DRUG / NUTRIENT DEPLETION and DRUG / NATURAL SUBSTANCE INTERATIONS

FOR HEALTH PROFESSIONAL USE

Drug / Substance	Micronutrient	Mechanism(s) of Action	Potential Action(s) to Minimize Risk
Alcohol	**Folate**	Chronic alcohol abuse has been associated with folate deficiency due to low dietary intake, decreased intestinal absorption, impaired hepatic uptake, and increased excretion of the vitamin.	Ensure adequate intake of folate through diet and/or a daily multivitamin.
	Riboflavin	Chronic alcohol abuse has been associated with riboflavin deficiency, presumably due to low dietary intake.	Ensure adequate intake of riboflavin through diet and/or a daily multivitamin.
	Thiamin	Chronic alcohol abuse is associated with thiamin deficiency due to low dietary thiamin intake, impaired absorption and utilization of thiamin, and increased excretion of thiamin.	Thiamin supplementation in alcoholics may prevent Wernicke-Korsakoff's syndrome.
	Vitamin A	Chronic alcohol abuse depletes the liver of retinol and increases retinol mobilization to extra-hepatic tissues, although the mechanisms are not understood.	Avoid high doses of vitamin A and **β-carotene** in alcoholics because chronic alcohol abuse increases the risk of retinol-induced hepatotoxicity.
	Vitamin B_6	Low vitamin B_6 status in alcoholics may result from inadequate intake and potentially from altered metabolism, although the mechanisms are not fully understood.	
Alendronate (Binosto; Fosamax): see Bisphosphonates			
Amiloride: see Potassium-sparing diuretics			
Antacids	**Folate**	Use of antacids may slightly impair absorption of synthetic folic acid from supplements due to gastrointestinal pH changes.	Separate folic acid supplementation and drug use by 3 hours.
	Fluoride	Use of aluminum-containing antacids can decrease fluoride absorption.	Separate antacid intake and fluoride supplements by at least 2 hours.
	Iron	Use of antacids increases the pH of gastrointestinal contents, which may lead to reduced iron solubility and decreased intestinal absorption of iron.	Separate antacid intake and iron supplements by at least 2 hours.
	Magnesium	Use of magnesium-containing antacids can result in hypermagnesemia in those with impaired renal function since the mineral is not properly excreted.	This might only occur with long-term antacid use; prudent to monitor magnesium intake and magnesium status in patients with renal insufficiency.
	Manganese	Use of magnesium-containing antacids may decrease absorption of manganese from food or supplements.	Separate antacids and manganese intake by at least 2 hours.
	Phosphate	Use of aluminum-containing antacids may decrease phosphate absorption and cause hypophosphatemia at high doses.	Hypophosphatemia is usually only a concern with excessive antacid use and very low dietary intake of

			phosphorus.
Antibiotics: see Chloramphenicol; Cycloserine; Ethambutol (Myambutol); Isoniazid; Rifampin/Rifampicin (Rifadin); Tetracycline-class antibiotics; Trimethoprim (Primsol); and Quinolone-class antibiotics			
Aspirin	**Vitamin C**	High doses of aspirin may increase urinary excretion of vitamin C; aspirin might also impair vitamin C absorption in the small intestine. Vitamin C may protect against aspirin-induced damage of the gastric mucosa, possibly through inhibition of iNOS expression.	Long-term use of aspirin might impair vitamin C status. Ensure adequate vitamin C intake from diet and/or supplements.
	Vitamin E	High doses of supplemental vitamin E may potentiate the antiplatelet effects of aspirin.	Avoid high-dose vitamin E supplements in those taking aspirin.
Bisphosphonates (alendronate [Binosto, Fosamax], etidronate, ibandronate [Boniva], pamidronate, risedronate [Actonel, Atelvia], zoledronic acid [Reclast])	**Calcium**	Concomitant intake may decrease bisphosphonate absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.
	Iron	Concomitant intake may decrease bisphosphonate absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.
	Magnesium	Concomitant intake may decrease bisphosphonate absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.
	Zinc	Concomitant intake may decrease bisphosphonate and zinc absorption due to complex formation with multivalent cations.	Separate drug and nutrient intake by 2 hours.
Bumetanide (Bumex): see Loop diuretics			
Calcitriol (Rocaltrol) and some vitamin D analogs	**Phosphate**	High doses of calcitriol and some vitamin D analogs may increase intestinal calcium/phosphate absorption and cause hypercalcemia/hyperphosphatemia.	Be aware of a possible interaction in patients with chronic kidney disease.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	**Biotin**	Carbamazepine may competitively inhibit intestinal absorption of biotin, inhibit renal reabsorption of biotin, as well as accelerate biotin catabolism.	Biotin status might be impaired with long-term carbamazepine therapy, although the clinical significance of marginal biotin deficiency is unclear.
	Grapefruit (flavonoids)	The flavonoids in grapefruit inhibit CYP3A4, increasing the bioavailability and risk of toxicity from carbamazepine.	
	Psyllium	When taken at the same time, psyllium may reduce the intestinal absorption of carbamazepine.	Separate taking carbamazepine and psyllium supplements by at least 2 hours.
Chloramphenicol	**Folate**	Chloramphenicol has been documented to induce aplastic anemia in rare cases. Chloramphenicol use might reduce the efficacy of supplemental folic acid by interfering with the hematopoietic response.	Monitor hematological parameters in patients taking chloramphenicol.

