Folic Acid

SCIENTIFIC NAME
Pteroylglutamic acid, Pteroylmonoglutamic acid, Pteroylpolyglutamate

FAMILY

Other Common Names

5'-methyltetrahydrofolate, 5'-methyltetrahydrofolic acid, 5'-MTHF, (6S)-5-methyltetrahydrofolate, (6s)-5-methyltetrahydrofolic acid, (6S)-5-MTHF, Acide Folique, Acide Ptéroylglutamique, Acide Ptéroylmonoglutamique, Acido Folico, B Complex Vitamin, Complexe de Vitamines B, Complexe Vitaminique B, Dihydrofolate, Dihydrofolic Acid, Folacin, Folacine, Folate, Folinic Acid, L-5-Methyltetrahydrofolate, L-5-MTHF, L-methylfolate, Levomefolate, Levomefolic acid, Metafolin, Nutrifolin, Methylfolate, Méthylfolate, Methylfolic Acid, Quatrefolic, Tetrahydrofolate, Tétrahydrofolate, Vitamin B9, Vitamine B9.

Overview

Folate and folic acid are forms of the water-soluble B9 vitamin. Folate occurs naturally in foods such as leafy vegetables, legumes, and fruits. Folic acid, the synthetic form, is frequently formulated in combination with other B vitamins in vitamin B complex formulations (3022,91313). In 1998, the US government required folic acid fortification of all cold cereals and baking flour, which extends to pastas, bakery items, etc. (6241).

In the US, foods containing at least 60 mcg of folic acid are allowed to be labeled with a health claim stating that "women who consume healthful diets with adequate folate may reduce their risk of having a child with birth defects of the brain or spinal cord" (102369).

Safety

LIKELY SAFE ...when used orally or parenterally and appropriately. Folic acid has been safely used in amounts below the tolerable upper intake level (UL). The UL for folic acid is based only on supplemental folic acid and is expressed in mcg folic acid. Dietary folate is not included in UL calculations, as dietary folate consumption has not been associated with adverse effects. The UL for folic acid in adults is 1000 mcg (6241). In cases of megaloblastic anemia resulting from folate deficiency or malabsorption disorders such as sprue, oral doses of 1-5 mg per day can also be used safely until hematologic recovery is documented, as long as vitamin B12 levels are routinely measured (6241,7725,8739).

POSSIBLY SAFE ...when L-5-methyltetrahydrofolate (L-5-MTHF), the reduced form of folate, is used orally and appropriately, short-term. L-5-MTHF has been used with apparent safety at a dose of 416 mcg daily for 16 weeks (104913,104914) and a dose of 113 mcg daily for 24 weeks (104920). A specific L-5-MTHF product (Metafolin, Eprova) has been used with apparent safety at a dose of 1.3 mg daily for 12 weeks (104912).

POSSIBLY UNSAFE ...when used orally in large doses, long-term. Clinical research shows that taking folic acid daily in doses of 800 mcg to 1200 mcg for 3-10 years significantly increases the risk of developing cancer and adverse cardiovascular effects compared to placebo (12150,13482,16822,17041). Doses above 1 mg per day should also be avoided if possible to prevent precipitation or exacerbation of neuropathy related to vitamin B12 deficiency (6241,6242,6245). However, there is contradictory evidence suggesting that higher doses may not be harmful. There is some evidence that doses of 5 mg per day orally for up to 4 months can be used safely if vitamin B12 levels are routinely measured (7725). Also, other clinical research suggests that folic acid supplementation at doses up to 5 mg, usually in combination with vitamin B12, does not increase the risk of cancer when taken for 2-7 years (91312). Very high doses of 15 mg per day can cause significant central nervous system (CNS) and gastrointestinal side effects (505).

CHILDREN: **LIKELY SAFE** ...when used orally and appropriately. Folic acid has been safely used in children in amounts below the tolerable upper intake level (UL). The ULs for folic acid are based only on supplemental folic acid and are expressed in mcg folic acid. Dietary folate is not included in UL calculations, as dietary folate consumption has not been associated with adverse effects. The UL for children is: 1-3 years of age, 300 mcg; 4-8 years of age, 400 mcg; 9-13 years of age, 600 mcg; 14-18 years of age, 800 mcg (6241). **POSSIBLY SAFE** ...when L-5-methyltetrahydrofolate (L-5-MTHF), the reduced form of folate, is used orally and appropriately. One clinical study in infants aged 27 days and younger shows that consuming a formula containing L-5-MTHF (Metafolin, Merck & Cie) 10.4 mcg/100 mL daily has been used with apparent safety for up to 12 weeks (104918).

PREGNANCY AND LACTATION: LIKELY SAFE ...when used orally and appropriately. Folic acid 300-400 mcg is commonly used during pregnancy for prevention of neural tube defects (8739). Miscarriage rates and negative impacts on fetal growth have not been shown to increase with peri-conception supplemental folic acid intakes of 4 mg per day (91320,91322). However, other research shows that taking more than 5 mg per day during pregnancy may reduce development of cognitive, emotional, and motor skills in infants (91318). Also, the tolerable upper intake level (UL) of folic acid for pregnant or lactating women is 800 mcg daily for those 14-18 years of age and 1000 mcg daily for those 19 years and older (6241).

POSSIBLY SAFE ...when L-5-methyltetrahydrofolate (L-5-MTHF), the reduced form of folate, is used orally and appropriately, short-term. L-5-MTHF has been used with apparent safety at a dose of 416 mcg daily for 16 weeks during lactation. Compared to folic acid, this form seems to further increase the folate concentration of red blood cells, but not breast milk (104913,104914).

Adverse Effects

General: Orally, folic acid is generally well-tolerated in amounts found in fortified foods, as well as in supplemental doses of less than 1 mg daily.

Most Common Adverse Effects:

Orally: At doses of 5 mg daily - abdominal cramps, diarrhea, and rash. At doses of 15 mg daily - bitter taste, confusion, hyperactivity, impaired judgment, irritability, nausea, sleep disturbances.

Serious Adverse Effects (Rare):

Orally: Cancer (long-term use), cardiovascular complications, liver injury, seizures.

All ROAs: Allergic reactions such as bronchospasm and anaphylactic shock.

Cardiovascular

There is some concern that high oral doses of folic acid might increase the risk of adverse cardiovascular outcomes. Clinical research shows that taking doses of 800 mcg to 1.2 mg/day might increase the risk of adverse cardiovascular events in patients with cardiovascular disease (12150,13482). High doses of folic acid might promote cell growth by providing large amounts of the biochemical precursors needed for cell replication. Overgrowth of cells in the vascular wall might increase the risk of occlusion (12150). Although some research suggests that use of folic acid might increase the need for coronary revascularization, analysis of multiple studies suggests that taking folic acid up to 5 mg/day for up to 24 months does not appear to affect coronary revascularization risk (90798).

Dermatologic

Orally, folic acid 1-5 mg daily can cause rash (7225,90375,91319). Folic acid 15 mg daily can sometimes cause allergic skin reactions (15).

Gastrointestinal

Orally, folic acid 5 mg daily can cause abdominal cramps and diarrhea (7225). Folic acid 15 mg daily can sometimes cause nausea, abdominal distention, flatulence, and bitter taste in the mouth (15). In children aged 6-30 months at risk of malnourishment, taking a nutritional supplement (Nutriset Ltd) enriched in folic acid 75-150 mcg daily, with or without vitamin B 12 0.9-1.8 mcg daily, for 6 months increases the likelihood of having persistent diarrhea (90391).

Hepatic

Liver dysfunction, with jaundice and very high liver enzymes, occurred in a 30-year-old pregnant patient with severe nausea and vomiting taking a folic acid supplement (Folic acid, Nature Made) 400 mcg daily. Based on the timing of ingestion, the lack of other etiological factors, a positive drug-induced lymphocyte stimulation test, and liver function normalization once the folic acid had been stopped, the authors suggest the folic acid supplement was the cause. However, the authors did not determine which substance in the folic acid supplement was responsible and therefore it cannot be determined that folic acid itself was the cause (91309).

Neurologic/CNS

Orally, folic acid 15 mg daily can sometimes cause altered sleep patterns, vivid dreaming, irritability, excitability, hyperactivity, confusion, and impaired judgment (15). Large doses of folic acid can also precipitate or exacerbate neuropathy in people deficient in vitamin B12 (6243). Use of folic acid for undiagnosed anemia has masked the symptoms of pernicious anemia, resulting in lack of treatment and eventual neurological damage (15). Patients should be warned not to self-treat suspected anemia. There is also some concern that consuming high amounts of folic acid from the diet and/or supplements might worsen cognitive decline in older people. A large-scale study suggests that people over 65 years of age, who consume large amounts of folic acid (median of 742 mcg/day), have cognitive decline at a rate twice as fast as those consuming smaller amounts (median of 186 mcg/day). It's not known if this is directly attributable to folic acid. It is theorized that it could be due to folic acid masking a vitamin B12 deficiency. Vitamin B12 deficiency is associated with cognitive decline (13068). More evidence is needed to determine the significance of this finding. For now, suggest that most patients aim for the recommended folic acid intake of 400 mcg/day.

Oncologic

There is some concern that high dose folic acid might increase the risk of cancer, although research is unclear and conflicting. A large-scale population study suggests that taking a multivitamin more than 7 times per week with a separate folic acid supplement significantly increased the risk of prostate cancer (15607). Clinical research also shows that taking folic acid 1 mg daily increase the absolute risk of prostate cancer by 6.4% over a 10-year period when compared with placebo. However, those with a higher baseline dietary intake of folic acid had a lower rate of prostate cancer, but this was not statistically significant. Also, folate and folic acid intake in patients with prostate cancer is not associated with the risk of prostate cancer recurrence after radical prostatectomy (91317). However, it is possible that discrepancies are due to dietary folate versus folic acid intake. Large analyses of population studies suggest that while dietary folate/folic acid is not associated with prostate cancer, high blood folate/folic acid increases the risk of prostate cancer (50411,91316).

Additional clinical research shows that taking folic acid 800 mcg daily, in combination with vitamin B12 400 mcg, significantly increases the risk of developing cancer, especially lung cancer, and all-cause mortality in patients with cardiovascular disease (17041). However, this may be due to vitamin B12, as other observational research found that higher vitamin B12 levels are linked with an increased risk for lung cancer (102383). Meta-analyses of large supplementation trials of folic acid at levels between 0.5-2.5 mg daily also suggest an increased risk of cancer (50497,110318). Also, in elderly individuals, taking folic acid 400 mcg daily with vitamin B12 500 mcg daily increased the risk of cancer. The risk was highest in individuals over 80 years of age and in females and mainly involved gastrointestinal and colorectal cancers (90393).

Not all researchers suspect that high intake of folic acid supplements might be harmful. Some research suggests that

increased dietary intake of folic acid, along with other nutrients, might be protective against cancer (16822). A meta-analysis of multiple clinical trials suggests that folic acid supplementation studies with folic acid levels between 500 mcg to 50 mg/day does not increase the risk of general or site-specific cancer for up to 7 years (91312,91321). Also, a post-hoc subgroup analysis of results from clinical research in adults with a history of recent stroke or ischemic attack suggests that taking folic acid, vitamin B12, and vitamin B6 does not increase cancer risk overall, although it was associated with an increased risk of cancer in patients who also had diabetes (90378).

Psychiatric

Orally, folic acid 15 mg daily can sometimes cause exacerbation of seizure frequency and psychotic behavior (15).

Pulmonary/Respiratory

Folic acid use in late pregnancy has been associated with an increased risk of persistent and childhood asthma at 3.5 years in population research (50380). When taken pre-pregnancy or early in pregnancy, population research has not found an association with increased risk of asthma or allergies in childhood (90799,103979). Folic acid use in pregnancy has been associated with a slightly increased risk of wheeze and lower respiratory tract infections up to 18 months of age in population research (50328).

Effectiveness

EFFECTIVE

Folate deficiency. Oral or intravenous folic acid is effective for the prevention or treatment of folate deficiency.
Details: Administering folic acid orally or parenterally improves and prevents folate deficiency (505,8739). Clinical research shows that supplementation with folic acid 100 mcg to 5 mg daily during pregnancy decreases the risk of developing megaloblastic anemia by up to 79% (91307).

