effects are due to vitamin B12, other ingredients, or the combination.

Anxiety. Although there is interest in using oral vitamin B12 for anxiety and panic attacks, there is insufficient reliable information about the clinical effects of vitamin B12 for these uses.

Asthma. Although there is interest in using oral vitamin B12 for asthma, there is insufficient reliable information about the clinical effects of vitamin B12 for this condition.

Atherosclerosis. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: One small clinical study in patients with intermediate risk for coronary heart disease shows that taking vitamin B12 100 mcg, aged garlic extract 250 mg, folic acid 300 mcg, vitamin B6 12.5 mg, and L-arginine 100 mg daily for 12 months reduces coronary artery calcium progression when compared with placebo (88385). It is unclear if this effect is due to vitamin B12, other ingredients, or the combination.

Atopic dermatitis (eczema). It is unclear if topical vitamin B12 reduces the severity of eczema.
^ Details: Preliminary clinical research shows that applying a specific topical vitamin B12 0.07% cream (Regividerm) twice daily reduces the extent and severity of atopic dermatitis when compared with placebo (15765).

Attention. Although there is interest in using oral vitamin B12 for improving attention and focus, there is insufficient reliable information about the clinical effects of vitamin B12 for this use.

Cancer. It is unclear if oral vitamin B12 reduces overall cancer risk when used in combination with other B vitamins.
^ Details: An ancillary clinical study in middle-aged and elderly adults with cardiovascular disease shows that taking a combination of vitamin B12 (cyanocobalamin) 0.02 mg, folic acid 0.56 mg, and vitamin B6 3 mg, with or without eicosapentaenoic acid (EPA) 400 mg plus docosahexaenoic acid (DHA) 200 mg, for a median of 4.7 years does not reduce th risk of cancer when compared with placebo (90666). An additional secondary analysis of clinical research in patients recoverin from stroke or transient ischemic attack shows that taking vitamin B12 500 mcg, folic acid 2 mg, and vitamin B6 25 mg daily for around 3.4 years does not reduce the risk of cancer when compared with placebo (90378). The validity of these findings is limited because the studies were not designed nor adequately powered to test for cancer risk.

Cardiovascular disease (CVD). Oral vitamin B12, taken along with other B vitamins, does not seem to improve secondary prevention of death or myocardial infarction in patients with CVD. However, it might slightly reduce the risk of stroke.
^ Details: Overall evidence from clinical research and meta-analyses shows that taking vitamin B12 in combination with folic acid and/or vitamin B6 does not seem to reduce the risk for secondary death or myocardial infarction in patients with or at risk for CVD (11387,13482,34540,50423,83050,90379,97619). In fact, some research suggests that long-term supplementation with vitamin B6, folic acid, and vitamin B12 for secondary prevention increases the risk of CVD by 20% despite lowering homocysteine levels by 30% (13482). However, other research shows that taking vitamin B12 in combination with other B vitamins modestly reduces the risk of stroke, although results are conflicting (11387,13482,50423,83050,96150,96165,97619,107136). It is unclear which specific combination of B vitamins, if any, might be optimal for reducing stroke risk and which patients are most likely to benefit.

In 2001, prior to the publication of the highest quality research on this topic, the US Food and Drug Administration (FDA) approved a qualified health claim stating that, as part of a well-balanced diet that is low in saturated fat and cholesterol, folic acid, vitamin B6, and vitamin B12 may reduce the risk of vascular disease (102368).

Cervical cancer. It is unclear if oral vitamin B12 reduces cervical cancer risk.
^ Details: Some epidemiological evidence has found that increasing vitamin B12 intake from dietary and supplement sources, along with folic acid, thiamine, and riboflavin, might decrease the risk of precancerous cervical lesions (11074). Also, an analysis of two case control studies has found that increased intake of vitamin B12 is associated with a 75% reduced odds of cervical cancer (34609).

Chemotherapy-induced peripheral neuropathy. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research in patients receiving chemotherapy shows that a combination of B vitamins that includes vitamin B12 (cyanocobalamin) 1000 mcg, taken daily starting one week prior to treatment and finishing 12 weeks after treatment is completed, does not prevent peripheral neuropathy when compared with placebo (96173).

Child development. It is unclear if oral vitamin B12 is beneficial for child development.
^ Details: Population research has found that daily dietary intake of less than 2.26 mcg vitamin B12 in the third trimester of pregnancy is associated with an increased risk of poorer outcomes in the offspring for some measures of speech and mathematics ability, including vocabulary at 24 months, combining words at 38 months, speech intelligibility at 6 years, and math comprehension between ages 8-11 years, when compared with dietary intakes of at least 2.26 mcg daily. There was no association between prenatal vitamin B12 intake and reading or spelling abilities, vocabulary at other ages, or full-scale Intelligence Quotient (IQ) at ages 8 or 15 (107143). Furthermore, a very large clinical study in infants of pregnant adults, 71% of whom were deficient in vitamin B12 at baseline, shows that taking vitamin B12 50 mcg daily starting in early pregnancy (<15 weeks gestation) until 6 months postpartum does not improve neurodevelopment as measured by language, motor, socioemotional, or cognitive scores at 12 months old and may worsen early motor performance at 8-12 weeks when compared with placebo. However, the negative effects on motor performance resolved by 6 and 12 months of age (112431).

Child growth. Oral vitamin B12 taken by pregnant adults does not seem to be beneficial for infant growth.
^ Details: A very large clinical study in infants of pregnant adults, 71% of whom were deficient in vitamin B12 at baseline, shows that taking vitamin B12 50 mcg daily starting in early pregnancy (<15 weeks gestation) until 6 months postpartum does not improve the infant's linear growth, length, or weight at 12 months of age (112431).

Chronic obstructive pulmonary disease (COPD). It is unclear if oral vitamin B12 reduces the risk of COPD.
^ Details: Clinical research in patients with COPD shows that taking vitamin B12 500 mg daily for 8 weeks modestly improves endurance on the cycle ergometer, but does not improve oxygen consumption, when compared with placebo (96172).