	Vitamin B_{12}	Chloramphenicol has been documented to induce aplastic anemia in rare cases. Chloramphenicol can cause bone marrow suppression. The drug may decrease intestinal absorption of food-bound, but not supplemental, vitamin B_{12} and possibly interfere with the efficacy of supplemental vitamin B_{12} to treat anemia.	Monitor vitamin B_{12} status in patients taking chloramphenicol. Multivitamin or single-nutrient vitamin B_{12} supplementation would be needed with long-term drug treatment.
	Iron	Chloramphenicol has been documented to induce aplastic anemia in rare cases. Chloramphenicol can cause bone marrow suppression; the efficacy of supplemental iron to treat anemia may be affected by chloramphenicol use.	Monitor iron status in patients taking chloramphenicol. Use the lowest effective dose (<25-30 mg/kg) or select a different antibiotic.
Chlorothiazide (Diuril, Sodium Diuril): see Thiazide diuretics			
Chlorpromazine (Thorazine)	**Riboflavin**	Chlorpromazine has been shown to inhibit the incorporation of riboflavin into FAD and FMN, as well as increase urinary excretion of riboflavin in the context on inadequate dietary intake of riboflavin.	Available data come from rodent models as human data are lacking. Assess riboflavin status, and if needed, consider a riboflavin-containing supplement. Separate drug from riboflavin supplements by at least 4 hours to minimize interaction.
Chlortetracycline: see Tetracycline-class antibiotics			
Chlorthalidone (Hygroton, Thalitone): see Thiazide diuretics			
Cholestyramine (Prevalite, Questran, Questran Light)	**Folate**	Cholestyramine can bind to folate polyglutamates and decrease absorption of folate from food, thus increasing the risk of folate deficiency.	Folic acid supplementation may help prevent deficiency in patients on long-term cholestyramine therapy. Advise taking folic acid supplements 1 hour before or 4-6 hours following drug intake.
	Vitamin A	Through interfering with fat absorption, cholestyramine might decrease the absorption of vitamin A.	Separate drug and vitamin supplementation by at least 4 hours.
	Vitamin B_{12}	Cholestyramine might decrease intestinal absorption of vitamin B_{12}, perhaps by binding to intrinsic factor, which is needed for ileal vitamin absorption.	The extent of such an interaction is not clear, as a study in children found that long-term administration of cholestyramine did not alter serum cobalamin. Monitor vitamin B_{12} status; measuring methylmalonic acid is the specific indicator of vitamin B_{12} deficiency.
	Vitamin D	Through interfering with bile acids and fat absorption, cholestyramine might decrease the absorption of vitamin D.	Separate drug and vitamin D supplementation by at least 4 hours.
	Vitamin E	Cholestyramine may theoretically decrease the absorption of fat-soluble vitamins, including vitamin E, through interfering with fat absorption.	Separate drug and vitamin E supplementation by at least 4 hours.
	Vitamin K	There have been a few case reports of bleeding in those taking cholestyramine. Through interfering with bile acids and fat absorption, cholestyramine might decrease the absorption of vitamin K.	Long-term administration of cholestyramine to children did not affect prothrombin time. To avoid a potential interaction, separate drug and vitamin

			supplementation by at least 4 hours.
	Minerals	Cholestyramine might impair intestinal absorption of various minerals (e.g., iron, magnesium, zinc); increased urinary excretion of calcium and magnesium has also been documented.	Human data on the effect of cholestyramine on mineral balance are lacking. Multivitamin/mineral supplementation may help ensure adequacy; separating drug and nutrient supplementation by at least 4 hours would prevent any interaction.
	Carotenoids	Cholestyramine may inhibit intestinal absorption of carotenoids.	Separate drug and nutrient supplementation by at least 4 hours.
	Psyllium	Psyllium might enhance the lowering of cholesterol by cholestyramine.	
Cimetidine (Cimetidine Acid Reducer [OTC], Tagamet, Tagamet HB): see Histamine-2 receptor antagonists			
Colchicine (Colcrys, Gloperba, Mitigare)	**Vitamin B_{12}**	Colchicine may decrease the absorption of vitamin B_{12} from food by disrupting normal function of the ileal mucosa.	Prudent to monitor vitamin B_{12} status in patients taking colchicine; methylmalonic acid buildup is the specific indicator of vitamin B_{12} deficiency.
Colestipol (Colestid, Colestid Flavored)	**Folate**	Colestipol may bind to folate polyglutamates and might decease absorption of folate from food, increasing the risk of folate deficiency.	Studies are limited. Folic acid supplementation may help prevent deficiency in patients on long-term colestipol therapy. Advise taking folic acid supplements 1 hour before or 4-6 hours following drug intake.
	Fat-soluble vitamins (vitamins A, D, E, K) and carotenoids	As a bile acid sequestrant, colestipol may interfere with the absorption of fat-soluble vitamins and carotenoids.	Studies are limited and have not shown major effects. Monitor patients on long-term colestipol therapy.
	Iron	Colestipol and iron may form a chelation complex, decreasing intestinal absorption of iron.	Human data are lacking. Separate drug and iron supplements by at least 4 hours.
Cycloserine	**Vitamin B_6**	Cycloserine forms an inactive covalently bound complex with pyridoxal 5'-phosphate and may cause a functional vitamin B_6 deficiency, possibly leading to anemia and peripheral neuropathy.	Vitamin B_6 supplementation (≤50 mg/day) might help prevent deficiency.
Demeclocycline: see Tetracycline-class antibiotics			
Dexlansoprazole (Dexilant): see Proton-pump inhibitors			
Digoxin (Digitek, Digox, Lanoxin, Lanoxin Pediatric)	**Calcium**	High doses of supplemental calcium could increase the occurrence of abnormal heart rhythms in those taking digoxin due to calcium elevations in plasma and cardiomyocytes, influencing heart contractility and frequency.	Consider advising patients to maintain a stable intake of calcium and avoid daily fluctuations in intake. Monitor serum concentrations of calcium in patients taking digoxin.
	Magnesium	Digoxin causes reductions in intracellular magnesium concentrations, as well as increased urinary excretion of	Separate drug and any magnesium supplements by at least 2 hours. Monitor