LIKELY EFFECTIVE

Kidney failure. Taking folic acid orally reduces homocysteine levels in people with kidney failure who are on hemodialysis.
Details: Over 85% of people with kidney failure have hyperhomocysteinemia. Treatment of hyperhomocysteinemia in kidney failure is often more difficult than with normal kidney function (1489,3324,7289,9413,9414,9416). The reasons for this are not fully understood; renal uptake and metabolism of homocysteine may be reduced in severe kidney failure, and hemodialysis may contribute to vitamin deficiencies (6884,9414,9417). Folic acid 0.8-15 mg daily or 3 times weekly is generally used, but the degree of homocysteine reduction varies between 12% to 50%, and normal homocysteine levels (less than 12 µmol/L) cannot always be achieved. Adding vitamin B12 400-1000 mcg daily and vitamin B6 20-50 mg daily produces an additional reduction in homocysteine (1489,6884,7289,7881,9322,9413,9414,9415,9416,9417). Folic acid doses greater than 15 mg daily do not seem to provide additional benefit. Also, doses of 30-60 mg might cause a rebound in homocysteine levels when treatment is stopped (9219). Despite the homocysteine-lowering effect of folic acid in kidney failure, the most robust meta-analysis of 11 clinical trials suggests that folic acid supplementation does not seem to reduce the risk of cardiovascular events (50527). A smaller meta-analysis of 7 clinical trials that used a different primary composite outcome suggests that folic acid might reduce the risk of cardiovascular events by 15% when compared with control (91311).

There has also been interest in using a reduced form of folic acid, L-5-methyltetrahydrofolate (L-5-MTHF). One study in patients on hemodialysis suggests that taking L-5-MTHF 17 mg daily for 12 weeks might lower homocysteine levels to a greater extent than an equimolar 15 mg of folic acid (104908). Another clinical trial in patients on hemodialysis suggests that giving intravenous L-5-MTHF 50 mg three times weekly is associated with an increased survival of about 36 months, compared with about 26 months with folic acid 5 mg daily. There was no difference in homocysteine reduction between groups (104909). These results should be interpreted with caution because they have not been replicated, and there was no placebo control. Furthermore, survival may have been affected by the availability of kidney transplants.

Hyperhomocysteinemia. Oral folic acid, taken alone or in combination with other B vitamins, lowers homocysteine levels in most patients. However, it is unclear if this has cardiovascular benefits.
Details: Taking folic acid orally 0.4-5 mg daily lowers fasting homocysteine levels by 20% to 30% in people with normal to moderately elevated homocysteine levels at baseline. Folic acid 0.8-1 mg daily seems to provide maximal reduction (9307,9400,9401,9405,9408,11337,11338,50145). Doses above 1 mg daily do not seem to add benefit (9307), except in some people with certain gene mutations that cause homocysteine levels of 20 µmol/L or higher (9408). The higher the initial homocysteine levels, the lower the folic acid dose needed to attain maximum homocysteine reduction (9307). The effects of folic acid supplementation on homocysteine concentrations appear to be greater in females than males (50145). Adding vitamin B6 25-250 mg or vitamin B12 500 mcg seems to further reduce homocysteine levels (1489,9400,9405,9406,9408,107136). Some experts recommend routine use of vitamin B12 in homocysteine-lowering regimens to avoid the risk of neuropathy in people with undetected vitamin B12 deficiency (9405).

Increasing folic acid intake with supplements or folate-fortified cereal products is more effective for reducing homocysteine levels than increasing intake of folate-rich foods (6367). Fortification of cereals and flour with 140 mcg folic acid per 100 grams reduces the mean homocysteine level in the general population by about 7% (7881,9404,9407).

Elevated homocysteine levels are considered by some to be an independent risk factor for atherosclerosis progression, recurrent thromboembolism, deep vein thrombosis, myocardial infarction, ischemic stroke, and other vascular complications (3886,3887,6236,7725,9314,9318,50509). However, elevated homocysteine levels may be a marker, as opposed to a cause, of vascular disease (11387,11388). Although folic acid lowers homocysteine levels, it is not yet known whether this reduces the risk of vascular disease. One meta-analysis shows that taking folic acid can reduce the risk of stroke by about 10% in patients with cardiovascular disease (CVD); the reduction is greatest in patients for whom homocysteine levels are lowered by at least 25% (96157). A meta-analysis of 10 clinical trials, including over 44,000 patients at risk for or with a history of CVD, shows that B vitamin supplementation reduces the relative risk of stroke by 10% when compared with placebo (97619). Also, a meta-analysis in patients with a history of stroke shows that B vitamin supplementation, including folic acid, reduces the relative risk of stroke recurrence by 13% and the risk of vascular death by 11% when compared with placebo (107136). However other research does not agree. Meta-analyses of clinical research show that folic acid does not prevent CVD or coronary heart disease, in spite of lowering homocysteine by up to 55%, when individuals with normal or high levels of homocysteine are considered (50539,96147,97619). Furthermore, most research shows that folic acid supplementation, alone or in combination with vitamin B6

and vitamin B12, does not improve endothelial function or improve secondary prevention of cardiovascular events such as myocardial infarction in people with existing CVD despite a homocysteine-lowering effect (9313,11337,11387,13482,50437,97619). Some research even suggests an increase in CVD risk concurrent with homocysteine lowering (13482). Large randomized controlled trials are needed to confirm or refute these findings.

Some researchers hypothesize that different genetic profiles might explain some of these conflicting results. For instance, individuals with a homozygous 677TT MTHFR genotype typically have increased homocysteine levels. However, a meta-analysis suggests that treatment with folic acid does not reduce the risk of ischemic heart disease despite reducing homocysteine levels in individuals with 677TT MTHFR (50456). It has also been theorized that a reduced form of folic acid, 5-methyltetrahydrofolate (5-MTHF) might work better in these individuals. Although [6RS]-5-MTHF has been shown to lower homocysteine levels (104915), studies assessing its cardiovascular benefits are lacking.

Methotrexate toxicity. Oral folic acid reduces the severity of methotrexate toxicity.
^ Details: Oral folic acid reduces methotrexate toxicity symptoms, such as nausea and vomiting, in the treatment of rheumatoid arthritis (RA) and psoriasis (768,2162,2163,2164,4492,4493,4494,9369,9419). Folic acid also seems to reduce methotrexate-induced hepatic side effects by approximately 36% (50320). Some research shows that a low, 0.8 mg weekly dose of folic acid is equally effective to a higher dose of 5 mg weekly for the prevention of methotrexate toxicity (102388).

Neural tube birth defects. Oral folic acid helps to prevent neural tube birth defects in newborns.
^ Details: Clinical practice guidelines recommend that anyone capable of becoming pregnant take folic acid 400 mcg daily from fortified foods or supplements to prevent neural tube birth defects in infants. Folic acid 600 mcg daily is advised during pregnancy (94811,96146). This recommendation is based on research showing that a higher intake of folic acid from food and supplements during pregnancy reduces the primary incidence of neural tube birth defects by 41% to 69% (3325,9309,50344,50403,50468,95156). Individuals with a history of children with neural tube birth defects usually take a higher dose of folic acid 4000 mcg daily starting one month before and continuing for up to 3 months after conception (96146). Evidence shows that, when used for secondary prevention, folic acid supplementation reduces the incidence of neural tube defects by 66% to 87% (21235,50263,50344,50403,95156). In the US, foods containing at least 60 mcg of folic acid can be labeled with a health claim stating that healthful diets with adequate folic acid intake may reduce the risk of having a child with a brain or spinal cord defect (102369).

POSSIBLY EFFECTIVE
Cognitive impairment. Taking folic acid alone, with other B vitamins or with docosahexaenoic acid (DHA), might improve thinking and memory skills in older patients with cognitive impairment.
^ Details: One clinical trial in patients aged 65 years and older with mild cognitive impairment (MCI) shows that taking folic acid 400 mcg daily for 2 years increases IQ scores when compared with placebo (100952). Two small, low-quality clinical studies in patients aged 70-90 years with cognitive impairment and low folate levels or folate deficiency shows that taking folic acid 5 or 15 mg daily for up to 63 days improves cognitive function, including measures such as memory and attention, when compared with placebo or baseline (50301,104911).

Folic acid also appears to be beneficial when used in combination with other B vitamins or with DHA. A clinical trial in patients aged 70 years and older with MCI shows that taking folic acid 800 mcg, vitamin B6 20 mg, and vitamin B12 500 mcg daily for 2 years mitigates decline in executive function and, in patients with high baseline homocysteine levels, improves cognition and memory when compared with placebo (50480). Taking folic acid 800 mcg with or without DHA 800 mg daily for 6 months modestly improves cognition, as measured on the full-scale intelligence quotient, when compared with placebo (103978,109196). However, this benefit is no longer present at 6 months after treatment discontinuation (109196).

Depression. Oral folic acid seems to modestly reduce depression severity when added to conventional antidepressant therapy. It is unclear if folic acid can reduce the prevalence of depression or the risk for suicide.
^ Details: Observational studies suggest that depression is correlated with low folate status, particularly in females (50105,50127,50243). Taking folic acid 0.2-15 mg daily for up to 6 months with conventional antidepressants seems to improve treatment response in patients with major depressive disorder (3657,10884,10887,50566,109190). One meta-analysis shows that taking L-methylfolate or folic acid as an adjunct to treatment with conventional antidepressants modestly reduces depression severity when compared with placebo and conventional antidepressants. The response and remission rates were improved by 36% and 39%, respectively (109190). However, limited clinical research suggests that folic acid is not effective as a replacement for conventional antidepressant therapy (10886). Also, a small clinical study in adolescents at high familial risk for mood disorders suggests that taking folic acid 2.5 mg daily for up to 36 months does not prevent mood disorders when compared with placebo. However, in the patients that were eventually diagnosed with depression, the time of onset was delayed from 5 months to 15.5 months in the group using folic acid when compared with placebo (91313). Guidelines from The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce state that folic acid is not currently recommended as monotherapy treatment for unipolar depression (110318).

Observational research has also evaluated the association between folic acid supplementation and suicidal events in patients with or without depression. One within-person cohort study, in which only 12% of patients were diagnosed with depression, has found that filling a folic acid prescription of 0.4-5 mg daily, either alone or as part of a multivitamin, is associated with a reduced risk for suicidal events during the following months when compared with months without a prescription (109201). It is unclear what percentage of these patients, if any, had folate deficiency at baseline.

Hypertension. Oral folic acid seems to modestly reduce hypertension.
^ Details: A meta-analysis of clinical research shows that taking folic acid 5-10 mg daily for at least 6 weeks reduces systolic blood pressure by 2mmHg and improves flow-mediated dilation by 1.6% in hypertensive individuals (50364). Some research has evaluated folic acid in hypertensive patients when used with antihypertensive drugs. Results show that taking folic acid 400-800 mcg in combination with enalapril 10 mg daily for about 4.5 years does not improve blood pressure when compared with enalapril alone (50302,96158). However, in hypertensive patients with heavy proteinuria, this combination seems to reduce the risk of all-cause mortality by about 41% when compared with enalapril alone (96158).

Phenytoin-induced gingival hyperplasia. Topical folic acid seems to reduce gingival hyperplasia due to phenytoin. The effect of oral folic acid is unclear.
^ Details: Applying folic acid topically seems to inhibit gingival hyperplasia secondary to phenytoin therapy (2151). However, taking folic acid orally does not seem to improve gingival hyperplasia secondary to phenytoin therapy in adults (2150,2151,2152), although some evidence suggests that taking folic acid 500 mcg daily reduces the risk of phenytoin-induced gingival hyperplasia by 33% in children when compared with placebo (50463).

Stroke. Although some clinical research has shown that oral folate reduces stroke risk by a small amount, more research is needed to determine who is most likely to benefit. Most individual clinical trials show that folic acid seems to reduce stroke risk only in regions without food-fortification policies.
^ Details: Multiple clinical studies have shown that folic acid supplementation reduces the risk of stroke by 10% to 25% in regions WITHOUT established policies mandating folic acid fortification of grain products (50240,50485,50525,50539,91325,96154,96157,96159,97308). The effect appears to be greatest when folic acid is taken in low doses (usually 0.8 mg daily or lower) (50525,96157,96159), in regions with a low prevalence of statin use (50525,96159), in patients with high cholesterol levels at baseline (96152), in patients who achieve homocysteine reduction of at least 20% (50407,96157), and in patients with the lowest folate levels at baseline (96154,96157). There is also some evidence that the effect of folic acid on stroke risk is greatest in patients with low baseline levels of vitamin B12 (96159). In 2001, 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).

Most research shows that folic acid supplementation does not reduce the risk of stroke in regions WITH established policies mandating folic acid fortification (50240,50485,50525,50539,96157,96159,97308). However, there is some evidence that folic acid may reduce the risk of stroke in patients from regions with folic acid fortification who have recently had a stroke or transient ischemic attack and are not using antiplatelet drugs (90379).