Cognitive function. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A moderate-sized clinical study in healthy, middle-aged adults shows that taking a combination product containing vitamin B12, other B vitamins, bacopa, and gingko biloba twice daily for 12 weeks does not improve measures of memory, attention, cognition, mood, or stress reactivity when compared with placebo (111334).

Colorectal cancer. It is unclear if oral vitamin B12 reduces colorectal cancer risk.
^ Details: Some epidemiological evidence has found that increased dietary intake of vitamin B12 is associated with a reduced risk of developing colorectal cancer (90383). However, preliminary clinical research shows that taking vitamin B12 1 mg, folic acid 2.5 mg, and vitamin B6 50 mg daily for up to 7.3 years does not reduce the risk of colorectal adenoma in females at high risk for cardiovascular disease (90389). Furthermore, a secondary analysis of clinical research in elderly patients suggests that taking vitamin B12 500 mcg and folic acid 400 mcg daily for 2 years might increase the risk of colorectal cancer when compared with placebo (90393).

Coronavirus disease 2019 (COVID-19). It is unclear if oral vitamin B12 is beneficial for patients with COVID-19.
^ Details: A small observational study in hospitalized patients with COVID-19 pneumonia has found that higher plasma vitamin B12 levels may be associated with an increased risk of transfer to intensive care or death than lower plasma levels. However, when multivariate regression was conducted, only patient age was associated with worsened outcomes. Additionally, the total study population was small, with only nine of 49 patients experiencing the worsened outcomes (107138).

Dementia. It is unclear if oral vitamin B12 reduces the risk of developing dementia.

^ Details: A large cohort of Danish adults has found that vitamin B12 levels or intake does not seem to impact the risk of developing Alzheimer disease or other dementias (104922). However, vitamin B12 might be beneficial in specific patient populations. A small observational study in patients with Parkinson disease has found that higher vitamin B12 levels (648.5 ng/L) are associated with a lower risk of developing dementia when compared with lower vitamin B12 levels (452 ng/L) (103975). It is not yet known if supplementation with vitamin B12 reduces the risk for dementia in these patients.

Depression. It is unclear if oral vitamin B12 is beneficial for reducing depression risk.
^ Details: A meta-analysis of epidemiological research has found that the highest dietary intake of vitamin B12 is associated with a 14% reduced risk of depression. However, in a sub-analysis, this association was not significant in males (107133). In contrast, one epidemiological study in older males included in the analysis has found that daily dietary intake of at least 4.79 mcg vitamin B12 is linked with a 58% lower risk of depression when compared with daily intake of less than 3.16 mcg. In this study, this inverse association was not observed in females (96168). Other observational research has found that low-normal serum vitamin B12 levels are associated with a 3.8 times increased risk for depression during pregnancy when compared with normal vitamin B12 levels (102384). It is unclear if increased intake of vitamin B12 through the diet or supplements reduces the risk for depression or is beneficial for treating symptoms of depression in any population. However, a meta-analysis of clinical research in elderly populations shows that supplementation with vitamin B12 100-1000 mcg daily, usually in combination with folic acid 400-2000 mcg daily, does not reduce symptoms of depression. Most individuals in these studies were not specifically diagnosed with depression (107140).

Diabetes. It is unclear if oral vitamin B12 improves glycemic indices or prevents loss of skeletal muscle in patients with diabetes.
^ Details: A small clinical study in patients with diabetes in India who are stabilized on metformin and/or a sulfonylurea shows that taking vitamin B12 (methylcobalamin) 500 mcg with or without folic acid 5 mg daily for 8 weeks seems to reduce glycated hemoglobin (HbA1C) by 1.3% to 1.5%, compared with a 0.3% increase with placebo (104917). This study is limited due its small sample size and lack of blinding. In elderly adults with type 2 diabetes, population research has found a lower dietary intake of vitamin B12 (average of 11.2 mcg daily) in individuals with a loss of skeletal muscle mass of at least 1.2%, compared with an average intake of 13.4 mcg daily in those with a skeletal muscle mass loss of less than 1.2%. However, further analysis determined that any relationship between vitamin B12 intake and loss of skeletal muscle mass was only significant in individuals with insufficient energy intake overall (107151).

Diabetic neuropathy. Small clinical studies suggest that oral vitamin B12 may modestly improve pain in patients with diabetic neuropathy.
^ Details: Two small clinical studies in patients with diabetic peripheral neuropathy show that taking vitamin B12 (methylcobalamin) 1-1.5 mg for 4-12 months modestly improves pain when compared with baseline or placebo (82841,104923). Some research also shows that vitamin B12 may be beneficial in combination with other ingredients. Studies have evaluated products containing vitamin B12 (methylcobalamin or cyanocobalamin), benfotiamine, and vitamin B6 daily for 9-12 weeks (82931,82939); and vitamin B12 (methylcobalamin) 2 mg, folic acid (L-methylfolate) 3 mg, and vitamin B6 (pyridoxal-5'-phosphate) 35 mg (Metanx; Pamlab) daily for 24 weeks (90375).

Diarrhea. It is unclear if oral vitamin B12 is beneficial for reducing diarrhea in children.
^ Details: Preliminary clinical research in children aged 6-30 months from low- and middle-income countries shows that taking vitamin B12 at twice the recommended dietary allowance, with or without folic acid, does not reduce the risk for diarrhea when compared with placebo (90391).

Fatigue. It is unclear if intramuscular vitamin B12 is beneficial for improving well-being in those with fatigue or tiredness.
^ Details: A small crossover trial in patients complaining of tiredness or fatigue shows that receiving intramuscular injections of vitamin B12 (hydroxocobalamin) 5 mg twice weekly for 2 weeks seems to improve general well-being and happiness, and has a trend toward improving fatigue, when compared with placebo (10127). The validity of this study is limited by a large drop-out rate and unstandardized outcome measures.