		the mineral. Magnesium-containing antacids or magnesium supplements may decrease digoxin absorption, which may decrease drug efficacy. Hypomagnesemia may increase the risk for digoxin toxicity through a number of mechanisms, including inhibition of the magnesium-dependent enzyme Na^+/K^+-ATPase and increased activity of the Na^+/Ca^{2+} exchanger, thereby increasing intracellular calcium.	magnesium status in patients taking digoxin.
Diuretics (see Loop diuretics, Potassium-sparing diuretics, Thiazide diuretics)			
Doxorubicin (Adriamycin)	**Riboflavin**	Doxorubicin may inhibit the incorporation of riboflavin into active coenzyme, FAD, due to structural similarities.	Available data come from rodent models; human data are lacking. Separate drug and riboflavin intake by at least 4 hours to avoid any interaction; consider riboflavin supplementation.
Doxycycline (Acticlate, Avidoxy, Doryx, Doryx MPC, Doxy 100, Mondoxyne NL, Morgidox, Oracea, Soloxide, Targadox, Vibramycin): see Tetracycline-class antibiotics			
Eplerenone (Inspra): see Potassium-sparing diuretics			
Eravacycline (Xerava): see Tetracycline-class antibiotics			
Esomeprazole (Esomep-EZS, GoodSense Esomeprazole [OTC], Nexium, Nexium 24HR [OTC], Nexium I.V.): see Proton-pump inhibitors			
Ethacrynic acid (Edecrin, Sodium Edecrin): see Loop diuretics			
Ethambutol (Myambutol)	**Zinc**	Ethambutol chelates zinc, which could prevent its absorption. This might increase the risk of zinc deficiency and associated visual impairments, including optic neuropathy.	Zinc supplementation may be needed, but long-term, excessive zinc supplementation can cause copper deficiency.
	Copper	Ethambutol chelates copper, but the exact MOA that leads to optic neuropathy is not known.	Separate drug and copper supplements by at least 2 hours. Due to the potential for ocular toxicity, it is prudent to closely monitor visual function, including changes in color vision.
Etidronate: see Bisphosphonates			
Famotidine (Acid Controller Max St [OTC], Acid Controller Original Str [OTC], Acid Reducer [OTC], Acid Reducer Maximum Strength [OTC], Famotidine Maximum Strength [OTC], Heartburn Relief [OTC], Heartburn Relief Max St [OTC], Heartburn Relief Max St [OTC], Pepcid, Pepcid AC Maximum Strength [OTC]): see Histamine-2 receptor antagonists			
Fluoroquinolone-class			

antibiotics (see Quinolone-class antibiotics)			
Fluorouracil (5-Fluorouracil)	**Niacin**	Use of 5-fluorouracil increases the reliance on dietary niacin by interfering with the tryptophan-kynurenine-niacin pathway, which converts tryptophan to nicotinamide adenine dinucleotide (NAD).	Oral niacin supplementation has been shown to relieve deficiency symptoms.
	Thiamin	5-Fluorouracil use may lead to thiamin deficiency as the drug inhibits the phosphorylation of thiamin to thiamin diphosphate/thiamin pyrophosphate, a required enzymatic cofactor in glucose and amino acid metabolism.	
Furosemide (Lasix): see Loop diuretics			
Histamine-2 (H_2) receptor antagonists (cimetidine [Cimetidine Acid Reducer [OTC], Tagamet, Tagamet HB], famotidine [Acid Controller Max St [OTC], Acid Controller Original Str [OTC], Acid Reducer [OTC], Acid Reducer Maximum Strength [OTC], Famotidine Maximum Strength [OTC], Heartburn Relief [OTC], Heartburn Relief Max St [OTC], Pepcid, Pepcid AC Maximum Strength [OTC]], nizatidine)	**Vitamin B_{12}**	Use of H_2 receptor antagonists may decrease the absorption of food-bound, but not supplemental, vitamin B_{12} due to decreased gastric acidity (gastric acid is needed to liberate the vitamin from proteins in food). Long-term drug use might result in vitamin B_{12} deficiency.	Monitor vitamin B_{12} status (buildup of methylmalonic acid), and consider vitamin B_{12} supplementation with long-term drug use.
	Calcium	Decreased gastric acidity may impair release of ionized calcium from insoluble calcium salts (calcium carbonate and calcium phosphate), potentially decreasing its absorption in the upper small intestine.	Meet the RDA of calcium from dietary sources. If supplementation is needed, consider the calcium citrate form.
	Iron	Long-term use might decrease absorption of iron and thus decrease iron status, but this interaction may not be clinically significant.	Separate iron supplementation and drug use by at least 2 hours.
HMG-CoA reductase inhibitors (statins; atorvastatin [Lipitor], fluvastatin [Lescol XL], lovastatin [Altoprev], pitavastatin [Livalo, Zypitamag], pravastatin [Pravachol], rosuvastatin [Crestor, Ezallor Sprinkle], simvastatin [FloLipid, Zocor])	**Nicotinic acid**	Some case reports of co-administration of nicotinic acid with an HMG-CoA reductase inhibitor raise concern for an increased risk of myopathy and rhabdomyolysis; the mechanism is not known. Data from clinical trials are largely lacking, and it is not known whether the risk is higher than that associated with HMG-CoA reductase inhibitor monotherapy.	Patients should be aware of possible symptoms of myopathy and rhabdomyolysis and report any symptoms immediately to their healthcare provider.
	Pantethine (metabolite of pantothenic acid)	Concomitant use of pantethine with any cholesterol-lowering drug may have additive effects on blood cholesterol.	
	Grapefruit	Grapefruit consumption inhibits intestinal CYP3A4 and may increase drug bioavailability and thus increase the risk of drug toxicity, especially HMG-CoA reductase inhibitors with low bioavailability (e.g., atorvastatin, lovastatin, and simvastatin).	Eliminate grapefruit from the diet in patients taking certain HMG-CoA reductase inhibitors, e.g., atorvastatin, lovastatin, or simvastatin. Alternatively, consider a statin that is not metabolized by CYP3A4, such as pravastatin or pitavastatin.
	Plant stanols or **plant sterols**	Concomitant use of plant stanols or sterols with any cholesterol-lowering drugs may have additive effects on blood cholesterol.	
Hydrochlorothiazide: see Thiazide diuretics			
Hydroflumethiazide: see Thiazide diuretics			