Meta-analyses of clinical research have been conducted. However, possible confounding due to the presence or absence of folic acid fortification is unclear. A meta-analysis of the available research in adults with existing CVD shows that folic acid supplementation at a daily dose of less than 2 mg reduces the risk for stroke by about 10% (102386). Also, a meta-analysis of 10 clinical trials, including over 44,000 patients at risk for or with a history of CVD, shows that B vitamin supplementation, including folic acid, reduces the relative risk of stroke by 10% when compared with placebo (97619). In patients with a history of stroke, a meta-analysis shows that B vitamin supplementation reduces the relative risk of stroke recurrence by 13% and the risk of vascular death by 11% when compared with placebo (107136).

It is unclear if folic acid reduces the stroke risk in patients with impaired kidney function. Some research shows that taking folic acid in combination with high doses of vitamin B12 (cyanocobalamin) does not reduce the risk of stroke in these patients (11387,96150). However, there is concern that the lack of benefit may have been due to the decline in kidney function from high doses of cyanocobalamin (96150). Additional research is needed to determine if folic acid supplementation is beneficial in patients with impaired kidney function when used with other forms of vitamin B12 such as methylcobalamin or hydroxycobalamin.

Vitiligo. Oral folic acid seems to improve vitiligo symptoms.
^ Details: Taking folic acid orally seems to improve symptoms of vitiligo (2153,2154). This finding is supported by a meta-analysis of observational research which shows that patients with vitiligo have higher serum homocysteine levels when compared with patients without vitiligo (100951).

POSSIBLY INEFFECTIVE
Anemia. Adding oral folic acid to oral iron therapy does not seem to improve hematologic parameters in patients with anemia.
^ Details: In postpartum patients with anemia, clinical research shows that taking iron as ferrous fumarate 600 mg and folic acid 1 mg daily is no more effective than iron alone for improving hemoglobin status (91319). Also, clinical research in non-pregnant menstruating females shows that taking folic acid 0.4 mg daily or 2.8 mg once weekly for 16 weeks with iron 60 mg daily does not reduce anemia or improve iron status when compared with iron alone (109193). During pregnancy, clinical research shows that folic acid supplementation does not decrease the risk of pre-delivery anemia or low hemoglobin levels (91307).

Age-related cognitive decline. Oral folic acid does not seem to prevent cognitive decline in healthy elderly adults.
^ Details: Most clinical research shows that taking folic acid, alone or in combination with other B vitamins, does not improve cognitive function, including memory, language, or executive function, in elderly adults with age-related cognitive decline (50318,50412,50510). In fact, a large-scale observational study in the US has found that people over 65 years of age who consume large amounts of folic acid (median of 742 mcg daily) have cognitive decline at a rate twice as fast as those consuming smaller amounts (median of 186 mcg daily) (13068).

While most research on folic acid for age-related cognitive decline lacks positive findings, many of the studies are small, short-term (<1 year), underpowered to detect significant differences, and not specific to patients with high homocysteine levels. Population research has found that high homocysteine levels are associated with decreased cognition in older adults, suggesting that using folic acid to lower homocysteine levels might mitigate cognitive decline in these patients (50094). Two long-term clinical trials examining the effects of folic acid in elderly adults with high homocysteine levels show mixed results. A large-scale clinical trial of patients aged 50-70 years from the Netherlands who have high homocysteine levels shows that taking folic acid 800 mcg daily for 3 years increases memory, information processing, and other measures of cognitive function when compared with placebo (15271). However, another large-scale clinical trial of patients aged 65 years and older from the Netherlands who have high homocysteine levels shows that taking folic acid 400 mcg and vitamin B12 500 mcg daily for 2 years lowers homocysteine levels, but does not appear to improve overall measures of cognitive function, when compared with placebo (90392). The reasons for the discrepant findings in these two studies are not clear but might relate to differences in the dose of folic acid, duration of treatment, and age of patients included.

Cataracts. Oral folic acid does not seem to reduce cataract development.
^ Details: Clinical research in females with existing cardiovascular disease (CVD) or with risk factors for CVD shows that taking folic acid 2.5 mg, vitamin B6 50 mg, and vitamin B12 1 mg daily for an average of 7.3 years does not reduce the risk of developing cataracts. Furthermore, the risk of cataract extraction was increased by 28% in these patients (96149).

Diarrhea. Oral folic acid does not seem to reduce the risk of diarrhea, and might even increase the incidence of diarrhea in children.
^ Details: In children aged 6-30 months at risk of malnourishment, clinical research shows that taking a nutritional supplement (Nutriset Ltd) enriched in folic acid 75-150 mcg, with or without vitamin B12 0.9-1.8 mcg, daily for 6 months does not reduce the incidence of diarrhea when compared with placebo. Enrichment with folic acid, with or without vitamin B12, actually seems to increase the likelihood of having more episodes of both persistent diarrhea and diarrhea lasting over 3 days (90391).

Fall prevention. Oral folic acid does not seem to reduce the risk of falls.

^ Details: Clinical research shows that taking a combination of 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).

Fetal and premature infant mortality. Oral vitamin B12 does not seem prevent mortality in premature infants.
^ Details: Clinical research shows that supplementation with folic acid during pregnancy does not decrease the risk of miscarriage, stillbirth, or neonatal death (91307,96156).

Leukemia. Oral vitamin B12 does not seem to reduce the risk for pediatric acute lymphoblastic leukemia.
^ Details: A meta-analysis of results from two case-control studies has found that increased folate intake during pregnancy is not associated with a reduced risk of childhood acute lymphoblastic leukemia (50247).

Male infertility. Oral folic acid does not seem to improve sperm parameters or pregnancy rates in males with infertility.
^ Details: Some small clinical studies show that taking folic acid, alone or with zinc, increases sperm count in males with idiopathic infertility or in males with a grade III varicocele (9334,90194). However, another small study in males with asthenozoospermia shows that taking folic acid 5 mg, selenium 200 mcg, and vitamin E 400 IU daily for 3 months does not improve sperm parameters when compared with placebo (104907). Furthermore, there seems to be no improvement in clinical outcomes. One large, high-quality clinical study in males with idiopathic infertility shows that taking folic acid 5 mg with zinc 30 mg daily for 6 months does not improve sperm morphology, pregnancy rate, or live birth rate when compared with placebo (102085).

Folic acid has also been evaluated in combination with other ingredients. A retrospective study in males with or without varicocele-related infertility suggests that taking a specific combination product containing folic acid 0.2 mg, vitamin C, zinc, L-carnitine fumarate, acetyl-L-carnitine, coenzyme Q10, selenium, and vitamin B12 (Proxeed Plus, Sigma-Tau) twice daily for 6 months is associated with improvements in sperm count, sperm concentration, and sperm motility when compared to baseline. Improvement in semen parameters were greatest in subjects with more severe varicoceles (111296). The validity of this study is limited by the lack of a comparator group.

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

Pre-eclampsia. Oral folic acid does not seem to prevent pre-eclampsia in pregnant patients.
^ Details: While the effect of low-dose prenatal folic acid is unclear, high-dose folic acid does not seem to reduce the risk of pre-eclampsia. Some population research has found that low-dose folic acid is associated with a 22% reduced odds of pre-eclampsia, while other research has found no association (91308,99370,99372,110447). A large clinical trial evaluating high-dose folic acid in pregnancies at risk for pre-eclampsia shows that taking 4 mg daily, starting at 8-16 weeks of gestation and continuing until delivery, does not reduce the risk of pre-eclampsia when compared with placebo (103929). A secondary analysis of this study in twin pregnancies has also found no benefit with high-dose folic acid supplementation (103977).

Respiratory tract infections. Oral folic acid does not seem to prevent respiratory tract infections.
^ Details: Clinical research in children aged 6-30 months at risk of malnourishment shows that taking a nutritional supplement (Nutriset Ltd) enriched in folic acid 75-150 mcg, with or without vitamin B12 0.9-1.8 mcg, daily for 6 months does not reduce the incidence of lower respiratory infections when compared with a supplement not enriched with folic acid and vitamin B12 (90391).

LIKELY INEFFECTIVE

Colorectal adenoma. Oral folic acid does not prevent colorectal adenomas.
^ Details: Although some population research and one clinical study has found that high folate intake is associated with reduced colorectal adenoma risk (2142,2143,91303), most clinical research does not support this finding. Clinical research shows that taking a combination of B vitamins, including folic acid 2.5 mg, vitamin B6 50 mg, and vitamin B12 1 mg daily for up to 9.2 years, does not reduce the risk of colorectal adenoma in females at high risk of cardiovascular disease when compared with placebo (90389). Other clinical research suggests that taking folic acid does not reduce the occurrence or recurrence of adenomas or incidence of advanced adenomas (34596,50241,50265,50369,50394,50449,50522). Furthermore, treatment with folic acid for more than 3 years seems to be associated with an increased risk of advanced adenomatous lesions (50378).

Fragile X syndrome. Oral folic acid does not improve symptoms in children with fragile X syndrome.
^ Details: Clinical research shows that taking folic acid orally does not improve symptoms of fragile X syndrome (2155,2156,2157,2158,2159,2160,50575).

Preterm labor. Oral folic acid does not seem to reduce the risk of preterm birth.
^ Details: Meta-analyses of clinical research show that supplementation with folic acid 200 mcg to 5 mg during pregnancy does not decrease the risk of preterm birth (91307,96155). An observational study in patients with and without epilepsy found that folic acid supplementation during pregnancy was associated with a lower odds of preterm birth in patients receiving antiseizure medications; however, no link between folic acid and preterm labor was reported in patients without epilepsy or in those with epilepsy not receiving antiseizure medications (110447).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Abdominal wall defects. It is unclear if oral folic acid helps to prevent abdominal wall defects in newborns.
^ Details: Observational research in a population in northern China has found that taking folic acid supplements until the end of the first trimester modestly reduces the risk of abdominal wall defects and the risk of omphalocele, specifically, in the newborn when compared with not taking folic acid. However, this association was not found in a population in southern China (109191). These differing outcomes may be related to the lower dietary folate intakes in northern China.

Acne. Oral folic acid has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research in adults and children with inflammatory acne shows that taking 1-4 tablets of a specific product (NicAzel, Elorac Inc.) containing folic acid, vitamin B6, nicotinamide, azelaic acid, zinc, and copper for 8 weeks reduces inflammatory lesions and improves appearance in 88% and 81% of patients, respectively, when compared with baseline (90800).

Age-related macular degeneration (AMD). Oral folic acid 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 folic acid 2.5 mg, vitamin B6 50 mg, and vitamin B12 1 mg daily reduces the risk of developing AMD in females over 40 years of age with a history of cardiovascular disease (CVD) or with 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 folic acid, other ingredients, or the combination.

Age-related testosterone deficiency. Folic acid has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A very small clinical study in males with overweight or obesity, mild erectile dysfunction, and normal to low androgen levels shows that taking a combination product containing folic acid 400 mcg, alpha-lipoic acid, myo-inositol, and apple (Sinopol Forte) increases testosterone, luteinizing hormone, and measures of erectile dysfunction but not follicle-stimulating hormone or sperm parameters when compared to baseline (111674). The validity of these effects is limited by the small sample size and the lack of a comparator group, and it is unclear if these effects are due to folic acid, other ingredients, or the combination.

Alzheimer disease. It is unclear if oral folic acid reduces the risk of developing this condition.
^ Details: Low levels of folate and high levels of homocysteine have been linked to a greater risk of Alzheimer disease (50094). Also, some observational studies have found that higher intake of folate from the diet and supplements in elderly adults is associated with a reduced risk of developing Alzheimer disease when compared with lower intake (13165,15270). One small clinical trial in patients with Alzheimer disease who are taking cholinesterase inhibitors shows that taking folic acid 1 mg daily for 6 months increases the likelihood of treatment response, classified as global improvement in behavioral and/or functional status with no decline in mental status scores, by 78% to 87% when compared with placebo (50246). Also, 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).

However, not all research agrees. Clinical research in patients with probable Alzheimer disease using routine medications shows that taking folic acid 5 mg, vitamin B12 1 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 (50319). However, all patients in this study were also consuming a folate-fortified diet.

Angioplasty. Oral folic acid has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Some evidence suggests that folic acid 1 mg, vitamin B12 400 mcg, and pyridoxine 10 mg daily can decrease the rate of restenosis in patients treated with balloon angioplasty (8009,9412). 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, 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 bare metal coronary stenting also does not seem to reduce restenosis and might actually increase restenosis (12150,12151). 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).

Atopic dermatitis (eczema). It is unclear if oral folic acid during pregnancy reduces the risk of eczema in the child.
^ Details: Observational research has found that consuming both iron and folic acid supplements during pregnancy is associated with a four-fold reduced risk for developing atopic dermatitis in the child. However, use of either iron or folic acid supplementation alone is not associated with an effect on the child's risk for atopic dermatitis (102387).