Hearing loss. Oral vitamin B12 has only been evaluated in combination with adenosine triphosphate; its effect when used alone is unclear.
^ Details: A small observational study in adults with idiopathic sudden sensorineural hearing loss has found that taking vitamin B12 1.5 mg with adenosine triphosphate 300 mg daily for 8-16 weeks is associated with modestly reduced hearing loss at 4-6 months after starting treatment when compared with taking the combination for less than 8 weeks (104924). This finding is limited due to its observational nature and lack of a control group.

Hepatitis C. It is unclear if intramuscular vitamin B12 is beneficial for sustaining viral response in patients with chronic hepatitis C infection.
^ Details: A small clinical study in patients with chronic hepatitis C infection shows that intramuscular vitamin B12 (cyanocobalamin) 5000 mcg every 4 weeks along with standard care improves sustained viral response when compared with standard of care alone (90386).

Hypertriglyceridemia. It is unclear if oral vitamin B12 is beneficial for reducing triglyceride levels.
^ Details: Some evidence shows that taking vitamin B12 7.5 mcg with fish oil 5 grams might be superior to fish oil alone when used daily to reduce total serum cholesterol and triglycerides. This suggests vitamin B12 might have an independent effect in lowering serum cholesterol and triglycerides, but further investigation is needed to confirm this effect (8694).

Hypotension. It is unclear if oral vitamin B12 is beneficial for treating hypotension.
^ Details: A meta-analysis of 3 observational studies in patients hospitalized with hypotension secondary to cardiac surgery vasoplegia suggests that administration of intravenous vitamin B12 (hydroxocobalamin) is associated with an 8 mmHg higher mean arterial pressure (MAP) at 1 hour but no change in vasopressor dosage at 1 hour or mortality rate when compared with methylene blue (112264). The validity of these findings is limited by the inclusion of only retrospective studies.

Infant development. It is unclear if taking oral vitamin B12 during pregnancy is beneficial for improving infant development. Giving oral vitamin B12 to infants does not seem to be beneficial.
^ Details: Clinical research shows that supplementation with vitamin B12 50 mcg daily from less than 14 weeks gestation until 6 weeks postpartum does not improve cognitive development in infants by 9 months of age when compared with placebo (96174). When these children were evaluated at 30 months of age, a very small benefit of vitamin B12 on expressive language was identified; however, there was no effect on cognition, receptive language, fine motor skills, or gross motor skills (100169). It is unknown whether a longer duration of postpartum supplementation or supplementation in specific populations might be beneficial.

Vitamin B12 supplementation in infants has also been evaluated. A large clinical trial in marginally stunted Nepalese infants aged 6-11 months shows that giving vitamin B12 (cyanocobalamin) 2 mcg daily for 12 months reduces homocysteine levels, but does not improve motor or cognitive development, when compared with placebo (104926).

Inflammatory bowel disease (IBD). Although there is interest in using oral vitamin B12 for IBD, there is insufficient reliable information about the clinical effects of vitamin B12 for this condition.

Lung cancer. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: The association between vitamin B12 and lung cancer is unclear. Some population research found no relationship between blood levels of vitamin B12 and lung cancer (9454). However, other observational research involving over 5,000 case-control pairs found that higher vitamin B12 levels are linked with an increased risk for lung cancer (102383). It is unclear if increased intake of vitamin B12, either through the diet or supplementation, directly affects the risk of lung cancer.

Male infertility. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A retrospective study in adult males with idiopathic and varicocele-related infertility suggests that taking a combination product containing vitamin B12 1.5 mcg, L-carnitine, acetyl L-carnitine, citric acid, selenium, coenzyme Q10, vitamin C, zinc, and folic acid (Proxeed Plus) twice daily for 6 months is associated with improvements in ejaculate volume, sperm count, sperm concentration, total motility, and progressive motility in patients with idiopathic infertility when compared to baseline. However, improvement in sperm morphology was lacking. Furthermore, patients with more severe varicocele seem to benefit most, especially with regard to progressive motility (111296). The validity of these findings is limited by a lack of comparator group. Further, it is unclear if these effects are due to vitamin B12, other ingredients, or the combination.

Mastalgia. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A small clinical trial in patients with mastalgia shows that taking a combination of vitamin B12 as methylcobalamin 100 mg, gamma-linolenic acid, and vitamin C daily for 12 weeks does not improve the proportion of patients with minimal or no pain when compared with placebo (111059).

Multiple sclerosis (MS). Although there is interest in using oral vitamin B12 for MS, there is insufficient reliable information about the clinical effects of vitamin B12 for this condition.

Nonalcoholic fatty liver disease (NAFLD). It is unclear if oral vitamin B12 is beneficial for NAFLD.
^ Details: A small clinical study in adults with NAFLD shows that taking vitamin B12 1000 mcg daily for 12 weeks reduces serum levels of homocysteine but has no effect on serum aminotransferases, measures of steatosis, fibrosis scores, fasting blood glucose, serum insulin, measures of insulin resistance, triglycerides, low-density lipoprotein (LDL) cholesterol, or high-density lipoprotein (HDL) cholesterol when compared with placebo (111555).

Pancreatic cancer. It is unclear if oral vitamin B12 is beneficial for reducing the risk of pancreatic cancer.
^ Details: Most population research has found that increased intake of vitamin B12, as a supplement or in the diet, is not associated with a reduced risk of pancreatic cancer (9327,104927). However, a small, retrospective population study in which smoking and non-smoking adults recalled past eating habits found that increased dietary intake of vitamin B12 is associated with a 33% reduction in pancreatic cancer risk (97976). These conflicting findings may be related to study methodology, as well as the age, gender, or smoking status of the included patients.

Periodontitis. Although there is interest in using oral vitamin B12 for periodontitis, there is insufficient reliable information about the clinical effects of vitamin B12 for this condition.

Peripheral neuropathy. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research shows that taking a specific product containing vitamin B12 3 mcg, folic acid 400 mcg, and uridine monophosphate 50 mg (Keltican) daily for 60 days reduces pain by 44% and decreases analgesic use by over 75% when compared to baseline in patients with peripheral neuropathy, including those with lumbar/lumbosacral radiculopathy, sciatic pain, and cervical radiculopathy (90384). The validity of this finding is limited by the lack of a control group. Furthermore, it is unclear if the benefits are due to vitamin B12, other ingredients, or the combination.