Ibandronate (Boniva): see Bisphosphonates			
Indapamide: see Thiazide diuretics			
Isoniazid	**Niacin**	Indirect interaction as the drug affects vitamin B_6-dependent enzymes (see Isoniazid and vitamin B_6). Vitamin B_6 is a cofactor for kynureninase in the tryptophan-kynurenine pathway that converts tryptophan to nicotinamide adenine dinucleotide (NAD); inhibition of kynureninase can lead to niacin deficiency.	Niacin supplementation may be needed during long-term isoniazid treatment.
	Vitamin B_6	Isoniazid may cause a functional vitamin B_6 deficiency, leading to peripheral neuropathy, by forming an inactive, covalently bound complex with pyridoxal 5'-phosphate (PLP). The drug has also been shown to inhibit select PLP-dependent enzymes.	Consider vitamin B_6 supplementation in those taking isoniazid to prevent peripheral neuropathy.
	Vitamin K	When taken by pregnant women, isoniazid might increase the risk of vitamin K deficiency and hemorrhagic disease of newborn infants. Only case reports are available; there are no data on MOA.	Report of possible interaction comes from two case reports where isoniazid, rifampicin, and ethambutol were all administered during pregnancy.
Ketoconazole	**Vitamin D**	Ketoconazole inhibits 25-hydroxyvitamin D_3-1α-hydroxylase, including the renal enzyme, and has been found to reduce serum 1α,25-hydroxyvitamin D (calcitriol) concentrations.	Monitor vitamin D status, including $1,25(OH)_2D$ concentrations, in patients taking oral ketoconazole.
Lansoprazole (GoodSense Lansoprazole [OTC], Heartburn Treatment 24 Hour [OTC], Prevacid, Prevacid SoluTab, Prevacid 24HR [OTC]): see Proton-pump inhibitors			
Levodopa with carbidopa (Duopa, Rytary, Sinemet)	**Folate**	Levodopa use may increase blood concentrations of homocysteine: levodopa methylation by catechol O-methyltransferase and S-adenosylmethionine produces S-adenosylhomocysteine, which is converted to homocysteine.	Adequate dietary folate intake and/or folic acid (and other B vitamin) supplementation may help decrease homocysteine concentrations in patients taking levodopa.
	Vitamin B_6	Levodopa can form a covalent complex with pyridoxal 5'-phosphate and limit its bioavailability, creating a functional vitamin B_6 deficiency. High-dose pyridoxine supplementation has been found to decrease the efficacy of levodopa due to acceleration of levodopa-to-dopamine metabolism peripherally, thereby reducing availability of levodopa to the CNS.	Avoid vitamin B_6 supplementation with levodopa monotherapy. Co-administer levodopa with a dopamine decarboxylase inhibitor, such as carbidopa.
	Iron	Levodopa/carbidopa may bind to iron and reduce absorption of both iron and the drug.	Separate drug and iron intake by at least 2 hours.
Levothyroxine (Euthyrox, Levoxyl, Synthroid, Tirosint, Tirosint-SOL, Unithroid)	**Calcium**	Concomitant intake of levothyroxine and calcium supplements may decrease levothyroxine absorption, likely due to the formation of an insoluble complex. This interaction could decrease drug efficacy.	Separate levothyroxine and calcium supplementation by at least 4 hours. Preliminary evidence indicates that liquid levothyroxine might be less affected by concomitant mineral intake

			compared to tablet levothyroxine.
	Iron	Concomitant intake of levothyroxine and ferrous sulfate supplements may decrease the efficacy of levothyroxine, likely due to formation of an insoluble complex.	Separate levothyroxine and iron supplements by at least two hours. Preliminary evidence indicates that liquid levothyroxine might be less affected by concomitant mineral intake compared to tablet levothyroxine.
Lithium (Lithobid)	**Iodide**	Concomitant use of lithium and pharmacological doses of potassium iodide may increase the risk of hypothyroidism due to inhibition of thyroid hormone synthesis (i.e., Wolff-Chaikoff effect).	Monitor thyroid status in patients taking lithium.
	Psyllium	According to a case report, psyllium supplementation may decrease lithium absorption. Psyllium seeds are rich in polysaccharides and may interfere with drug absorption.	Separate taking psyllium supplements and drug by at least 2 hours to avoid any possible interaction.
Loop diuretics (bumetanide [Bumex], ethacrynic acid [Edecrin, Sodium Edecrin]; furosemide [Lasix], torsemide)	**Magnesium**	If taken for an extended period of time, high doses of loop diuretics can interfere with renal reabsorption of magnesium, increase urinary excretion of magnesium, and result in magnesium depletion.	Monitor magnesium status (dietary, serum, and urinary magnesium) in patients on long-term therapy with loop diuretics.
	Potassium	Use of loop diuretics can increase urinary excretion of potassium and may result in hypokalemia.	
	Thiamin	By increasing urinary flow, loop diuretics (especially furosemide) may prevent renal reabsorption of thiamin, thereby increasing urinary excretion of thiamin and increasing risk of thiamin deficiency.	A daily multivitamin containing thiamin may help prevent deficiency.
Lymecycline: see Tetracycline-class antibiotics			
Metformin (Fortamet, Glucophage, Glucophage XR, Glumetza, Riomet, Riomet ER)	**Vitamin B_{12}**	Metformin interferes with ileal absorption of the intrinsic factor-vitamin B_{12} complex.	Monitor vitamin B_{12} status; measuring methylmalonic acid, in blood or urine, is a specific indicator of deficiency.
	Guar gum (Cyamopsis tetragonolobus)	When taken concurrently, guar gum may slow the absorption of metformin and decrease the amount absorbed.	
Methyclothiazide: see Thiazide diuretics			
Methyldopa	**Iron**	Concomitant intake of methyldopa and ferrous sulfate or ferrous gluconate supplements may decrease the efficacy of methyldopa due to decreased intestinal drug absorption. MOA is unknown but postulated to be due to complex formation.	Separate drug and iron supplements by at least 4 hours.
Methotrexate (Otrexup, Rasuvo, RediTrex, Trexall, Xatmep)	**Folate**	Methotrexate inhibits enzymes involved in nucleotide synthesis, including dihydrofolate reductase. Due to its antagonism, methotrexate use can lead to folate deficiency.	Supplementation with folic or folinic acid (leucovorin), which is recommended for patients with rheumatoid arthritis, reduces the antifolate toxicity.
Metolazone: see Thiazide diuretics			