Autism spectrum disorder. It is unclear if oral folic acid intake during pregnancy reduces the risk of autism spectrum disorder in the child.
^ Details: A meta-analysis of population research has found that consumption of folic acid of at least 400 mcg daily from both diet and supplements during pregnancy is associated with a 45% reduced risk of autism in the child at 2-15 years of age. Also, supplementation with folic acid during the prenatal to early period of pregnancy is associated with an approximate 43% reduced risk of autism in the child. This association did not differ between countries with or without a folate fortification program (109198). An individual population study has also found that prenatal folic acid supplementation initiated the first day of the last menstrual period before conception is associated with a 39% reduced odds of autism in the child at age 3.3-10.2 years when compared to pregnancies without folic acid supplementation (91324).

Beta-thalassemia. There is limited evidence on the oral use of folic acid for beta-thalassemia minor.
^ Details: Patients with beta-thalassemia minor may experience decreased muscle strength and increased bone or muscle pain. A small clinical study in children with this condition shows that taking folic acid 1 mg, with or without L-carnitine 50 mg/kg, daily for 3 months reduces bone pain by 64% to 84% and increases the number of stairs climbed by 2- to 5-fold when compared with baseline (90631). The validity of this finding is limited by the lack of a control group.

Bipolar disorder. It is unclear if adding oral folic acid to conventional bipolar therapy further improves symptoms.
^ Details: Some clinical evidence suggests that folic acid does not improve the antidepressant effects of lithium in patients with bipolar disorder (50566). However, other clinical evidence suggests that taking folic acid in combination with valproate during the acute phase of mania improves the effects of valproate (50357).

Breast cancer. It is unclear if oral folic acid reduces breast cancer risk.
^ Details: Some older population research suggests that increased intake or levels of folic acid alone does not affect the risk of breast cancer or breast cancer-related mortality (50218,50224). However, in a specific group of women who also consume high amounts of dietary methionine, cyanocobalamin (vitamin B12), or pyridoxine (vitamin B6), dietary intake of folate is associated with a reduced risk of breast cancer (9328,50224). Also, more recent population research has found that folic acid plus folate dietary intakes between 153-400 mcg are associated with a reduced risk of breast cancer. This risk is further reduced in those who drink relatively large amounts of alcohol (90794). Folate intakes greater than 400 mcg daily do not appear to be protective against breast cancer (90794).

Cancer. It is unclear if oral folic acid prevents cancer.
^ Details: A large cohort study of children born to mothers with epilepsy on antiseizure medications suggests that prenatal folic acid exposure of 1 mg daily or more, at an average of 4.3 mg daily, is associated with a 2.7-fold greater risk of pediatric cancer when compared with children born to mothers with epilepsy but without prenatal exposure to high-dose folic acid. Additionally, this risk is not present in children of mothers without epilepsy taking high-dose folate (112103). It is unclear how maternal epilepsy, antiseizure medications, and folate interact to increase the risk of pediatric cancers. However, in the absence of clear guidelines, mothers with epilepsy should take no more than 4 mg of folic acid daily (112101,112102).

Cardiovascular disease (CVD). Although oral folic acid does not seem to prevent most CVD events, some research suggests that increased dietary folic acid might lower the risk of stroke and CVD-related mortality in patients at high risk for CVD.
^ Details: 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). Meta-analyses of available research show that folic acid might lower the risk of stroke in patients with CVD (97619,102386,107136). Some clinical research shows that taking folic acid reduces the risk of CVD by 15% in patients with kidney failure or chronic kidney disease (50444,91311). However, most research shows that folic acid supplementation, alone or in combination with vitamin B6 and vitamin B12, does not improve endothelial function or reduce the risk of death or CVD events in patients with existing hyperhomocysteinemia, coronary heart disease, CVD, kidney disease, or prior stroke, despite having a homocysteine-lowering effect (9313,9322,11337,11387,13482,50437) (50512,50527,96154,96147,97619,102386).

Some population research has evaluated adults at high risk for CVD. This research has found that dietary folate intake of at least 382 mcg daily is associated with a modest reduction in CVD-related mortality and possibly all-cause mortality. Consuming folic acid as a component of fortified food in doses of more than 251 mcg daily is associated with a modest reduction in CVD-related mortality. Conversely, folic acid supplementation is associated with a higher risk of CVD and overall mortality, and there is a J-shaped association between folate intake, serum folate levels, and red blood cell folate levels, with both CVD-related and all-cause mortality (109199).

Cervical cancer. It is unclear if oral folic acid prevents cervical cancer.
^ Details: Epidemiological evidence has found that increasing folate intake from dietary and supplement sources, along with thiamine, riboflavin, and vitamin B12, might decrease the risk of precancerous cervical lesions (11074).

Child development. It is unclear if oral folic acid supplementation during pregnancy improves child development.
^ Details: Clinical research in Northern Ireland shows that taking folic acid 400 mcg daily starting in the 14th week of gestation and continuing until the end of pregnancy improves word reasoning in the child at 7 years of age when compared with placebo. When compared with a historical cohort from Britain, folic acid supplementation was associated with an increase in full scale IQ, verbal IQ, performance IQ, and general language at 7 years of age (102385). At age 11, benefits in word reasoning were no longer significant. However, there were modest benefits in some measures of processing speed when compared with placebo. Verbal comprehension was modestly improved in females, but not males (109192). Observational research in pregnant individuals and their children in Spain has found that taking less than 400 mcg of folic acid daily during pregnancy is associated with lower mental alertness scores in children at ages 7-9 years when compared with folic acid 400-999 mcg daily, while taking folic acid 1000 mcg or more daily during pregnancy was associated with improvements in some measures of working memory in the children. However, no relationship between folic acid dosing and most other measures of cognitive function was identified (110449).

Chronic fatigue syndrome (CFS). Although there is interest in using oral or injectable folic acid for CFS, there is insufficient reliable information about the clinical effects of folic acid for this condition.

Chronic kidney disease (CKD). While adding oral folic acid to enalapril might slow CKD progression, adding folic acid to high-dose vitamin B12 does not seem to be beneficial.
^ Details: Clinical research in adults with hypertension and CKD shows that taking enalapril with folic acid 800 mcg for a median of 4.4 years reduces the risk of worsening kidney function by 21% and slows the rate of kidney function decline by 44% when compared with enalapril alone (96153). However, clinical research does not support the use of folic acid in patients with CKD when used in combination with high-dose vitamin B12 (cyanocobalamin). Vitamin B12 might increase the risk of negative outcomes (50253,50409,96150). More research is needed to determine the benefits of folic acid when used alone.

Colorectal cancer. It is unclear if oral folic acid prevents colorectal cancer.
^ Details: Although the majority of population research suggests that taking folic acid orally from dietary and supplemental sources reduces the risk of colorectal cancer (505,2140,2144,2145,2250,6271,9325,9326,50109,50427,50450) (91306,91323,96160,109188,110450), clinical evidence in general is not supportive. Most clinical research and meta-analyses of clinical trials suggest that taking folic acid from dietary or supplemental sources does not reduce the risk of colorectal cancer (2141,34596,50394). The reason for this discrepancy is unclear. Some observational research suggests that an inverse association between folate intake and risk of colorectal cancer was not apparent until at least 12 years after baseline folate intake was determined (109188). A meta-analysis of observational studies suggests that the benefits of folic acid supplementation on colorectal cancer risk might be limited to patients with moderate to high alcohol consumption (110450). Other clinical evidence suggests that the beneficial effect of folic acid may be limited to colon, but not rectal, cancer (21501). Furthermore, the beneficial effect for colon cancer may be limited to only certain subtypes. For instance, females with folate intake of at least 400 mcg daily seem to have a 46% reduction in the risk of p53-overexpressing colon cancer, but not p53-negative tumors, when compared with those who consume less than 200 mcg daily (21300). Also, the source of folic acid may influence its effects. Some observational research suggests that dietary folate, but not folic acid supplementation, reduces the risk of colon cancer (21501).

Congenital heart disease. It is unclear if oral folic acid prevents congenital heart disease.
^ Details: The exact cause of congenital heart disease is unknown but is thought to be a combination of genetic and environmental factors. Population research has found that supplementation with folic acid or folic acid-containing prenatal vitamins during pregnancy is associated with up to a 40% lower risk of congenital heart defects in newborns (99373).

Dementia. It is unclear if oral folic acid is beneficial for the prevention or treatment of dementia.
^ Details: While some preliminary research shows that folic acid might aid in the prevention and treatment of Alzheimer disease (13165,15270,50246,90374), two small clinical trials show that taking folic acid 15-20 mg daily for 10-12 weeks does not seem to improve cognitive function or the severity of dementia in patients with various forms of dementia, including vascular dementia, Lewy body dementia, probable Alzheimer disease, or dementia due to other causes (50062,50597).

Diabetes. Small clinical studies suggest that oral folic acid does not improve glycemic control.
^ Details: Meta-analyses of small clinical trials in patients with type 2 diabetes show that folic acid does not reduce glycated hemoglobin (HbA1C) when compared with placebo (50528,109197). Another small clinical study in patients with diabetes who are stabilized on metformin and/or a sulfonylurea shows that taking folic acid 5 mg daily for 8 weeks does not affect HbA1C when compared with placebo (104917). The validity of this study is limited by its small size and lack of blinding. Conversely, a meta-analysis of clinical research shows that taking folate modestly reduces fasting blood glucose and insulin levels, as well as measures of insulin resistance, when compared with placebo or no intervention (109197). There was no clear relationship between these changes and the dose or duration of folate. However, the studies included in this analysis evaluated multiple patient populations; the effect of folate in patients with diabetes, specifically, is unclear.

Beyond glycemic control, some research has assessed the impact of dietary folate intake on cardiovascular risk in patients with diabetes. An observational study in Chinese adults with type 2 diabetes has found that dietary intake of folate in the highest quartile is associated with 68% lower odds of developing cardiovascular disease, defined as a non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina, when compared with folate intake in the lowest quartile (110452).

Folic acid has also been evaluated in gestational diabetes. A meta-analysis of 20 studies shows that serum and red blood cell (RBC) folate levels are higher in patients with gestational diabetes than without gestational diabetes. Subgroup analysis suggests that patients with gestational diabetes have higher serum and RBC folate levels in the second trimester than in those without gestational diabetes, while RBC folate levels in patients with gestational diabetes were higher in the first trimester than those without gestational diabetes. Overall, higher serum folate levels are associated with a slight increase in the odds of gestational diabetes when compared with lower serum folate levels (112107).

Diabetic neuropathy. Oral folic acid has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research in patients with diabetic neuropathy shows that taking a combination of B vitamins, including folic acid (L-methylfolate), vitamin B12 (methylcobalamin), and vitamin B6 (pyridoxal-5'-phosphate), for 24 weeks does not improve neural dysfunction based on vibration perception, but does seem to improve total neuropathy symptoms, when compared with placebo. These symptoms, which include both sensation and pain, decreased by 25% with the B vitamin combination, compared with only 15% in those taking placebo (90375).

Epilepsy. It is unclear if oral folic acid reduces seizure frequency.
^ Details: A meta-analysis of preliminary clinical research shows that taking folic acid does not reduce seizure frequency in patients with epilepsy (50124). However, there is some speculation that folate deficiency might be linked to increased seizure frequency. A preliminary clinical study in folate-deficient children with epilepsy shows that taking folic acid 5 mg daily for 3 months reduces seizure frequency when compared to baseline, but not when compared with a control group that is not deficient in folate (99371).

Erectile dysfunction (ED). Oral folic acid has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: A very small clinical study in males with mild erectile dysfunction, overweight or obesity, and normal to low androgen levels shows that taking a combination product containing folic acid 400 mcg, alpha-lipoic acid, myo-inositol, and apple (Sinopol Forte, Laborest) improves measures of erectile dysfunction when compared to baseline (111674). The validity of these effects is limited by the small sample size and the lack of a comparator group, and it is unclear if these effects are due to folic acid, other ingredients, or the combination.

Esophageal cancer. Higher dietary folate intake is associated with a lower risk of esophageal cancer.
^ Details: One meta-analysis of observational research has found that higher levels of dietary folate are associated with a 34% lower risk of esophageal squamous cell carcinoma and a 50% lower risk of esophageal adenocarcinoma when compared with low levels of dietary folate (50208). Another meta-analysis of observational research has found that consuming high amounts of folate is associated with a 36% decrease in the odds of esophageal cancer when compared with lower dietary folate intake (100950).

Fenofibrate (Tricor)-induced hyperhomocysteinemia. Folic acid seems to attenuate increases in homocysteine in people taking fenofibrate.
^ Details: A small open-label clinical trial in patients taking fenofibrate shows that adding folic acid 10 mg every other day might reduce elevated plasma homocysteine levels by up to 59% when compared with taking fenofibrate alone (9321).