Psoriasis. Topical vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research shows that a specific cream containing vitamin B12 and avocado oil (Regividerm, Regeneratio Pharma AG) reduces symptoms of psoriasis as effectively as calcipotriol ointment (Psorcutan) after 12 weeks of therapy. The vitamin B12 combination cream also causes less irritation than calcipotriol (14909). It is unclear if the benefits are due to vitamin B12, other ingredients, or the combination.

Respiratory tract infections. A small study suggests that oral vitamin B12 does not reduce the rate of respiratory tract infections in children.
^ Details: Preliminary clinical research in children aged 6-30 months from low-and middle-income countries suggests that taking vitamin B12 at twice the recommended dietary allowance with or without folic acid does not reduce the risk for lower respiratory tract infections when compared with placebo (90391).

Schizophrenia. Oral vitamin B12 has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Clinical research shows that taking a combination of vitamin B12 400 mcg and folic acid 2 mg daily for 16 weeks improves negative symptoms when compared with placebo in patients with schizophrenia who have persistent symptoms and a specific genetic variant of the folate transporter gene FOLHI. This variant normally results in reduced folate absorption. However, in patients without this genetic variant, folate is not beneficial with respect to negative symptom improvement (90387).

Sickle cell disease. Oral vitamin B12 has only been evaluated in combination with other B vitamins; its effect when used alone is unclear.
^ Details: Preliminary clinical research in adults with sickle cell disease shows that taking vitamin B12 4.2-6 mcg, folic acid 700 mcg, and vitamin B6 4.2-6 mg daily might lower homocysteine levels. However, it is unknown if this will reduce the risk of endothelial damage in these patients (9324).

Stroke. It is unclear if oral vitamin B12, either alone or with other B vitamins, is beneficial for stroke prevention.
^ Details: Epidemiological research has found that people with a higher intake of vitamin B12 from dietary sources do not have a reduced risk of ischemic or hemorrhagic stroke (14316). A number of clinical studies and meta-analyses show that supplementation with folic acid, vitamin B6, and vitamin B12, alone or in combination, does not reduce the risk of stroke in patients with cardiovascular disease (CVD) or impaired kidney function (11387,13482,50420,50423,83050,90379,90380,96150). However, a more recent meta-analysis of 10 clinical trials including over 44,000 patients shows that B vitamin supplementa modestly reduces the relative risk of stroke by 10% when compared with placebo in patients at risk or with a history of CVI (97619). This meta-analysis differed from some of the earlier analyses due to the inclusion of several additional clinical trials. Also, a meta-analysis in adults with a history of stroke shows that B vitamin supplementation modestly reduces the relative risk of stroke recurrence by 13% and vascular death by 11% when compared with placebo (107136).

In 2001, prior to the publication of the highest quality research on this topic, the US Food and Drug Administration (FDA) allowed a qualified health claim stating that, as part of a well-balanced diet that is low in saturated fat and cholesterol, folic acid, vitamin B6, and vitamin B12 may reduce the risk of vascular disease (102368). Unfortunately, even after the publication of higher quality research, it is still unclear which specific combination of B vitamins is optimal and which patients are most likely to benefit. One network meta-analysis suggests that a combination of folic acid and vitamin B6 lowers the risk of stroke more effectively than B vitamin mixtures that include vitamin B12 (96165). However, this analysis is limited because it didn't account for dosing. Another meta-analysis suggests that exposure to low, but not high, amounts of vitamin B12 (cyanocobalamin) seems to reduce stroke risk (96150).

Tinnitus. It is unclear if intramuscular vitamin B12 is beneficial in patients with tinnitus.
^ Details: A small clinical study shows that intramuscular vitamin B12 2500 mcg weekly for 6 weeks reduces tinnitus severity by 22% when compared to baseline in patients with chronic tinnitus and vitamin B12 deficiency, but not in patients with normal levels of vitamin B12. Vitamin B12 does not improve pitch or volume in either group of patients (96170). The validity of this finding is limited by the lack of a control group.

Venous thromboembolism (VTE). It is unclear if oral vitamin B12 is beneficial for preventing VTE.
^ Details: Epidemiological research has found that low levels of vitamin B12 are associated with an increased risk for VTE. However, clinical trials evaluating the use of B vitamins for prevention of VTE have shown conflicting results (90398).

More evidence is needed to rate vitamin B12 for these uses.

Dosing & Administration

- **Adult**

  Oral:

  General: The daily recommended dietary allowances (RDAs) of vitamin B12 are: 18 years and older, 2.4 mcg; pregnancy, 2.6 mcg; lactation, 2.8 mcg.

  Since 10% to 30% of older adults do not absorb food-bound vitamin B12 efficiently, those over 50 years of age are advised to meet the RDA by eating foods fortified with vitamin B12 or by taking a vitamin B12 supplement. 25-100 mcg daily has been taken to maintain vitamin B12 levels in older people. A healthcare professional should be consulted for use for other indications (6243). See Effectiveness section for condition-specific information.

  Excessive alcohol intake lasting longer than two weeks can decrease vitamin B12 absorption from the gastrointestinal tract (15).

  All other ROAs:

  Research is limited; typical dosing is unavailable. See Effectiveness section for condition-specific information.

- **Children**

  Oral:

  General: The daily recommended dietary allowances (RDAs) have not been established for all pediatric age groups; therefore, adequate intake (AI) levels have been used instead. The RDAs or AI levels of vitamin B12 by age are: 0-6 months, 0.4 mcg (AI); 7-12 months, 0.5 mcg (AI); 1-3 years, 0.9 mcg; 4-8 years, 1.2 mcg; 9-13 years, 1.8 mcg (6243).

  See Effectiveness section for condition-specific information.