Nitrous oxide	**Vitamin B_{12}**	Nitrous oxide oxidizes and inactivates vitamin B_{12}, thus inhibiting both of the vitamin B_{12}-dependent enzymes, methionine synthetase and L-methylmalonyl-coenzyme A mutase. This can produce many of the clinical features of vitamin B_{12} deficiency, including megaloblastic anemia and neuropathy.	Since nitrous oxide is commonly used for surgery in the elderly, consider ruling out vitamin B_{12} deficiency prior to its use.
Nizatidine: see Histamine-2 receptor antagonists			
Olestra (Olean)	**Fat-soluble vitamins**	Olestra may sequester fat-soluble nutrients and cause impaired absorption of carotenoids and fat-soluble vitamins; vitamins A, D, E, and K may be added to olestra-containing foods for this reason.	The clinical significance of this interaction is not clear.
Omadacyclin (Nuzyra): see Tetracycline-class antibiotics			
Omeprazole (Acid Reducer [OTC], Prilosec, Prilosec OTC [OTC]): see Proton-pump inhibitors			
Orlistat (Alli [OTC], Xenical)	**Fat-soluble vitamins**	Orlistat may decrease the intestinal absorption of carotenoids and fat-soluble vitamins (vitamins A, D, E, and K).	Orlistat and vitamin supplements should be separated by at least 2 hours.
Oxytetracycline: see Tetracycline-class antibiotics			
Pamidronate: see Bisphosphonates			
Pantoprazole (Protonix): see Proton-pump inhibitors			
Penicillamine (Cuprimine, Depen Titratabs)	**Vitamin B_6**	Penicillamine may cause a functional vitamin B_6 deficiency by forming an inactive, thiazolidine complex with pyridoxal 5'-phosphate. This complex formation may also impair penicillamine action.	Supplemental pyridoxine has been used to prevent vitamin B_6 deficiency and may be considered in those with low vitamin B_6 status. Separating drug and supplement intake by at least 2 hours may help minimize the interaction.
	Copper	Penicillamine chelates copper and increases its urinary excretion.	It is generally advised that patients taking penicillamine to reduce copper status (e.g., in Wilson's disease) limit copper intake from food and avoid any copper-containing supplements.
	Iron	Penicillamine chelates iron and increases its excretion. Concomitant intake of penicillamine and iron supplements decreases drug absorption and efficacy. Discontinuation of oral iron supplements while on penicillamine therapy has been associated with glomerulonephritis, presumably due to increased drug absorption and toxicity.	Separate drug and iron supplements by at least 2 hours.
	Magnesium	Magnesium and penicillamine may complex together and prevent intestinal absorption of both magnesium and the drug.	Separate drug and magnesium supplements or magnesium-containing antacids by at least 2 hours. Assess magnesium status

			before high-dose penicillamine.
	Zinc	Penicillamine is a metal chelator, and its use may reduce intestinal absorption of zinc and increase its excretion, increasing risk of zinc deficiency. Use of zinc supplements may decrease the absorption of penicillamine.	Separate drug and zinc supplements by at least 2 hours. Closely monitor patients as zinc supplementation can reduce copper status through inhibiting copper absorption and increasing copper excretion.
Phenytoin (Dilantin, Dilantin Infatabs, Phenytek)	**Folate**	Phenytoin inhibits the intestinal absorption of folate and lowers serum folate concentrations. Supplementation with high-dose folic acid may lead to decreased serum concentrations of phenytoin.	Long-term phenytoin use may decrease folate status. Folic acid supplementation is often recommended when beginning phenytoin. Closely monitor serum concentrations of phenytoin.
	Thiamin	Lower blood concentrations of thiamin have been reported in those taking phenytoin for epilepsy. MOA is not known.	Research is limited. Monitor thiamin status and consider thiamin supplementation if necessary.
	Vitamin B_6	Extremely high dosages of pyridoxine (≥80 mg/day) have been associated with decreased phenytoin concentrations in patients taking multiple anticonvulsants for epilepsy. MOA is not known.	Avoid high doses of pyridoxine.
	Vitamin D	Phenytoin use has resulted in decreased serum concentrations of 25-hydroxyvitamin D, perhaps due to increased metabolism of vitamin D to inactive metabolites in the liver.	Long-term phenytoin use may require vitamin D and calcium supplementation to prevent deleterious effects on bone health.
	Vitamin K	Phenytoin may increase the risk of vitamin K deficiency and hemorrhagic disease of newborn infants when taken by pregnancy women. MOA hypothesized to include induction of fetal hepatic enzymes that increase oxidative degradation of vitamin K.	Hemorrhagic disease of the newborn may be more serious in newborns of women treated with anticonvulsants. Vitamin K is administered to newborns immediately after birth to prevent hemorrhagic disease.
	Piperine (in some curcumin supplements)	Piperine may increase the bioavailability and slow the elimination of phenytoin through interfering with efflux drug transporters and phase I cytochrome P450 enzymes.	Data on an interaction are limited.
Polythiazide (Renese): see Thiazide diuretics			
Potassium-sparing diuretics (amiloride, eplerenone [Inspra], spironolactone [Aldactone, CaroSpir], triamterene [Dyrenium])	**Folate**	Triamterene impairs intestinal absorption of folate and inhibits dihydrofolate reductase, which converts dihydrofolate to the active form of folate, tetrahydrofolate.	Encourage patients on long-term triamterene therapy to consume the RDA for folate through diet and/or supplements. Measuring folate concentrations in red blood cells is a better indicator of folate status than serum folate concentrations.
	Phosphate	If taken with phosphate supplements, potassium-sparing diuretics may result in hyperkalemia.	Be aware of the potential interaction and of supplement intake by patients.
	Zinc	Some, but not all, studies have found that amiloride use decreases urinary excretion of zinc – the effect may depend on drug dosage. One small	Amiloride has been used in combination with thiazide diuretics to mitigate the risk of zinc depletion.