Gastric cancer. It is unclear if oral folic acid reduces gastric cancer risk.
^ Details: Observational research has found that taking folic acid reduces the risk of gastric cardia adenocarcinoma by 17% and the risk of noncardia gastric cancer by 33%, but does not reduce the risk of gastric cancer overall (50208). Also, a meta-analysis of 13 small clinical studies in patients with gastric precancerous conditions shows that taking folic acid 20-30 mg daily for 3-6 months improves gastric mucosal atrophy and intestinal metaplasia but does not seem to improve symptoms when compared with a control (110448). Whether these findings are associated with a lower risk of gastric cancer is unclear.

Gout. It is unclear if oral folic acid reduces the risk for gout.
^ Details: An observational study has found that increased dietary folate intake is associated with a lower incidence of gout (50454).

Head and neck cancer. It is unclear if oral folic acid is beneficial for head and neck cancer prevention.
^ Details: Population research has found that the highest intake of dietary folate is associated with a 50% reduced risk of head and neck cancer when compared with the lowest intake of folate. Each 100 mcg increase per day seems to reduce the risk by about 4% (96151).

Hearing loss. It is unclear if oral folic acid prevents hearing loss.
^ Details: Low levels of serum folate seem to be a risk factor for sudden sensorineural hearing loss in adults (21283). Observational research in females has found that serum folate levels in the lowest quintile are associated with a 19% increased risk for hearing loss when compared with levels in the second quintile. Also, folate levels in the highest quintile are associated with a 12% lower risk of hearing loss when compared with the second quintile (109807). A clinical study in older adults from the Netherlands shows that taking folic acid 800 mcg daily for 3 years slows the decline of age-related low-threshold hearing loss when compared with placebo (15163). However, at the time of this study, folate enrichment of foods was not allowed in the Netherlands. As a result, baseline folate levels in this study population were about 50% lower than in the US population. The effect of folic acid supplementation in people with higher baseline folate levels is unclear.

Infertility. It is unclear if oral 5-methyltetrahydrofolate (5-MTHF) in combination with vitamin B6 and vitamin B12 is more beneficial than folic acid alone for increasing pregnancy rate in females undergoing assisted reproductive technology (ART).
^ Details: Retrospective research from Italy suggests that taking 5-MTHF 400 mcg, vitamin B12 5 mcg, and vitamin B6 3 mg daily results in clinical pregnancy and live birth rates of approximately 60% and 49%, respectively, compared with 45% and 35% of those taking folic acid 400 mcg daily. A sub-analysis suggests that beneficial effects on pregnancy rates are limited to individuals aged less than 40 years (109189). The findings from this study are limited by its retrospective design. Also, it is unclear if these findings are generalizable to countries with folate fortification.

Kidney failure. It is unclear if oral folic acid is beneficial in patients with kidney failure.

^ Details: Because hemodialysis removes folate from the body, there is concern that folate deficiency may cause complications in patients with kidney failure receiving hemodialysis. Observational research in Taiwanese patients with kidney failure undergoing hemodialysis has found that taking folic acid 5 mg daily for an average of 5.8 years is associated with a 31% lower risk of arteriovenous access thrombosis when compared with folic acid 5 mg weekly. However, daily folic acid supplementation was not linked to a lower risk of cardiovascular events, cancer, or mortality when compared with weekly folic acid (110120).

Oral folic acid has also been evaluated in combination with other ingredients. A small, low-quality clinical study in adults with kidney failure undergoing regular hemodialysis shows that taking oral folic acid 30 mg daily with thiamine 90 mg daily for 96 weeks reduces overall mortality by 67% and improves cognitive scores by 31% when compared with no intervention (107724). It is unclear if these findings are due to folic acid, thiamine, or the combination.

Lometrexol toxicity. While oral folic acid might reduce lometrexol toxicity, intravenous folic acid does not seem to help.
^ Details: In a phase I trial, intravenous folic acid 5-25 mg administered 1 hour or 3 hours prior to lometrexol 15-30 mg/m2 every 3 weeks does not seem to reduce cumulative lometrexol toxicity (2161). However, in a phase II study, taking oral folic acid 3 mg/m2 daily in addition to lometrexol 10 mg/m2 weekly seems to attenuate cumulative toxicity and improve its tolerability in cancer patients (104948).

Low birth weight. It is unclear if oral folic acid supplementation during pregnancy reduces the risk of a low birth weight.
^ Details: Clinical research shows that supplementation with folic acid 200 mcg to 5 mg daily during pregnancy increases mean birth weight when compared with placebo (91307). Furthermore, some population research has found that pre- or peri-conception folic acid supplementation, usually 400 mcg daily, is associated with a reduced risk of a child born small-for-gestational age. However post-conception folic acid supplementation is not associated with reduced risk (91304,103983). An observational study in pregnant Chinese patients found that supplementation with folic acid is associated with a 20% lower odds of low birth weight when compared with no supplementation. This association was observed when folic acid was used both before conception and during pregnancy for at least 24 weeks or during pregnancy only for at least 12 weeks. Increased dietary folate intake was not linked to a lower risk of low-birth-weight infants (110446). However, other observational research has found no association between folic acid supplementation during pregnancy and the risk for small-for-gestational age births (110447).

Lung cancer. It is unclear if oral folic acid reduces lung cancer risk.
^ Details: There does not appear to be a relationship between deficiency of folate and lung cancer (9454). However, consuming at least 130.4 mcg of folate per 1000 kcal daily seems to reduce the risk of lung cancer by 40% in former smokers when compared to those with lower dietary folate intake (50065).

Melanoma. It is unclear if oral folic acid reduces melanoma risk.
^ Details: Population research has found that folic acid supplementation of 2-2.5 mg daily in combination with vitamin B6 and vitamin B12 is linked with a 53% reduced risk of melanoma (91312).

Metabolic syndrome. Although there is interest in using oral folic acid for metabolic syndrome, there is insufficient reliable information about the clinical effects of folic acid for this condition.

Nitrate tolerance. It is unclear if oral folic acid helps to prevent the development of tolerance to treatment with nitroglycerin.
^ Details: Some clinical evidence suggests that taking folic acid 1 mg daily for 1 week does not prevent the development of nitroglycerin-induced endothelial dysfunction or tolerance in healthy individuals (50442). However, other research suggests that taking folic acid 10 mg daily for 1 week prevents nitric oxide synthase dysfunction caused by continuous nitroglycerin (9316).

Nonalcoholic fatty liver disease (NAFLD). It is unclear if oral folic acid is beneficial for NAFLD.
^ Details: A cross-sectional analysis suggests that adults with NAFLD have lower levels of serum folate and its major component 5-MTHF when compared with healthy controls. Additionally, adults with NAFLD seem to consume less supplementary and dietary folate when compared with healthy controls. Overall, serum folate levels are negatively associated with the risk of NAFLD, and inadequate folate intake is associated with an increased risk of NAFLD (112104).

Oral clefts. It is unclear if oral folic acid reduces the risk of oral clefts in infants.
^ Details: Observational research has found that maternal folic acid supplementation is associated with an up to 49% reduced risk of cleft lip with or without cleft palate (50220,104921). Furthermore, a large clinical trial in pregnancies at-risk for oral cleft suggests that taking a higher dose of folic acid 4 mg from pre-conception until the end of the first trimester results in a similar oral cleft recurrence rate of 2.5%, compared with a 2.9% recurrence with a lower dose of folic acid (400 mcg). Both doses demonstrate a lower incidence of oral clefts when compared with historical rates of 6.3% (91322). Although there is speculation that genetic markers of folate status impact the effect of folic acid on orofacial cleft incidence, the current data do not show a relationship (104921).

Overall mortality. It is unclear if oral folic acid reduces the risk of overall mortality.
^ Details: Observational research in US adults has found that dietary intake of folic acid in the highest quintile is associated with a 14% to 23% lower risk of all-cause mortality and a 41% to 47% lower risk of cardiovascular mortality when compared with the lowest quintile of dietary folic acid intake (110451).

Pancreatic cancer. It is unclear if oral folic acid reduces pancreatic cancer risk.
^ Details: Consuming greater than 280 mcg daily of dietary folate is associated with a decreased risk of exocrine pancreatic cancer (9327). A meta-analysis of case-control and cohort studies suggests that consuming higher amounts of dietary folate reduces the risk of pancreatic cancer by 51% compared to low levels of dietary folate (50208). However, another meta-analysis of prospective cohort studies suggests that folate/folic acid intake does not significantly affect the overall risk of pancreatic cancer (50499). The contradictory results may be associated with the form of intake or may be related to the gender of the participants. A meta-analysis of clinical research shows that dietary folate, but not folic acid, significantly reduces the risk of pancreatic cancer (50387). Also, one meta-analysis of observational studies has found that high dietary folate decreases the risk of pancreatic cancer in females, but not males (50387).

Peripheral neuropathy. Oral folic acid has only been evaluated in combination with other ingredients; its effect when used alone is unclear.
^ Details: Preliminary clinical research shows taking a combination of folic acid 400 mcg, vitamin B12 3 mcg, and uridine monophosphate 50 mg daily (Keltican) for 60 days reduces pain associated with peripheral neuropathy. Use of this product reduces pain intensity by approximately 44%, with loss of burning pain in approximately 50% of patients, strong tingling or pricking in approximately 57% of patients, strong pain attacks in 92% of patients, and numbness in 90% of patients when compared with baseline. Radiating pain and the use of concomitant medications are also reduced (90384). The validity of this

finding is limited by the lack of a comparator group. Furthermore, it is unclear if the benefits are due to folic acid, other ingredients, or the combination.

Pharyngeal cancer. It is unclear if oral folic acid reduces pharyngeal cancer risk.
^ Details: Population research has found that intake of folic acid and folate from natural, fortified, and supplemented sources, may protect against oropharyngeal cancer. Intake of at least 258-816 mcg total folate/folic acid reduces the odds by 35% when compared with intakes of less than 344 mcg. Furthermore, folate/folic acid may be more beneficial for oral cancer versus pharyngeal cancer and in heavy alcohol users versus non users or light users (91302).

Polycystic ovary syndrome (PCOS). It is unclear if oral folic acid is beneficial for PCOS.
^ Details: One clinical study in overweight or obese patients with PCOS shows that taking folate 1 mg or 5 mg daily for 8 weeks modestly reduces levels of homocysteine, as well as insulin resistance, when compared with placebo. However, only the 5 mg dose modestly reduces insulin, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels. Neither dose appears to affect fasting plasma glucose, high-density lipoprotein (HDL) cholesterol, or triglyceride levels when compared with placebo (109200). Other clinical research in patients with PCOS taking metformin shows that taking folate 400 mcg daily for 6 months does not affect glycemic parameters, plasma lipid levels, or hormone levels when compared with placebo (109194). The reasons for discrepancies between studies are unclear but may relate to patient characteristics. One study included only overweight or obese individuals with at least two of the three PCOS criteria, whereas the other study limited enrollment to patients in any weight category but with all three PCOS criteria (109194,109200).

Pregnancy-induced hypertension. It is unclear if oral folic acid reduces the risk of hypertension during pregnancy.
^ Details: Population research has found that taking folic acid during pregnancy is not associated with a reduced risk of gestational hypertension (91308,99370,99372).

Restless legs syndrome (RLS). Although there is interest in using oral folic acid for RLS, there is insufficient reliable information about the clinical effects of folic acid for this condition.

Schizophrenia. Oral folic acid 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 folic acid 2 mg and vitamin B12 400 mcg 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 folic acid 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).

Suicidal ideation. It is unclear if oral folic acid reduces the risk of suicidal ideation or suicide attempts.
^ Details: One observational study has evaluated the association between folic acid supplementation and suicidal events in patients with various underlying conditions, including 12% with depression, 15% with anxiety, and 46% with pain. This within-person cohort study found that filling a prescription for folic acid 0.4-5 mg daily, either alone or as part of a multivitamin, is associated with a 44% reduced rate of suicidal events during the months after the prescription when compared with the months without the prescription. For the 48% of patients who received folic acid 1 mg daily, each additional month of taking the prescription was associated with a 5% decrease in suicidal events (109201). Prospective clinical research is needed to confirm any benefits of folic acid and to determine whether baseline folate deficiency plays a role in these outcomes.

More evidence is needed to rate folic acid for these uses.

Dosing & Administration

- **Adult**

  Oral:

  General: The recommended dietary allowances (RDAs) for folate are expressed in Dietary Folate Equivalents (DFE). DFEs reflect the difference in bioavailability between supplemental folic acid and folate found in foods. Folic acid is estimated to be 85% bioavailable. Dietary folate, however, is only 50% bioavailable. Thus, 1 mcg DFE is equivalent to 1 mcg dietary folate or 0.6 mcg folic acid.