- **Standardization & Formulation**

  The term "vitamin B12" refers to any of the cobalamins, a group of chemically-related molecules that all have a cobalt-containing center. Methylcobalamin is the active form of vitamin B12 in the human body, but it is rarely used in supplements because it is light sensitive (90948). Cyanocobalamin is the most common form of vitamin B12 used in supplements in the United States (74154). This form of vitamin B12 must be metabolized before becoming active (90948). In one branded product (Eligen B12), cyanocobalamin has been formulated with salcaprozate sodium (SNAC) to increase oral absorption (103973). Hydroxocobalamin is another form of vitamin B12 that is commonly used in some parts of Europe (90948). When administered intramuscularly, hydroxocobalamin is retained in the body for longer than cyanocobalamin (90949).

Interactions with Drugs

None known.

Interactions with Supplements

FOLIC ACID: When taken in large doses, folic acid can mask vitamin B12 deficiency.

Details

Folic acid can produce hematologic improvement in megaloblastic anemia, which may allow potentially irreversible neurological damage to progress in patients with vitamin B12 deficiency. Vitamin B12 status should be determined before folic acid is given as monotherapy (2677,3092,5646,9411,20504,20505).

POTASSIUM: Potassium might contribute to vitamin B12 deficiency in some people with other risk factors, but routine supplements aren't necessary.

Details

Potassium supplements can reduce absorption of vitamin B12 in some people (4511,4512). This might be due to acidification of the ileal contents, which reduces the activity of intrinsic factor (4512). This effect has been reported with potassium chloride and, to a lesser extent, with potassium citrate (10501).

VITAMIN C: Theoretically, vitamin C supplements might reduce vitamin B12 levels.

Details

Some research suggests that vitamin C supplements can destroy dietary vitamin B12, resulting in lower blood levels of vitamin B12 in humans (20507,20509). However, other components of food, such as iron and nitrates, might counteract this effect (9511,20508). It is not clear whether this interaction is clinically significant, and it can likely be avoided if vitamin C supplements are taken at least 2 hours after meals.

Interactions with Conditions

ANGIOPLASTY

There is some concern that B vitamins might increase the rate of restenosis after bare metal stent placement. An intravenous loading dose of folic acid, vitamin B6, and vitamin B12, followed by oral administration of folic acid 1.2 mg, vitamin B6 48 mg, and vitamin B12 60 mcg daily after coronary stenting might actually increase restenosis rates (12150). Due to the potential for harm, this combination of vitamins should not be recommended for patients receiving coronary stents (12151).

COBALAMIN OR COBALT HYPERSENSITIVITY

Vitamin B12 contains cobalamin and cobalt and might cause allergic reactions in those with hypersensitivity to these compounds (15).

Interactions with Lab Tests

ANTI-XA ASSAY

Hydroxocobalamin has a distinct red color and might cause falsely lowered readings in colorimetric lab tests such as the anti-Xa assay. A case of undetectable anti-Xa level has been reported in a patient treated with hydroxocobalamin for catecholamine-resistant shock followed by treatment with heparin. Hydroxocobalamin may interfere with chromogenic anti-Xa assays levels regardless of heparin dosage adjustments, leading to a lack of reliability in monitoring and adjusting heparin infusion rates. This could cause excessive bleeding or clotting (112282).

CARBOXYHEMOGLOBIN

Hydroxocobalamin has a distinct red color and might cause falsely lowered readings in colorimetric lab tests. Cases of falsely lowered carboxyhemoglobin levels have been reported in patients treated with hydroxocobalamin for carbon monoxide poisoning (90382). This lab test interaction may lead to inaccurate diagnoses or inappropriate therapy in some patients.

DIALYSIS BLOOD LEAK DETECTOR

Hydroxocobalamin has a distinct red color and causes chromaturia which might trigger a false-positive blood leak during dialysis. Cases of hydroxocobalamin permeating dialysis membranes, discoloring dialysate, and then triggering false-positive blood leak detection have been reported. When blood leaks are detected, dialysis may automatically be stopped. This could cause serious injury or death in patients requiring dialysis (90368,90376,90390,112264).

INTRINSIC FACTOR

Vitamin B12 can cause a false-positive test result for intrinsic factor antibodies (15).

Nutrient Depletion

SOME DRUGS CAN AFFECT VITAMIN B12 LEVELS:

AMINOSALICYLIC ACID

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Aminosalicylic acid might reduce the absorption of vitamin B12 and increase the risk of deficiency.

Details

Aminosalicylic acid can reduce oral vitamin B12 absorption, possibly by as much as 55%, as part of a general malabsorption syndrome (9574). Megaloblastic changes and occasional cases of symptomatic anemia have occurred, usually after doses of grams daily for several months (4558,9395,9397). Monitor vitamin B12 levels in people taking aminosalicylic acid for more th one month. For information on foods that are rich in vitamin B12, see our **chart**.

ANTIBIOTIC DRUGS

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Antibiotics might reduce the absorption of vitamin B12, but this effect is unlikely to be clinically significant.

Details

Disruption of the normal gastrointestinal (GI) flora may interrupt enterohepatic recirculation of vitamin B12 and increase fecal excretion (4436). Vitamin B12 is also synthesized by the GI flora, but mainly in the colon where absorption is poor. The majority of bacterially-synthesized vitamin B12 is therefore excreted in the feces and does not significantly contribute to the body's store of vitamin B12 (4437,9502). The effects of antibiotics on gastrointestinal bacteria are unlikely to have clinically significant effects on vitamin B12 levels. In people with bacterial overgrowth of the small bowel, antibiotics such as metronidazole (Flagyl) can actually improve vitamin B12 status. An increased bacterial load can bind significant amounts of vitamin B12 in the gut, preventing its absorption (4437,9502).

ASPIRIN

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Aspirin might reduce levels of vitamin B12 and increase the risk of deficiency.

Details

Clinical research suggests that using aspirin is associated with a higher prevalence of vitamin B12 deficiency when compared with nonusers (20394). For information on foods that are rich in vitamin B12, see our **chart**.

BILE ACID SEQUESTRANTS

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Bile acid sequestrants might reduce vitamin B12 absorption, but this is unlikely to be clinically significant.

Details

These resins can decrease gastrointestinal (GI) absorption of vitamin B12 by binding intrinsic factor and vitamin B12-intrinsic factor complexes (10542,10543). However, absorption isn't completely prevented (10542). It's 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 no change in serum vitamin B12 levels (4455). Routine supplements aren't necessary.