		study found no effect of triamterene on urinary excretion of zinc.	
Proton-pump inhibitors (dexlansoprazole [Dexilant], esomeprazole [Esomep-EZS, GoodSense Esomeprazole [OTC], Nexium, Nexium 24HR Clear Minis [OTC], Nexium 24HR [OTC], Nexium I.V.], lansoprazole [GoodSense Lansoprazole [OTC], Heartburn Treatment 24 Hour [OTC], Prevacid, Prevacid 24HR [OTC], Prevacid SoluTab], omeprazole [Acid Reducer [OTC], Prilosec, Prilosec [OTC]], pantoprazole [Protonix], rabeprazole [Aciphex, AcipHex Sprinkle])	**Vitamin B_{12}**	Use of proton-pump inhibitors may decrease the absorption of food-bound, but not supplemental, vitamin B_{12} due to decreased gastric acidity (gastric acid is needed to liberate the vitamin from proteins in food). Long-term drug use can result in vitamin B_{12} deficiency.	Monitor vitamin B_{12} status (buildup of methylmalonic acid), and consider vitamin B_{12} supplementation with long-term drug use.
	Calcium	Decreased gastric acidity may impair release of ionized calcium from insoluble calcium salts (calcium carbonate and calcium phosphate), potentially decreasing its absorption in the upper small intestine.	Meet the RDA of calcium from dietary sources. If supplementation is needed, consider the calcium citrate form.
	Iron	Long-term use of proton-pump inhibitors might decrease intestinal absorption of iron and iron status, but this interaction may not be clinically significant.	Separate iron supplementation and drug use by at least 2 hours.
	Phosphate	A reduction in stomach acidity may limit efficacy of oral phosphate-binder therapy in patients with kidney failure.	
Pyrimethamine (Daraprim)	**Folate**	Pyrimethamine has been shown to competitively inhibit dihydrofolate reductase. Supplemental folic acid may interfere with the antitoxoplasmic effect of the drug, sulfadoxine/pyrimethamine.	Consider supplemental folinic acid.
Quinolone-class antibiotics (ciprofloxacin [Cipro]; gemifloxacin; levofloxacin; lomefloxacin [Maxaquin]; moxifloxacin; ofloxacin)	**Calcium**	Concomitant administration of calcium supplements and quinolone antibiotics may decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Separate antibiotic dose by 2 hours before or 6 hours after calcium intake from food (including calcium-fortified foods) and supplements, or from calcium-containing drugs (e.g., antacids).
	Iron	Concomitant administration of ferrous sulfate supplements and quinolone antibiotics may decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Separate antibiotic dose by 2 hours before or 6 hours after iron intake from food or supplements.
	Magnesium	Concomitant administration of magnesium supplements and quinolone antibiotics might decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Studies are lacking, but an interaction may occur given the reported interaction with magnesium-containing antacids and ciprofloxacin, although the antacids studied also contained aluminum hydroxide. Prudent to separate antibiotic dose by 2 hours before or 6 hours after magnesium supplements.
	Zinc	Concomitant administration of zinc supplements and quinolone antibiotics might decrease both antibiotic and mineral absorption, presumably due to formation of nonabsorbable chelates in the intestine.	Research is limited. Separating antibiotic dose by 2 hours before or 6 hours after zinc intake from food or supplements would help minimize any interaction.
Rabeprazole (Aciphex, AcipHex Sprinkle): see Proton-pump inhibitors			
Rifampin/Rifampicin	**Vitamin D**	Rifampin may increase the metabolism of vitamin D to inactive metabolites by	Vitamin D supplementation may be needed.