  The daily RDA for adults is 400 mcg DFE. In pregnancy, the RDA is 600 mcg DFE; in lactation, the RDA is 500 mcg DFE (6243). See Effectiveness section for condition-specific information.

  Absorption of supplemental folic acid is reduced by about 15% when taken with food (6241,6243). This reduction may not be clinically significant.

  All other ROAs:

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

- **Children**

  Oral:

  General: The daily adequate intakes (AI) for infants are 65 mcg DFE for 0-6 months of age and 80 mcg DFE for 7-12 months of age (6243). The daily recommended dietary allowances (RDAs) for folate are: 1-3 years, 150 mcg DFE; 4-8 years, 200 mcg DFE; 9-13 years, 300 mcg DFE; 14-18 years, 400 mcg DFE. For pregnancy, 600 mcg DFE; for lactation, 500 mcg DFE (6243). See Effectiveness section for condition-specific information.

- **Standardization & Formulation**

  Supplements typically contain synthetic folic acid (96155). However, some products contain reduced folate formulations such as L-5-methyltetrahydrofolate (L-5-MTHF), also known as [6S]-5-MTHF (104912,104913,104916).

Interactions with Drugs

5-FLUOROURACIL
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**
Theoretically, high doses of folic acid might increase the toxicity of 5-fluorouracil.
Details
Increases in gastrointestinal side effects of 5-fluorouracil, such as stomatitis and diarrhea, have been described in two clinical studies when leucovorin, a form of folic acid, was administered with 5-fluorouracil (16845).

CAPECITABINE (Xeloda)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**
Use of high-dose folic acid might contribute to capecitabine toxicity.
Details
Clinical research suggests that higher serum folate levels are associated with an increased risk for moderate or severe toxicity during capecitabine-based treatment for colorectal cancer (105402). Additionally, in one case report, taking folic acid 15 mg daily might have contributed to increased toxicity, including severe diarrhea, vomiting, edema, hand-foot syndrome, and eventually death, in a patient prescribed capecitabine (16837).

METHOTREXATE (Trexall, others)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**
Folic acid might reduce the efficacy of methotrexate as a cancer treatment when given concurrently.
Details
Methotrexate exerts its cytotoxic effects by preventing conversion of folic acid to the active form needed by cells. There is some evidence that folic acid supplements reduce the efficacy of methotrexate in the treatment of acute lymphoblastic leukemia, and theoretically they could reduce its efficacy in the treatment of other cancers (9420). Advise cancer patients to consult their oncologist before using folic acid supplements. In patients treated with long-term, low-dose methotrexate for rheumatoid arthritis (RA) or psoriasis, folic acid supplements can reduce the incidence of side effects, without reducing efficacy (768,2162,4492,4493,4494,4546,9369).

PHENOBARBITAL (Luminal)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**
Folic acid might have antagonistic effects on phenobarbital and increase the risk for seizures.
Details
Folic acid can have direct convulsant activity in some people, reversing the effects of phenobarbital and worsening seizure control (4427,9357,9358). Monitor closely for increased seizure activity.

PHENYTOIN (Dilantin)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**
Folic acid might reduce serum levels of phenytoin in some patients.
Details
Folic acid may be a cofactor in phenytoin metabolism (4471). Folic acid, in doses of 1 mg daily or more, can reduce serum levels of phenytoin in some patients (4471,4477,4531,4536). Increases in seizure frequency have been reported. If folic acid supplements are added to established phenytoin therapy, monitor serum phenytoin levels closely. If phenytoin and folic acid are started at the same time and continued together, adverse changes in phenytoin pharmacokinetics are avoided (4471,4472,4473,4531). Note that phenytoin also reduces serum folate levels.

PRIMIDONE (Mysoline)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**
Folic acid might have antagonistic effects on primidone and increase the risk for seizures.
Details
Folic acid can have direct convulsant activity in some people, reversing the effects of primidone and worsening seizure control (4427,9357,9358). Monitor closely for increased seizure activity. Note that primidone also reduces serum folate levels.

PYRIMETHAMINE (Daraprim)
Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**
Folic acid might antagonize the effects of pyrimethamine.
Details
Folic acid can antagonize the antiparasitic effects of pyrimethamine against toxoplasmosis and Pneumocystis carinii pneumonia. Folic acid doesn't antagonize the effects of pyrimethamine in the treatment of malaria, because malarial parasites cannot use exogenous folic acid. Use folinic acid as an alternative to folic acid when indicated (9380).

Interactions with Supplements

GREEN TEA: Theoretically, green tea might decrease the activity of folic acid.
Details

In vitro, the green tea constituent, epigallocatechin gallate (EGCG), appears to inhibit the activity of the enzyme dihydrofolate reductase (15012). Dihydrofolate reductase is responsible for converting folic acid to its active form, tetrahydrofolate. In pregnancy, consuming more than 57 mL green tea per 100 kcal decreases circulating folate levels (91314). Theoretically, green tea could lead to functional folic acid deficiency.

ZINC: Theoretically, folic acid might reduce the absorption of zinc.
Details
There is concern that folic acid might reduce the absorption of zinc. However, evidence on the effects of supplemental folic acid on dietary zinc absorption is conflicting (9389,9390,9391,9392,9393,9421). Of note, normal supplemental doses of folic acid are unlikely to have an adverse effect on zinc balance in people with adequate dietary zinc intake (7135,9391).

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).

CANCER

There is some concern that folic acid might increase the risk of certain cancers. Preliminary clinical research suggests folic acid in doses of 0.8-1 mg daily might increase the risk of cancer, possibly by increasing cell growth. However, other research has shown no effect. Until more is known, avoid folic acid in doses higher than the RDA in people with a history of cancer (12150,13482,16822).

SEIZURE DISORDERS

High supplemental doses of folic acid might exacerbate seizures in people with seizure disorders. Doses less than 1 mg have rarely been associated with increased seizure activity (9901).

VITAMIN B12 DEFICIENCY

There is some concern that folic acid can improve hematologic signs of megaloblastic anemia, without resolving the underlying cause, thereby masking vitamin B12 deficiency. This may allow potentially irreversible neurological damage to progress in patients with vitamin B12 deficiency (2677,3092,5646,9411,20504,20505).

Interactions with Lab Tests

None known.

Nutrient Depletion

SOME DRUGS CAN AFFECT FOLIC ACID LEVELS:

ALCOHOL (Ethanol)
Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.
Theoretically, alcohol might reduce serum folate levels and increase the risk of folate deficiency.
Details

Animal research and clinical evidence suggests that alcohol use decreases the intestinal absorption of folic acid by inhibiting the expression of the reduced folate carrier (50038). For information on foods that are rich in folate, see our **chart**.

AMINOSALICYLIC ACID
Depletion Rating = **Moderate Depletion** Monitor for depletion; a supplement is needed in some patients.
Aminosalicylic acid might reduce serum folate levels and increase the risk of folate deficiency.
Details

Aminosalicylic acid can reduce dietary folate absorption, worsening folate deficiency often seen with active tuberculosis, or preventing reversal during treatment (9363,9388,9395,9396,9397). Megaloblastic anemia occurs rarely, and usually with other contributing factors such as concurrent vitamin B12 malabsorption (4559). Advise patients being treated for tuberculosis to take folic acid supplements if their dietary folate intake is low. For information on foods that are rich in folate, see our **chart**.

ANTACIDS
Depletion Rating = **Insignificant Depletion** A supplement is not needed for most patients.
Theoretically, antacids might reduce folate absorption; however, this is not likely to be clinically significant.
Details

Folic acid absorption in the small intestine is optimal at a pH of 5.5-6 (8441). Chronic use of large doses of antacids can reduce folic acid absorption, but this is likely only significant if dietary folate intake is very low (2677,8441). Advise patients to maintain the recommended daily intake of folic acid in their diet. For information on foods that are rich in folate, see our **chart**.

ANTIBIOTIC DRUGS

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

Theoretically, antibiotics might reduce folate absorption; however, this is not likely to be clinically significant.

Details

Antibiotic therapy can disrupt the normal gastrointestinal (GI) flora, interfering with enterohepatic recirculation (reabsorption) of folic acid (4436). The normal GI flora also synthesizes and consumes folic acid, which may also be disrupted by antibiotics (2677,4437,6243). Folic acid synthesized by GI bacteria can be absorbed in the large intestine, but the amount synthesized and absorbed is variable (4437,6243). For instance, it can depend on dietary fiber intake and gastric pH; hypochlorhydria causes bacterial overgrowth and increased folate synthesis (4437,9364). In most people it's unlikely that a course of antibiotics will reduce folic acid levels significantly, and therefore supplements are unnecessary. For information on foods that are rich in folate, see our **chart**.

ASPIRIN

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

Aspirin might affect folate protein binding and affect folate excretion; however, this is not likely to be clinically significant.

Details

Aspirin may decrease serum folate levels by reducing binding to plasma proteins, especially when large doses are taken regularly (e.g., for treatment of rheumatoid arthritis). But there doesn't seem to be an increase in urinary folate losses and red blood cell levels remain normal (9351,9360). This suggests folate is being redistributed in the body and deficiency isn't likely. For information on foods that are rich in folate, see our **chart**.

CARBAMAZEPINE (Tegretol)

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

Carbamazepine might reduce serum folate levels and increase the risk of folate deficiency.

Details

Carbamazepine can reduce serum folate levels, but megaloblastic anemia has not been reported (4426,4427,4428,4429,9359). Reduced folate levels might contribute to mild, asymptomatic reductions in nerve conduction velocities, and mental changes seen with carbamazepine (4427,4429). Possible mechanisms include reduced folic acid absorption and increased metabolism by induced hepatic enzymes (4426,4428,4429). Pregnant patients taking carbamazepine may be especially at risk from reduced folate levels, as low folate levels during pregnancy may contribute to birth defects and pregnancy loss (9355,9356). However, folic acid supplements have worsened seizure control in some people with epilepsy (4427). Advise patients taking carbamazepine chronically to consult their physician before starting folic acid supplements. For information on foods that are rich in folate, see our **chart**.

CHOLESTYRAMINE (Questran)

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

Cholestyramine might interfere with folic acid absorption and reduce serum folate levels.

Details

Cholestyramine reduces folic acid absorption. It can lower serum and red blood cell folate levels in children taking large doses (0.2 to 1.1 grams/kg/day) for several months (4455). There aren't any reports of deficiency in adults. Encourage patients to maintain a good dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

COLESTIPOL (Colestid)

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

Colestipol might interfere with folic acid absorption and reduce serum folate levels.

Details

Colestipol can interfere with absorption of folic acid, and reduce serum folate levels (4461). Encourage patients to maintain good dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

CYCLOSERINE (Seromycin)

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

Cycloserine might reduce serum folate levels and increase the risk of folate deficiency.

Details

Cycloserine can reduce serum folate levels; rare cases of megaloblastic anemia have occurred (4531,4536,9363). The mechanism is uncertain, but may involve changes to the absorption and metabolism of folate (4531,4536). Advise patients receiving long-term treatment to maintain a good dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

DIURETIC DRUGS

Depletion Rating = **Insufficient Evidence to Rate** Clinical significance is not known.

Diuretics might increase folate excretion; however, the clinical significance of this is unclear.

Details

Limited data suggests diuretics may increase excretion of folic acid. Reduced red blood cell folate levels, possibly contributing to increased homocysteine levels, were found in one group of people taking diuretics for six months or longer (1898). The need for folic acid supplementation during diuretic therapy hasn't been adequately studied. Advise patients to maintain a good dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

ESTROGENS

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

Estrogens might reduce serum folate levels and increase the risk of folate deficiency.

Details

Reduced serum and red blood cell folate levels can occur with the use of conjugated estrogens (Premarin) or oral contraceptives, although this is unlikely with adequate dietary folate intake (4459,4498,7843,7844,9371,9373). There are rare reports of megaloblastic anemia associated with oral contraceptive use, usually in patients with other conditions contributing to folate deficiency (9371,9372). Possible mechanisms by which estrogens contribute to folate deficiency include reduced absorption of dietary folate, increased excretion, induction of liver enzymes, and increased protein binding of folate in serum (4459,9371). There is some evidence that oral contraceptives can increase the rate of progression of cervical dysplasia to cervical cancer, and that folic acid can slow or reverse this dysplasia (9352,9370). Advise patients taking oral contraceptives or other estrogens to maintain a good dietary intake of folate. Recommend supplements only for those with inadequate dietary intake or other conditions that contribute to folate deficiency (4459,9371,9373), and for those diagnosed with, or at increased risk for, cervical dysplasia. For information on foods that are rich in folate, see our **chart**.