CARBAMAZEPINE (TEGRETOL)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Carbamazepine, especially when taken long-term, might reduce vitamin B12 absorption and increase the risk of deficiency.

Details

A small observational study in children started on carbamazepine monotherapy and continued for 3 months has found marked reductions in folate and vitamin B12 blood levels. This might increase the risk of megaloblastic anemia (103984). Encourage patients to maintain adequate dietary vitamin B12 intake, and check folate and vitamin B12 status if symptoms of anemia develop. If considering alternatives, oxcarbazepine (Trileptal), an analog to carbamazepine, does not seem to produce clinically significant reductions in vitamin B12 levels (103985). Additionally, levetiracetam (Keppra) and valproate have not been associated with reduced vitamin B12 levels (103986,103987,104946). For information on foods that are rich in vitamin B12, see our **chart**.

COLCHICINE

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Colchicine might reduce the absorption of vitamin B12 and increase the risk of deficiency.

Details

Colchicine in doses of 1.9-3.9 mg daily can disrupt normal intestinal mucosal function, leading to malabsorption of several nutrients, including vitamin B12 (4543,4544,4545). Lower doses don't seem to have a significant effect on vitamin B12 absorption after 3 years of colchicine therapy (5921). The significance of this interaction isn't clear. Monitor vitamin B12 levels in people taking large doses of colchicine for prolonged periods. For information on foods that are rich in vitamin B12, see our **chart**.

CONTRACEPTIVE DRUGS

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Oral contraceptives might reduce levels of vitamin B12; however, research is conflicting.

Details

The data regarding the effects of oral contraceptives on vitamin B12 serum levels are conflicting. Some studies have found reduced serum levels in oral contraceptive users (4547,9371,9373,9505), but others have found no effect despite use of oral contraceptives for up to 6 months (4498,7843,9372). When reduced serum levels are detected, vitamin B12 absorption, urinary excretion, tissue and erythrocyte levels, methylmalonic acid levels, and homocysteine are normal (9371,9373,9505,10123). When oral contraceptive use is stopped, normalization of vitamin B12 levels usually occurs (10123). It's suggested that oral contraceptives reduce production of transcobalamin I, the protein which transports vitamin B12 in the blood (4547,9373,9505).

Thus, more of the vitamin is available for tissue uptake and serum levels may be reduced. Vitamin B12 supplements don't seem to increase serum levels of vitamin B12 (9373). Lower vitamin B12 serum levels seen with oral contraceptives probably aren't clinically significant.

H2-BLOCKERS

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

H2-blockers might reduce the absorption of vitamin B12 and increase the risk of deficiency.

^ Details

Reduced secretion of gastric acid and pepsin produced by H2-blockers can reduce absorption of protein-bound (dietary), but not supplemental, vitamin B12 (4539,4540,4541,9513,9514,9528). This is because gastric acid is needed to release vitamin B12 from protein for absorption (4541,9513,9514,9528). Clinically significant vitamin B12 deficiency and megaloblastic anemia are unlikely, unless H2-blocker therapy is prolonged (2 years or more) or dietary vitamin B12 is low (4539,9513,9514,18966). The odds of developing vitamin B12 deficiency are 25% higher in individuals taking H2-blockers for 2 years or more compared to non-users. Vitamin B12 deficiency is also more likely with prolonged, high-dose H2-blocker therapy than with prolonged, low-dose therapy (18966) and in people rendered achlorhydric (4483), which occurs more frequently with proton pump inhibitors than H2-blockers. Vitamin B12 deficiency is expected to diminish upon discontinuation of H2-blocker therapy (18966). For information on foods that are rich in vitamin B12, see our **chart**.

METFORMIN (Glucophage)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Metformin reduces vitamin B12 levels in a dose and duration-dependent manner, which might result in deficiency.

^ Details

Metformin might interfere with intrinsic factor secretion or uptake, affect bowel motility, or cause bacterial overgrowth, resulting in vitamin B12 malabsorption and hyperhomocysteinemia (32,4490,7839,9521,102382,107149,111552). There are also rare reports of megaloblastic anemia in people who have taken metformin for 5 years or more (9520,9521,9522). Reduced absorption occurs in up to 30% of people taking metformin chronically and appears to be a dose-dependent effect (4490,9520,9521,9523,102382,111552). However, clinically significant deficiency isn't likely to develop if dietary intake of vitamin B12 is adequate, including the intake of a multivitamin or vitamin B12 supplement (8834,9521,9523,102382). The risk of deficiency is higher in those taking a higher metformin dose for 3 years or more and also in older people and vegetarians (15134). Deficiency can be corrected with vitamin B12 supplements even if metformin is continued (9520,9522). Monitor for signs and symptoms of vitamin B12 and folic acid deficiency. Advise people taking metformin chronically to include adequate amounts of vitamin B12 in the diet and to have serum vitamin B12 and homocysteine levels checked annually. For information on foods that are rich in vitamin B12, see our **chart**.

NEOMYCIN

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Neomycin, when taken in typical doses and for a typical duration, is unlikely to reduce levels of vitamin B12.

^ Details

Absorption of vitamin B12 can be reduced by neomycin, but prolonged use of large doses is needed to induce pernicious anemia (3046,8434). Supplements aren't needed with normal doses. For information on foods that are rich in vitamin B12, see our **chart**.

NITROUS OXIDE

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Nitrous oxide might inactivate vitamin B12 and produce symptoms of deficiency.

^ Details

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) (9527,9532). In people with risk factors for vitamin B12 deficiency, check vitamin B12 levels prior to using nitrous oxide anesthesia.

PHENOBARBITAL (Luminal)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Phenobarbital, especially when taken long-term, might reduce vitamin B12 absorption and increase the risk of deficiency.