(Rifadin)		induction of liver enzymes, thereby decreasing serum concentrations of 25-hydroxyvitamin D.	
	Vitamin K	When taken by pregnant women, rifampin might increase the risk of vitamin K deficiency and hemorrhagic disease of newborn infants. Only case reports; there are no data on MOA.	Report of possible interaction comes from two case reports where isoniazid, rifampicin, and ethambutol were all administered during pregnancy.
Risedronate (Actonel, Atelvia): see Bisphosphonates			
Sarecycline (Seysara): see Tetracycline-class antibiotics			
Spironolactone (Aldactone, CaroSpir): see Potassium-sparing diuretics			
Sulfasalazine (Azulfidine, Azulfidine EN-tabs)	**Folate**	Sulfasalazine is a folate antagonist that can inhibit the reduced folate carrier and the proton-coupled folate transporter, decreasing intestinal absorption of folate.	Monitor folate status and consider supplemental folic acid if needed. Separating drug and folate intake may help prevent an interaction.
Tetracycline-class antibiotics (chlortetracycline, demeclocycline, doxycycline [Acticlate, Avidoxy, Doryx, Doryx MPC, Doxy 100, Mondoxyne NL, Morgidox, Oracea, Soloxide, Targadox, Vibramycin], eravacycline [Xerava], lymecycline; omadacyclin [Nuzyra], oxytetracycline, sarecycline [Seysara], tetracycline)	**Calcium**	Calcium from food (e.g., milk) or supplements may decrease absorption of the antibiotic due to chelate formation in the intestine; absorption of calcium may also be decreased.	Separate antibiotic dose by 2 hours before or 6 hours after calcium intake from food or supplements.
	Iron	Iron from food or supplements may decrease absorption of the antibiotic due to chelate formation in the intestine; absorption of iron may also be decreased.	Separate iron supplements from antibiotics by at least 2 hours.
	Magnesium	Concomitant intake may decrease both drug and mineral absorption due to chelate formation in the intestine.	Separate antibiotic dose from magnesium-rich food or supplements by 2 hours or 4-6 hours after magnesium.
	Manganese	Concomitant intake may decrease manganese absorption due to complex formation in the intestine.	
	Zinc	Concomitant intake may decrease both drug and mineral absorption due to chelate formation in the intestine. One small, cross-over study found that zinc sulfate did not inhibit absorption of doxycycline.	Separate antibiotic dose from zinc supplements by at least 2 hours.
Thiazide diuretics (nadolol/bendroflumethiazide, chlorothiazide [Diuril, Sodium Diuril], chlorthalidone [Hygroton, Thalitone], hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone)	**Calcium**	Thiazide diuretics increase renal reabsorption of calcium and thus decrease its excretion.	If taken in combination with calcium supplements, thiazide diuretics may increase the risk of hypercalcemia.
	Magnesium	If taken for an extended period of time, high dosages of thiazide diuretics can interfere with renal reabsorption of magnesium, increase urinary excretion of magnesium, and result in magnesium depletion.	Monitor magnesium status (dietary, serum, and urinary magnesium) in patients on long-term therapy with thiazide diuretics.
	Potassium	Thiazide diuretics increase urinary excretion of potassium in a dose-dependent manner; their use may result in potassium depletion.	Monitor serum potassium concentrations in patients taking thiazide diuretics.
	Zinc	Thiazide diuretic use may inhibit zinc reabsorption in the distal tubule of the kidneys and thus increase urinary	Prolonged use of thiazide diuretics may increase risk of zinc depletion.

		excretion of zinc, possibly decreasing zinc status.	
Torsemide: see Loop diuretics			
Trimethoprim (Primsol); Trimethoprim-sulfamethoxazole (Bactrim, Bactrim DS, Sulfatrim Pediatric)	**Folate**	Trimethoprim inhibits dihydrofolate reductase, which converts dihydrofolate to the active form of folate, tetrahydrofolate. Sulfamethoxazole inhibits bacterial production of dihydropteroate. Use of trimethoprim or trimethoprim-sulfamethoxazole may thus increase the risk of folate deficiency.	Inhibition of the bacterial enzyme by trimethoprim is thousands-fold more efficient than the mammalian enzyme; risk of folate deficiency increases with higher dosages of trimethoprim, especially when administered for prolonged periods. Measuring folate concentrations in red blood cells is a better indicator of folate status than serum folate concentrations. Supplementation with folinic acid (leucovorin) may reduce the antifolate toxicity.
Valproic acid (Depakote, Depakote ER, Depakote Sprinkles)	**Carnitine**	Valproic acid may decrease carnitine status and lead to deficiency if the drug is taken for a prolonged period of time. Valproic acid interferes with L-carnitine biosynthesis in the liver and forms with L-carnitine a valproylcarnitine ester that is excreted in the urine.	L-carnitine supplements may be necessary in a subset of patients taking valproic acid. Risk factors for L-carnitine deficiency with valproic acid include young age (<2 years), severe neurological problems, use of multiple antiepileptic drugs, poor nutrition, and consumption of a ketogenic diet.
Verapamil (Calan SR, Verelan, Verelan PM)	**Calcium**	Calcium may decrease the hypotensive effect of intravenously provided verapamil.	
Warfarin (Jantoven)	**Vitamin C**	Some evidence from case reports indicate that large oral doses might inhibit the action of warfarin.	Limit vitamin C intake from supplements to 1 g/day and monitor prothrombin time/INR.
	Vitamin E	High-dose supplementation with vitamin E may inhibit vitamin K-dependent carboxylase activity, thus interfering with the coagulation cascade.	Evaluate use of vitamin E supplements due to an increased risk of bleeding.
	Vitamin K	Warfarin prevents recycling of vitamin K by antagonizing the enzyme, vitamin K oxidoreductase, thereby creating a functional vitamin K deficiency. Low dietary intakes of vitamin K can cause an unstable INR, and very high dietary (>150 µg/day) or supplemental intake of vitamin K may compromise the anticoagulant effect of warfarin.	It is generally recommended that individuals using warfarin try to consume the adequate intake for vitamin K (90 µg/day for women and 120 µg/day for men) and avoid large fluctuations in vitamin K intake that might interfere with the adjustment of their anticoagulant dose.
	Boldo (*Peumus boldus*)-fenugreek (*Trigonella foenum-graecum*)	One case report of increased INR with co-supplementation of boldo and fenugreek while on warfarin therapy. MOA is not known. An active compound in boldo, baldine, inhibited aggregation of rabbit platelets *in vitro*. Fenugreek reportedly contains coumarin derivatives.	Interaction has been rated as 'highly probable' (182).
	Chitosan (*Swertia chirayita*)	Case report of increased INR with chitosan supplementation. MOA is	Monitor INR in those taking chitosan. Clinical studies are