H2 BLOCKERS

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

Theoretically, H2 blockers might reduce folate absorption; however, this is not likely to be clinically significant.

Details

Folic acid absorption from the small intestine is optimal at a pH of 5.5-6 (8441). The increased pH associated with use of H2 blockers may therefore reduce folic acid absorption, but this is probably only significant if dietary folate intake is very low (4483,8441). Advise patients to maintain the recommended daily dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

METFORMIN (Glucophage)

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

Metformin might reduce serum folate levels and increase the risk of folate deficiency.

Details

Reduced levels of vitamin B12 and, to a lesser extent, folic acid occur in some people with diabetes and can contribute to hyperhomocysteinemia, adding to their already increased risk of cardiovascular disease (32,4490,9366,9367). The reduced folate levels seen in people with diabetes have been linked to metformin use in some cases, possibly as a result of reduced folic acid absorption (32,9367,9368). Symptomatic folate deficiency is unlikely to occur with metformin, but people with diabetes may need folic acid supplements to reduce hyperhomocysteinemia (9367). For information on foods that are rich in folate, see our **chart**.

METHOTREXATE (Trexall, others)

Depletion Rating = **Major Depletion** A supplement is needed for most patients.

Methotrexate reduces serum folate levels and increases the risk of folate deficiency.

Details

Methotrexate is a folate antagonist which prevents conversion of folic acid to its active form, and lowers plasma and red blood cell folate levels (4492,4493,4494,4546). In patients treated with long-term, low-dose methotrexate for rheumatoid arthritis (RA) or psoriasis, the development of folate deficiency is associated with increased risk of certain side effects. These include gastrointestinal effects, stomatitis, alopecia, abnormal liver function tests, myelosuppression, megaloblastic anemia, and increased homocysteine levels (768,4492,4493,4494,4546). Folic acid 0.8-5 mg daily reduces these side effects without reducing the efficacy of methotrexate (768,2162,4492,4493,4494,9369,9418,102388). Advise patients taking methotrexate for these conditions to take a folic acid supplement, especially if their dietary folate intake is low and they are experiencing the side effects described (4494,4546,9369,9419). It's likely that people who have experienced side effects will need to continue taking folic acid for the duration of methotrexate therapy (9418). Advise patients being treated with methotrexate for cancer to avoid folic acid supplements, unless recommended by their oncologist. Folic acid could interfere with the anticancer effects of methotrexate (9420).

METHYLPREDNISOLONE

Depletion Rating = **Insufficient Evidence to Rate** Clinical significance is not known.

It is unclear if methylprednisolone can reduce serum folate levels.

Details

Reduced serum folate levels were noted in people with multiple sclerosis (MS) after treatment with methylprednisolone sodium succinate 1 gram daily for 10 days. The clinical significance of this change isn't known (9362). For information on foods that are rich in folate, see our **chart**.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Depletion Rating = **Insufficient Evidence to Rate** Clinical significance is not known.

It is unclear if NSAIDs can reduce serum folate levels.

Details

Folate-dependent enzymes are inhibited in vitro by NSAIDs with carboxylic acid-containing side chains (2677,9361). The clinical significance of this inhibition is unknown. For information on foods that are rich in folate, see our **chart**.

PANCREATIC ENZYMES

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

Pancreatic enzymes can reduce serum folate levels and increase the risk of folate deficiency.

Details

Reduced folate levels can occur in some people taking pancreatic enzymes. This may be due to reduced absorption, since folate can form insoluble complexes with pancreatic enzymes (9374). Advise patients to have their folate levels checked if they take pancreatic enzymes for prolonged periods, and to take a supplement if the level is low. For information on foods that are rich in folate, see our **chart**.

PENTAMIDINE (NebuPent)

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

Pentamidine can reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Pentamidine is a weak folate antagonist which prevents conversion of folic acid to its active form, although this isn't thought to contribute significantly to its antiprotozoal activity (9378). Decreased serum folate levels and megaloblastic bone marrow changes can occur rarely with prolonged parenteral pentamidine therapy (9378). Most patients are unlikely to need folic acid supplements. For information on foods that are rich in folate, see our **chart**.

PHENOBARBITAL (Luminal)

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

Phenobarbital can reduce serum folate levels and increase the risk of folate deficiency.

^ Details

In people with low dietary folate intake, phenobarbital might reduce serum folate levels leading to megaloblastic anemia, and possibly contributing to neurological side effects, mental changes, and cerebral atrophy (4427,4530,4536,9333,9357,9358,9359). Possible mechanisms include reduced folic acid absorption, increased metabolism, increased demand for folic acid as a coenzyme for induced hepatic enzymes, or competitive interaction between folate coenzymes and phenobarbital (9357). Pregnant patients taking phenobarbital may be especially at risk for reduced folate levels, as low folate levels during pregnancy may contribute to birth defects and pregnancy loss (9354,9355,9356). Folic acid therapy seems to reverse these neurological effects (9333). However, folic acid can worsen seizure control. Advise patients taking phenobarbital to consult their physician before taking folic acid supplements. For information on foods that are rich in folate, see our **chart**.

PHENYTOIN (Dilantin)

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

Phenytoin can reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Phenytoin can reduce serum folate levels, occasionally leading to megaloblastic anemia, and possibly contributing to neurological side effects and mental changes (4427,4536,9357,9358,9359,107146). Population research has found that taking phenytoin for over two years is associated with a reduction in folate levels and an approximately 6-fold increase in risk for folate deficiency when compared with taking phenytoin for less than one year (107146). Possible mechanisms include reduced folic acid absorption, increased metabolism, increased demand for folic acid as a coenzyme for induced hepatic enzymes, or competitive interaction between folate coenzymes and phenytoin (9357). Folic acid supplements may reduce phenytoin side effects (4471,4477). Pregnant patients taking phenytoin may be especially at risk from reduced folate levels, as low folate levels during pregnancy may contribute to birth defects and pregnancy loss (9354,9355,9356). However, folic acid can reduce phenytoin serum levels and increase seizure frequency. Advise patients taking phenytoin chronically to consult their physician before taking folic acid supplements. For information on foods that are rich in folate, see our **chart**.

PRIMIDONE (Mysoline)

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

Primidone can reduce serum folate levels and increase the risk of folate deficiency.

^ Details

In people with low dietary folate intake, primidone might further decrease serum folate levels and might lead to megaloblastic anemia, possibly contributing to neurological side effects, mental changes, and cerebral atrophy (4427,4530,4536,9333,9357,9358,9359). Possible mechanisms include reduced folic acid absorption, increased metabolism, or increased demand for folic acid as a coenzyme for induced hepatic enzymes (9357). Pregnant individual taking primidone may be especially at risk for reduced folate levels, as low folate levels during pregnancy may contribute to birth defects and pregnancy loss (9354,9355,9356). Folic acid therapy seems to reverse these neurological effects (9333). However, folic acid can worsen seizure control. Advise patients taking primidone to consult their physician before taking folic acid supplements. For information on foods that are rich in folate, see our **chart**.

PROTON PUMP INHIBITORS (PPIs)

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

Theoretically, PPIs might reduce folate absorption; however, folate deficiency has not been reported.

^ Details

Folic acid absorption in the small intestine is optimal at a pH of 5.5-6 (8441). The increased pH associated with use of PPIs could theoretically reduce folic acid absorption (8441), but preliminary data suggests use of PPIs for several years doesn't cause folate deficiency (4483). Advise patients to maintain the recommended dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

PYRIMETHAMINE (Daraprim)

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

Pyrimethamine can reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Pyrimethamine is a folate antagonist that prevents conversion of folic acid to its active form (4425,4532). At high doses, 50-75 mg daily, megaloblastic anemia may occur due to deficiency of active folate, and it's recommended that all patients receive folinic acid (leucovorin calcium, an active form of folic acid) (4532). Folinic acid doesn't antagonize the therapeutic effect of pyrimethamine because Toxoplasma does not have a membrane transport system for exogenous folinic acid (9380). Advise patients to avoid other forms of folic acid since they can antagonize the therapeutic effect of pyrimethamine against Toxoplasma and Pneumocystis carinii. Advise patients taking lower doses of pyrimethamine for prolonged periods to maintain the recommended dietary folate intake. Monitor for folate deficiency. For information on foods that are rich in folate, see our **chart**.

RETINOIDS

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

Retinoids reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Isotretinoin (Accutane), a retinoid vitamin A derivative, reduces serum levels of folic acid in patients with acne (91305). Advise patients taking isotretinoin to maintain the recommended dietary intake of folic acid. For information on foods that are rich in folate, see our **chart**.

SULFASALAZINE (Azulfidine)

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

Sulfasalazine can reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Sulfasalazine competitively inhibits absorption of folic acid in the intestine (2677,4515,4560,9353). It also interferes with the breakdown of dietary folate to its absorbable form, and can cause hemolysis, which increases folate requirements for formation of new red blood cells (4515,4560). Long-term sulfasalazine therapy can cause reduced serum and red blood cell folate levels and hyperhomocysteinemia (4515,9377). Occasionally, megaloblastic anemia develops, usually with high doses of sulfasalazine (>2 grams/day), and when there are other factors contributing to folate deficiency (4515,4516,4517,4536,9376,9377). Reduced folate levels might contribute to the increased risk of colon cancer and colonic mucosal dysplasia seen in people with ulcerative colitis (9379). Advise patients on chronic sulfasalazine therapy to increase their dietary folate intake, and to take a supplement if they have any other condition which could also contribute to deficiency (2677,9353,9379). For information on foods that are rich in folate, see our **chart**.

TRIAMTERENE (Dyrenium)

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

Triamterene might reduce folate absorption and increase the risk of folate deficiency.

^ Details

Triamterene is a folate antagonist that prevents conversion of folic acid to its active form, and also reduces folate absorption (4425,4536,4537,9375). Reduced serum and red blood cell folate and occasional cases of megaloblastic anemia have occurred, usually in people with other conditions contributing to folate deficiency (4537,9375). Advise patients on chronic triamterene therapy to maintain the recommended dietary folate intake, or to take a supplement if this is not possible. For information on foods that are rich in folate, see our **chart**.

TRIMETHOPRIM (Trimpex)

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

Trimethoprim might reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Trimethoprim, alone or combined with sulfamethoxazole (TMP/SMX, Bactrim, Septra), inhibits the enzyme involved in the conversion of folic acid to its active form (4468,4531). The bacterial and protozoal enzymes are 1,000-10,000 times more sensitive to trimethoprim than human enzymes (2677,4468,9382). Therefore, while low doses of trimethoprim (10 mg/kg daily) don't seem to reduce folate levels (9381,9383,9394), high doses of trimethoprim (20 mg/kg daily for 2-4 weeks or 500 mg daily for several months) might precipitate megaloblastic anemia, especially in those with other risk factors (4468,9382,9383,9384,9394). If megaloblastic anemia occurs, trimethoprim should be stopped and treatment with folinic acid (an active form of folic acid) should be initiated (9382). There is no consensus on the use of prophylactic folinic acid to prevent megaloblastic anemia with trimethoprim use. The practice may not be effective, especially in people with AIDS in whom immunologic reactions, as well as folate deficiency, probably contribute to hematologic changes (9385,9386,9398). There is a general belief that supplements don't interfere with the therapeutic effects of trimethoprim, because infecting organisms can't utilize exogenous folate sources (2677,9382,9384). However, this view has been challenged (4468,9386), and failure of trimethoprim therapy has occurred rarely when folinic acid is given concurrently (9387,9399). Advise patients taking low doses of trimethoprim (100-200 mg daily) for treatment or prophylaxis of urinary tract infections that they are unlikely to need folate supplements. Advise patients taking high doses of trimethoprim (20 mg/kg daily) to maintain good dietary folate intake, but to avoid folate supplements unless prescribed by their physician. For information on foods that are rich in folate, see our **chart**.

VALPROATE

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

Valproate might reduce serum folate levels and increase the risk of folate deficiency.

^ Details

Valproate may reduce folate levels in some people, but symptomatic deficiency has not been reported (4428,9356,9359). Pregnant patients taking valproate may be especially at risk from reduced folate levels, as low folate levels during pregnancy may contribute to birth defects and pregnancy loss (9355,9356). However, most research suggests that taking folic acid 1-5 mg daily perinatally with valproate does not reduce the rate of fetal malformations (104919). Furthermore, folic acid supplements

have worsened seizure control in some people with epilepsy (4427). Advise patients taking valproate chronically to consult their physician before taking folic acid supplements. For information on foods that are rich in folate, see our chart.

Overdose

There is insufficient reliable information available about the presentation or treatment of overdose with folic acid.