^ Details

In one case report, a 23-year-old male with epilepsy who was taking phenytoin with phenobarbital for two years presented with megaloblastic anemia due to severe decreases in vitamin B12 and folate levels (10503). Theoretically, phenytoin and/or phenobarbital may have interfered with vitamin B12 absorption. Encourage patients to maintain adequate dietary vitamin B12 intake, and check folate and vitamin B12 status if symptoms of anemia develop. If considering alternatives, neither oxcarbazepine (Trileptal), levetiracetam (Keppra), nor valproate have been associated with reduced vitamin B12 levels (103985,103986,103987,104946). For information on foods that are rich in vitamin B12, see our **chart**.

PHENYTOIN (DILANTIN)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

Phenytoin, especially with chronic use, might reduce vitamin B12 absorption and increase the risk of deficiency.

^ Details

Population research has found that taking phenytoin for over two years is associated with a reduction in vitamin B12 levels and an approximately 6-fold increase in risk for vitamin B12 deficiency when compared with taking phenytoin for less than one year

(107146). In one case report, a 23-year-old male with epilepsy who was taking phenytoin with phenobarbital for two years presented with megaloblastic anemia due to severe decreases in vitamin B12 and folate levels (10503). Encourage patients who are taking phenytoin long-term to maintain adequate dietary vitamin B12 intake, and check folate and vitamin B12 status if symptoms of anemia develop. If considering alternatives, neither oxcarbazepine (Trileptal), levetiracetam (Keppra), nor valproate have been associated with reduced vitamin B12 levels (103985,103986,103987,104946). For information on foods that are rich in vitamin B12, see our **chart**.

PROTON PUMP INHIBITORS (PPIs)

Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.

PPIs might reduce the absorption of vitamin B12, particularly with prolonged use.

^ Details

The reduced secretion of gastric acid and pepsin produced by PPIs can reduce absorption of protein-bound (dietary), but not supplemental, vitamin B12 (4483,4484,4485,4486,9513,9528). This is because gastric acid is needed to release vitamin B12 from protein for absorption (4484,4486,9513,9528,11153). Reduced vitamin B12 levels may be more common with PPIs than with H2-blockers, because they are more likely to produce achlorhydria (4483,4486). However, PPI therapy is unlikely to cause clinically significant vitamin B12 deficiency (111553). Some evidence suggests that vitamin B12 deficiency is more likely in the case of prolonged PPI therapy (2 years or more) or insufficient dietary vitamin B12 intake (4483,4484,9513,18966). The odds of developing vitamin B12 deficiency are 65% higher in individuals taking PPIs for 2 years or more when compared with non-users. Also, vitamin B12 deficiency is more likely with prolonged, high-dose PPI therapy than with prolonged, low-dose therapy. Vitamin B12 deficiency is expected to diminish upon discontinuation of PPI therapy (18966). The American College of Gastroenterology (ACG) does not recommend increased intake of vitamin B12 or routine monitoring of serum vitamin B12 levels for patients who are taking PPIs and have no other risk factors for vitamin B12 deficiency (107368). For information on foods that are rich in vitamin B12, see our **chart**.

ZIDOVUDINE (Retrovir)

Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.

Zidovudine might modestly reduce the absorption of vitamin B12.

^ Details

Reduced serum vitamin B12 levels may occur when zidovudine therapy is started (30,10531,111551). 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 (10531,10532,111551). Some data suggest vitamin B12 supplements aren't helpful for people taking zidovudine (10532,10533). However, one case report shows that zidovudine-associated refractory macrocytic anemia resolved within 3 months of discontinuing zidovudine and receiving parenteral vitamin B12 (111551). For information on foods that are rich in vitamin B12, see our **chart**.

Overdose

There is insufficient reliable information available about the presentation or treatment of overdose with vitamin B12.

Commercial Products Containing: Vitamin B12

View All

View Health Canada Licensed Products

^ View Certified Products

USP Verified Products

NSF Contents Certified Products

NSF Certified for Sport Products

ConsumerLab Quality Certified Products

Pharmacokinetics

Absorption: Vitamin B12 is primarily absorbed (60%) by binding with intrinsic factor to be actively transported in the terminal ileum. In addition to active absorption, it is estimated that about 1.2% of vitamin B12 is absorbed by passive diffusion. Dietary vitamin B12 is cleaved from proteins at normal gastric pH. Conditions involving increased gastric pH such as atrophic gastritis, use of acid-suppressing drugs, or partial gastrectomy, reduce vitamin B12 absorption. Loss of intrinsic factor in pernicious anemia and total gastrectomy also reduce absorption. Intramuscular administration is often used to avoid these absorption problems. More recently, high oral doses of vitamin B12 (300 to 1000 mcg) have been used to capitalize on absorption by passive diffusion and treat pernicious anemia and malabsorption from food (2909,9518,103972). A fasting state seems to increase vitamin B12 absorption when compared with a postprandial state, and a maximum concentration seems to occur about three hours after oral supplementation (82814).

Certain oral vitamin B12 formulations can increase bioavailability. In one branded product (Eligen B12), cyanocobalamin formulated with salcaprozate sodium (SNAC) has about a 2-fold greater absolute absorption when compared with cyanocobalamin alone (103973).

Elimination: Orally, vitamin B12 as cyanocobalamin and cyanocobalamin-SNAC has a half-life of about 25-30 hours.

Intravenously, vitamin B12 as cyanocobalamin has a half-life of about 15 hours (103973).

Mechanism of Action

General: Vitamin B12 is an essential water-soluble vitamin that is commonly found in a variety of foods, such as fish, shellfis meat, eggs, and dairy products (74154). The term vitamin B12 refers to all cobalamins that are active as coenzymes in humans, including dibencozide (adenosylcobalamin), methylcobalamin, and hydroxocobalamin (5133). Vitamin B12 is required for nucleoprotein and myelin synthesis, cell reproduction, normal growth, and normal erythropoiesis. The synthetic forms of vitamin B12, cyanocobalamin and hydroxocobalamin, can be converted to coenzyme B12, which is essential for the conversion of methylmalonate to succinate, and the synthesis of methionine from homocysteine (15,9320). Vitamin B12 is involved in maintaining sulfhydryl groups in the reduced form required by enzymes involved in fat and carbohydrate metabolism and protein synthesis. Vitamin B12 is essential for folate utilization, and its absence results in a functional folate deficiency (15).