		unknown, although the authors of the case report state impaired absorption of vitamin K may be likely.	needed to determine if there is an interaction.
	Coenzyme Q_{10}	Coenzyme Q_{10} and forms of vitamin K are structurally similar.	Avoid coenzyme Q_{10} supplements in patients taking warfarin due to increased risk of blood clotting. If concomitantly used, assess prothrombin time/INR frequently, especially in the first two weeks.
	Cranberry juice	An increased INR has been documented in case reports (MOA not clearly explored), but no interaction has been found in controlled studies.	Monitor INR if patients consume cranberry juice.
	Danshen (*Salvia miltiorrhiza* root)	Case reports of increased INR and prothrombin time, possibly through effects on CYP450 enzymes. Results of a rat study indicate tanshinone IIA, a bioactive compound of danshen, binds to albumin and displaces warfarin, thus increasing blood concentration of warfarin and its effect. Inhibition of warfarin hydroxylation has also been shown in one rat study.	Avoid supplementation with herb.
	Compound Danshen Dripping Pill (CDDP; *Salvia miltiorrhiza*, borneol, and tanshinol)	A clinical study in patients with coronary heart disease with atrial fibrillation found CDDP had no effect on warfarin pharmacokinetics or pharmacodynamics.	
	Devil's claw (*Harpagophytum procumbens*)	Report of purpura with co-administration of warfarin and devil's claw.	Little information is available in the published literature.
	Dong quai (*Angelica sinensis*)	Case report of increased INR with co-administration with warfarin. The herb contains coumarin derivatives.	Interaction has been rated as 'probable'.
	Echinacea	One small study in healthy men found co-treatment with echinacea and warfarin increased clearance and decreased plasma concentrations of (S)-warfarin, but did not affect INR or platelet aggregation. In a small, open-label study, echinacea had no effect on the metabolism of tolbutamide, which, like S-warfarin, is metabolized by CYP2C9.	Clinical studies are needed to determine if there is an interaction.
	Fish oil	One case report of an interaction, but more recent studies have found no effect of fish oil supplementation on coagulation measures or bleeding incidence when co-administered with warfarin.	Monitor INR in patients taking fish oil.
	Garlic	Garlic might enhance the anticoagulant effects of warfarin because of its antiplatelet properties. While two case reports have raised concern, clinical trials have found no adverse effects.	More research is needed to determine whether they are safe in patients on anticoagulant therapy. Closely monitor INR in patients taking garlic supplements.
	Ginger	Case reports have suggested an interaction of high-dose ginger supplementation with warfarin. An open-label, cross-over study found no effect of ginger supplementation on platelet aggregation or INR in healthy	Clinical studies are needed to determine if there is an interaction.

		individuals who were administered only a single dose of racemic warfarin (25 mg).	
	Ginkgo biloba	Several case reports of spontaneous bleeding with the use of the herb alone, but a meta-analysis of randomized controlled trials found no increased risk. Cross-over trials of its use with warfarin found no effects on INR and the pharmacokinetics or pharmacodynamics of warfarin or on INR.	Monitor INR if patients on warfarin are taking ginkgo extracts or supplements.
	Ginseng	One case report of decreased INR with ginseng supplementation (Ginsana, 3 times per day; dose not stated). One clinical study found American ginseng decreased INR after two weeks' supplementation. Other clinical studies have found no effect of Korean ginseng root or Korean red ginseng on INR, warfarin pharmacokinetics, or warfarin pharmacodynamics.	More research is needed. Monitor INR if patients on warfarin take ginseng supplements.
	Grapefruit	One case report of a possible interaction; a small clinical study found no effect of grapefruit juice on prothrombin time or INR.	Clinical studies are needed to evaluate whether there is an interaction.
	Green tea	Green tea is a source of vitamin K. Consumption of large amounts of green tea could decrease INR.	Avoid large amounts (>0.5L per day) of green tea. Patients taking warfarin should have consistent dietary intake of vitamin K intake and avoid large fluctuations.
	Mango	Case report of 13 older men with increased INR following mango consumption. MOA is not known but hypothesized to include inhibition of CYP2C19 by vitamin A.	Interaction has been rated as 'highly probable'.
	Papain from papaya	Papain intake may increase INR, e.g., may increase bleeding by harming the integrity of the mucosal membranes of the GI tract. However, the exact mechanism is unknown.	Only one case report. Avoid supplementation with papaya extract; encourage eating fresh papaya instead.
	Pomegranate (*Punica granatum*)	One case report of increased INR with high intake of pomegranate juice. Pomegranate juice has been found to inhibit CYP2C9 activity *in vitro*.	Clinical studies are needed to evaluate whether there is an interaction.
	Psyllium (*Plantago ovata*)	Psyllium supplements may slow and decrease intestinal absorption of warfarin if taken concomitantly.	Separate taking psyllium supplements and drug by at least 2 hours.
	Resveratrol	Resveratrol inhibits platelet aggregation *in vitro*.	Supplemental intake could theoretically increase the risk of bruising and bleeding when taken with warfarin.
	Soy protein	One case report of a decreased INR in a patient taking warfarin following consumption of soy milk. MOA is unknown.	Monitor INR if the patient adds or eliminates soy protein from diet.
	St. John's wort (*Hypericum perforatum*)	Use of St. John's wort has been shown to induce various CYP450 enzymes, increasing warfarin clearance and decreasing INR.	Closely monitor INR.
	Sweet clover	Interaction might be possible since the herb contains coumarin derivatives.	Human reports are lacking.
	**Turmeric (*Curcuma*	Curcumin from turmeric has been found	Clinical research is needed

	***longa*)**	to inhibit platelet aggregation *in vitro*, thus curcumin supplementation could theoretically affect risk of bleeding in patients taking warfarin. A small pilot study found no effect of the curcumin formulation, Meriva®, on INR.	to determine whether curcumin supplementation interacts with warfarin.
Zoledronic acid (Reclast): see Bisphosphonates			