Commercial Products Containing: Folic Acid

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: Folate in food is about 20% to 50% less bioavailable than synthetic folic acid, which is almost 100% bioavailable. Before folate from food can be absorbed, the polyglutamate side chain must undergo enzymatic deconjugation in the small intestine to form the absorbable monoglutamate form (6241,9300,50227). Folate deconjugation occurs maximally at a pH of 6-7 (6241,9300). Folate levels in the blood increase approximately 30 minutes following consumption in foods and levels remain elevated for up to 5 hours with no difference in the area under the curve (AUC) for monoglutamyl vs. polyglutamyl folates (50187). The bioavailability of polyglutamyl forms of folic acid appears to be approximately 50% to 78% of monoglutamyl folic acid (50084,50099,50217).

Some vitamin manufacturers claim that supplements containing L-methylfolate are better than folic acid-containing supplements. There is some evidence that L-methylfolate is slightly more bioavailable than folic acid. However, with continuing use of the supplements there is no difference in blood levels. Some manufacturers claim that L-methylfolate is a better alternative to folic acid because some people lack the enzymes to convert folic acid to L-methylfolate. But so far, there is no reliable evidence that this makes a meaningful difference. For example, equivalent doses of folic acid and L-methylfolate raise folate levels in pregnant women equally well (17321,17322,17323).

There is also interest in the reduced form of synthetic folate, L-5-methyltetra-hydrofolate (L-5-MTHF), which is dependent on vitamin B12 for metabolism. A single dose of L-5-MTHF seems to result in faster and greater absorption when compared with folic acid, both in those with the homozygous (TT) MTHFR and the wild-type (CC) MTHFR genotypes (104916). During longer supplementation periods of up to 16 weeks, this increased bioavailability seems to be less pronounced but maintained. Two small clinical studies in females show that taking L-5-MTHF (Metafolin, Eprova) 1.3 mg or L-5-MTHF 416 mcg daily for 12-16 weeks resulted in slightly higher folate concentration in red blood cells when compared with taking the molar equivalent of folate 1 mg or 400 mcg daily for 12-16 weeks (104912,104913).

Distribution: In patients with coronary artery disease, plasma 5-methyltetrahydrofolate increases proportionately with treatment dose of folic acid, whereas vascular tissue 5-methyltetrahydrofolate does not (50233).

Metabolism: After folic acid is absorbed, it is reduced to tetrahydrofolate and then enters a methylation cycle (9317). Tetrahydrofolate is then converted to L-methylfolate. In patients with coronary artery disease, plasma 5-methyltetrahydrofolate increases proportionately with treatment dose of folic acid (50233). However, unmetabolized folic acid is also found in both plasma and breast milk when folic acid is consumed (50327,50329).

Excretion: Folic acid is excreted mainly in the urine; however, it is also found in the feces (50306,50625,50657). Folate is also lost during hemodialysis (50002).

Mechanism of Action

General: Folate is the general term that refers to a variety of chemical forms of folic acid. Folic acid, or pteroylmonoglutamic acid, is the form used in vitamin supplements and fortified foods. Folate in food is pteroylpolyglutamate, which has a polyglutamate side chain with peptide linkages (6241). Foods that are naturally high in folate content with 60% to 90% bioavailability include asparagus, mushrooms, yeast, legumes, leafy vegetables such as spinach, broccoli, and lettuce, fruits such as bananas, melons, oranges, tomatoes, and lemons, and animal proteins such as beef liver and kidney (6241,8739,9300,9518). Folate in food is about 40% to 50% less bioavailable than synthetic folic acid, which is almost 100% bioavailable (6241,9300). Although some vitamin manufacturers claim that supplements containing L-methylfolate are better than folic acid-containing supplements, with continuing use of the supplements there is no difference in blood levels and there does not appear to be meaningful differences between the two products, including for neural tube defect reduction (17321,17322,17323).

Folic acid deficiency: In humans, tetrahydrofolate-based coenzymes play a major role in intracellular metabolism. Tetrahydrofolate plays an indirect role in the rate-limiting step of DNA synthesis. Abnormalities in this process that occur with folic acid deficiency can cause megaloblastic anemia. Folic acid reduces damage to DNA and prevents replication errors

(2139,2144). Folic acid deficiency disturbs cell cycling, induces cell apoptosis, and increases the rate of cell death (9329). In the bone marrow, abnormal cellular maturation and division caused by folic acid deficiency leads to the development of abnormal red blood cell precursors, which are known as megaloblasts. Megaloblasts are unable to mature into red blood cells properly and many of them are phagocytosed by macrophages in the bone marrow, which contributes to the development of megaloblastic anemia (9518).

Some patients with chronic fatigue syndrome (CFS) also have decreased folic acid levels (6082,6083), so some people try folic acid supplements for chronic fatigue. Crohn's disease (6269) and venous thrombosis (90398) have also been associated with decreased folate levels.

Alzheimer protective effects: Folic acid might play a role in Alzheimer disease. Preliminary evidence indicates that low folate concentrations might be related to atrophy of the cerebral cortex, particularly in people with neocortical lesions related to Alzheimer disease (6234). Also, homocysteine is thought to be neurotoxic, causing DNA damage and cell apoptosis (9331). Low serum folate levels are strongly correlated with cerebral atrophy on autopsy (6234). Functional and mental deterioration is also sometimes associated with low folate levels and low intake of folate in elderly people (6238,9330). In patients with Alzheimer disease, folic acid may improve the response to cholinesterase inhibitors by reducing homocysteine levels (50246).

Anti-depressive effects: Folic acid deficiency is common among people with depression (10879,10880,10881). Low folate levels have been linked to poor response to antidepressant treatment (6239,10880). In the general population, people with low folate status or lower dietary folate intake have a higher risk for depression (10882,10883). The exact role of folic acid in depression is unknown. It is required for the remethylation of homocysteine to methionine and for s-adenosylmethionine (SAMe) conversion (5232). Folate is also required for the methylation of tetrahydrobiopterin, an essential cofactor for the hydroxylase enzymes involved in the production of neurotransmitters such as serotonin (10884,10885).

Anti-inflammatory effects: Although some individual clinical trials disagree, most clinical research shows that taking folate reduces levels of the inflammatory marker C-reactive protein (CRP). A smaller number of studies suggest that folate does not affect levels of interleukin (IL)-6 or tumor necrosis factor (TNF)-alpha (109195).

Cancer effects: There is evidence in support of a relationship between folate/folic acid levels and both a prevention and a positive association with cancer. Some researchers suggest that folic acid is thought to prevent carcinogenesis. Folate and methionine are important factors in the methylation of DNA. There is evidence that folate deficiency might cause massive misincorporation of uracil into DNA and increased chromosomal breaks (9325,9236,9327,9328). Low red blood cell folate levels have been associated with the development of dysplasia and cancer in ulcerative colitis (2140). Also, there is some preliminary evidence that increased dietary folate intakes may reduce the risk of some specific cancers (9328,16822,50078,50109,50208,50387,50427,50450). However, the role of folic acid supplements in the development or prevention of cancer is unclear. There is some concern that high dose folic acid might increase the risk of cancer. Evidence from population research suggests that taking a folic acid supplement or having high blood levels of folate/folic acid might increase the risk of developing prostate cancer (15607,17041,50411,50497,90393,91316). Other research suggests that there is no association between folate and folic acid intake and the risk of various types of cancers (50411,91312,91316,91317,91321). It is possible that discrepancies are due to the different relationship with dietary folate/folic acid intakes vs. blood levels and cancer risk.

Cardiovascular effects: Folic acid might improve endothelial dysfunction, arterial blood flow, and the coagulation and oxidative status in individuals with high coronary risk and atherosclerotic disease. Improvements in endothelial dysfunction have been shown following an acute myocardial infarction (50509,50229), as well as in patients without cardiovascular disease (50087,50410). There is also preliminary evidence folic acid can decrease concentrations of von Willebrand factor, which is associated with endothelial dysfunction. Folic acid might also decrease fibrinogen concentrations, while increasing plasminogen, antithrombin III, glutathione peroxidase, red cell glutathione, and red cell superoxide dismutase concentrations (9319).

Low folate levels are associated with increased plasma homocysteine levels and hyperhomocysteinemia is a risk factor for coronary, cerebral, and peripheral atherosclerosis; recurrent thromboembolism; deep vein thrombosis; myocardial infarction; and ischemic stroke (1899,3323,9402,9405,9408), However, most analyses of clinical research suggest that folic acid supplementation, alone or in combination with pyridoxine and vitamin B12, does not improve endothelial function or reduce the risk of death or cardiovascular events in people with existing coronary artery disease, cardiovascular disease, chronic kidney disease, or prior stroke despite having a homocysteine-lowering effect (9313,9322,11337,11387,13482,50437,97619) (50512,50527).

Fetal development effects: Folic acid also plays an important role in pregnancy. Low folate levels are associated with recurrent spontaneous pregnancy loss (6237). Folic acid supplementation also prevents neural tube defects in the fetus, but the exact role of folic acid in this process is not completely understood.

Homocysteine-lowering effects: Folic acid is involved in the metabolism of homocysteine. Low folate levels are associated with increased plasma homocysteine levels. Hyperhomocysteinemia is a risk factor for coronary, cerebral, and peripheral atherosclerosis; recurrent thromboembolism; deep vein thrombosis; myocardial infarction; and ischemic stroke (1899,3323,9402,9405,9408). Low serum folate levels (less than 9.9 nmol/L) and low dietary folate intake (less than 211 mcg per day) are also associated with an increased risk for acute coronary events and cardiovascular disease mortality (9311,9312). A 5 micromole increase in plasma homocysteine increases the risk of cerebrovascular disease by 50%, and the risk of coronary heart disease by 60% in men and 80% women (9407,9411). The best predictor of response to folic acid therapy is the baseline homocysteine plasma concentration. The higher the homocysteine level, the better the response is to folic acid therapy. Folic acid has little effect on normal homocysteine levels. Genetic variations in the enzyme 5,10- methylenetetrahydrofolate reductase can influence the effectiveness of folate in reducing homocysteine levels (9219). The mechanisms of the adverse effects of homocysteine isn't fully understood, but might include vascular endothelial cell damage, impaired endothelium dependent vasodilation due to reduced nitric oxide activity, arterial stiffening due to increased oxidation and arterial deposition of low-density lipoproteins (LDL), increased platelet adhesiveness, and activation of the clotting cascade (9310,9403,9408).

Homocysteine is metabolized via two pathways; remethylation or trans-sulfuration. Remethylation of homocysteine to methionine requires folate and vitamin B12 as cofactors (9310,9320,9407). The methyl donor is 5-methyltetrahydrofolate, and the enzymes involved are 5,10-methyltetrahydrofolate reductase (MTHFR), and 5-methyltetrahydrofolate-homocysteine-methyltransferase, which is vitamin B12-dependent (2148,9310). Impairment of this pathway leads to increased fasting homocysteine levels, and can occur in people with folate deficiency, vitamin B12 deficiency, or who are homozygous for the mutations of the gene for MTHFR (TT genotype) (1489,9301,9315). Mutation of the MTHFR gene produces a variant of the

enzyme that is thermolabile, less active, and it impairs the formation of 5-methyltetrahydrofolate (9301,9320). Folic acid supplements increase the activity of this pathway, which lowers homocysteine levels (2146,2148,3886,9301). Trans-sulfuration of homocysteine results in degradation to cystathionine and then to cysteine by the pyridoxine (vitamin B6) dependent enzymes cystathionine-beta-synthase and cystathionine-gamma-synthase (2148,9310,9407). This pathway is primarily active after ingesting a methionine load (animal protein). Deficiencies of pyridoxine or cystathionine-beta-synthase impair this pathway, raising post-methionine load homocysteine levels (1489,2148,9408). Elevation of these levels is a risk factor for cardiovascular disease, independent of elevated fasting homocysteine levels (1489).

Neurologic effects: There is interest in the use of folic acid for improving nerve conduction velocity, a measure of nerve damage and dysfunction. A small clinical study in patients with diabetic neuropathy suggests that taking folic acid 1 mg daily for 16 weeks improves the amplitude of sensory nerve conduction and the amplitude and velocity of motor nerve conduction when compared with placebo, suggesting that folic acid may enhance nerve function in these patients (100949).

Nitrate tolerance effects: Folic acid might prevent nitroglycerin-induced nitrate tolerance and cross tolerance to endothelial nitric oxide. Nitrate tolerance is associated with an increased vascular production of superoxide anions by NADPH oxidase and endothelial nitric oxide synthase. Folic acid is thought to deplete NADPH and decrease the activity of these enzymes (9317).

Classifications

Seizure Threshold-Lowering Agents, 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 3/13/2024. If you have comments or suggestions, please tell the editors.

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