Vitamin B12 deficiency can take months to years to become symptomatic due to large body stores. Normal serum vitamin B12 levels range between 200-900 pg/mL. Serum concentrations less than 200 pg/mL indicate deficiency, and concentrations less than 100 pg/mL usually result in megaloblastic anemia or neurologic damage (15). Vitamin B12 deficiency results in megaloblastic anemia, gastrointestinal lesions, and neurologic damage, beginning with an inability to produce myelin and progressing to degeneration of the axon and nerve head (15). Neurologic symptoms caused by vitamin B12 deficiency can include neuropsychiatric disorders such as depression (6357), paresthesias, ataxia, memory loss, weakness, and personality and mood changes without anemia (1484,1485,3235,5646). Some neurologic symptoms and elevated homocysteine levels can occur without any signs of B12 deficiency anemia (1484,1485,3235). Vitamin B12 deficiency is associated with impaired cognitive performance in adolescents (aged 10-16 years) who have been fed a strict vegetarian diet from infancy to 6 years of age. Consequences of low vitamin B12 intake during childhood and its effect on cognitive functioning in adulthood are unknown (10125). Elevated methylmalonate or methylmalonic acid (MMA) levels occur early in vitamin B12 deficiency, and may precede other symptoms (1484,1485,5646). In combination with homocysteine levels, MMA levels can be used to diagnose vitamin B12 deficiency (5646).

The risk for vitamin B12 deficiency is higher with increased age, male gender, and in people of Caucasian and Latin American descent. Deficiency in vitamin B12 results from insufficient intake, malabsorption from food, and other medical conditions (1484,1485). However, body stores of vitamin B12 are large, and it is widely available in food. Vitamin B12 deficiency is almost always caused by a disorder of absorption (9518).

Deficiency of vitamin B12 can be masked by folic acid, particularly in large doses. Folate will improve vitamin B12 associated anemia, but it will allow the neurologic abnormalities to progress. There is some concern that food fortified with folic acid can cause under-recognition of vitamin B12 deficiency, particularly in the elderly (5646).

Anticancer effects: Vitamin B12 is believed to possess anticancer properties (82890), and supplementation of vitamin B12 may have a role in preventing cervical cancer (50130,34609). However, although some epidemiological research disagrees (9454), most research has found that elevated plasma levels of vitamin B12 are associated with an increased risk of various types of cancer, including lung and prostate cancers and solid tumors (50411,102383,107743). It is unclear if increased intake of vitamin B12, either through the diet or supplementation, directly affects the risk of cancer. It is possible that having cancer increases the risk of vitamin B12 elevation. However, one observational study has found that the highest quintile of dietary intake of vitamin B12 is associated with a 75% increased incidence of developing esophageal cancer when compared with the lowest quintile in never drinkers, but not drinkers (107147). Also, human research suggests that elevated serum vitamin B12 levels associated with tumor markers may indicate poor survival in hepatocellular carcinoma patients (82887).

Cardiovascular effects: Vitamin B12 is required in one of the pathways for homocysteine metabolism. Remethylation of homocysteine to methionine requires folate and the methylcobalamin form of vitamin B12 as a cofactor (9407,9409). Some evidence suggests elevated homocysteine levels might cause vascular endothelial cell damage, impaired endothelium-dependent vasodilation due to reduced nitric oxide activity, increased oxidation and arterial deposition of low-density lipoproteins (LDL), increased platelet adhesiveness, and activation of the clotting cascade (2147,9403,9408). Vitamin B12 supplements have a small additive effect to folic acid in lowering fasting homocysteine levels, but probably only in people with vitamin B12 deficiency (2147,50314,50222,50014,50164). Elevated homocysteine concentrations are possibly associated with other conditions such as developing age-related macular degeneration (AMD), decreased cognitive function, impaired memory, Alzheimer disease, and vascular dementia (5646,9330,9331).

Hepatic effects: In vitro research shows that vitamin B12 inhibits hepatitis C virus replication. Additionally, some liver diseases appear to be associated with vitamin B12 deficiency secondary to impaired storage of vitamin B12 in the liver. Theoretically, supplementation with vitamin B12 may restore liver stores of vitamin B12 and improve virological response in patients with hepatitis. This has been demonstrated in preliminary clinical research (90386).

Neurological effects: Low vitamin B12 levels are possibly associated with chronic fatigue syndrome (6082). Some researchers think that vitamin B12 supplements could help symptoms of chronic fatigue syndrome by correcting red blood cell abnormalities and improving oxygen delivery to tissues (6082). The methylcobalamin form of vitamin B12 might also influence melatonin levels. Methylcobalamin seems to improve alertness and reduce sleep time in humans with normal sleep patterns, possibly due to effects on melatonin (1349). Preliminary clinical research in elderly patients shows that taking B vitamins, including vitamin B12, reduces brain atrophy in the areas of the brain most affected by Alzheimer disease. This suggests that taking vitamin B12 along with other B vitamins might prevent or delay the progression to Alzheimer disease in some patients (90374). Additional evidence suggests that supplementation of B vitamins, including vitamin B12, may help prevent dementia by lowering homocysteine levels (50222,50277). Some research shows that elevated serum homocysteine and low folate and vitamin B12 levels may be associated with poor cognitive function, cognitive decline, and dementia (82884).

Otic effects: Low vitamin B12 levels have been associated with hearing loss in elderly women (1482).

Voice effects: A small study in active adult singers shows that receiving an intramuscular injection of vitamin B12

(cyanocobalamin) 1 mg tends to improve ease of singing and voice handicap, and reduce fatigue 3 days after the shot. However, the benefit did not reach statistical nor clinical significance when compared with baseline or placebo (104925).

Classifications

Water-Soluble Vitamins

References

See Monograph References

Monographs are reviewed on a regular schedule. See our Editorial Principles and Process for details. The literature evaluated in this monograph is current through 7/31/2024. This monograph was last modified on 9/3/2024. If you have comments or suggestions, please tell the editors.