

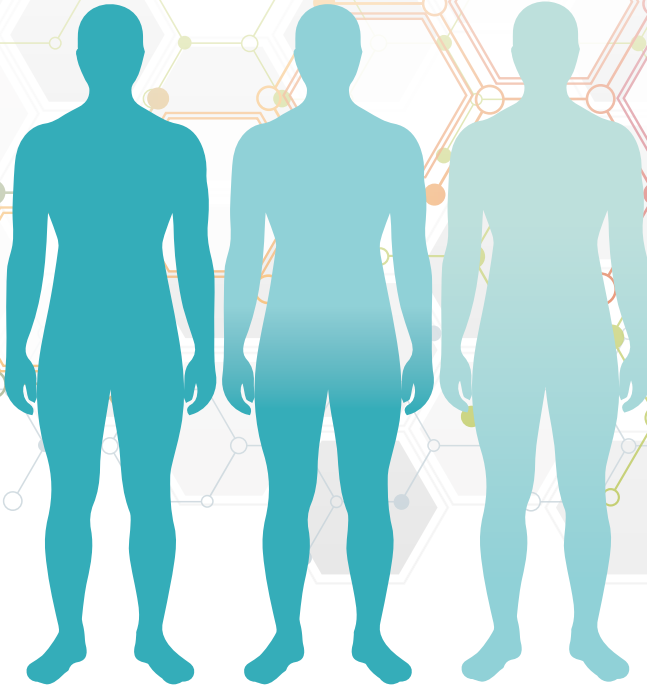


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NEW

DRUG-NUTRIENT DEPLETIONS GUIDE

For healthcare professionals



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About This Guide

In clinical practice, it is common for patients to use vitamin and dietary supplements alongside prescription medications. While medications are essential for managing a variety of acute and chronic conditions, they can lead to nutrient deficiencies. These deficiencies can occur due to impaired nutrient absorption, altered metabolism, or increased excretion. For healthcare practitioners, recognising these drug-nutrient depletions is critical when counselling patients on both their medications and nutritional requirements.

This guide has been developed to provide an evidence-based resource on nutrient depletions associated with commonly prescribed medications. It presents a systematic review of the mechanisms leading to depletion, evaluates the likelihood of interactions, and grades the strength of the evidence supporting these interactions. Importantly, the guide offers actionable recommendations to address and mitigate the risks of nutrient depletion, thereby supporting better patient outcomes through integrated care.

This guide is designed to be a dynamic resource, with the understanding that ongoing research may lead to new insights into drug-nutrient interactions. Healthcare professionals are encouraged to stay informed about the latest developments and to consider individual patient circumstances when applying the information provided.


Key

	Theoretical	Unlikely	Possible	Likely
LIKELIHOOD	Animal and/or <i>in vitro</i> evidence with unclear implications, however, it cannot exclude the possibility of occurring in humans	Evidence suggests this interaction can occur, but is not likely to occur in many patients	Evidence suggests this interaction might occur in some patients	Evidence suggests this interaction is likely to occur in most patients
LEVEL OF EVIDENCE	A	B	C	D
	At least one good quality randomised, placebo-controlled trial or meta-analysis or systematic review	Lower quality human study	Case reports	Animal and/or <i>in vitro</i>
	Indirect depletions The majority of nutrient depletions outlined in this guide are directly caused by the medications listed. However, some entries represent indirect depletions due to related conditions or secondary effects that result in depletion.			

Recommended supplementation doses are specific to replete patients from a state of deficiency. Maintenance doses are to follow the recommended daily intake (RDI), unless otherwise indicated.


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Anticoagulant and antiplatelet agents

DRUG	NUTRIENT	CLINICAL EFFECT
Aspirin	Iron	Long-term use is associated with lower serum ferritin and iron deficiency. ¹⁻⁴ This may be due to gastric irritation, occult blood loss, and cytokine-mediated effects. ^{2,5}
	Vitamin B12 (Cobalamin)	Aspirin use is associated with a higher prevalence of vitamin B12 deficiency when compared with non-users and may result in a moderate risk of depletion. ⁹
Heparin	 Calcium Vitamin D	Long-term use leads to reduced bone mineral density and increased fracture risk via the inhibition of osteoblast differentiation and function, and reduced bone formation. ¹⁰



EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Likely ¹⁻⁵	Monitor for depletion; supplementation may be needed in some patients. ⁵ Older adults on long-term, low-dose aspirin therapy may be at higher risk. ⁵ Recommended dose: 25 mg every two days to enhance absorption. ^{7,8}
B	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 1000 mcg/day. ¹⁰
A	Possible ¹⁰	Recommend supplementation for those at high risk of osteoporosis. ¹¹ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: For moderate deficiency, 3000–5000 IU/day for 6–12 weeks repletes stores, followed by a maintenance dose of 1000–2000 IU/day. ¹²

Antidepressants

DRUG	NUTRIENT	CLINICAL EFFECT
Antidepressants	Sodium	SSRIs, SNRIs, TCAs, Mirtazapine, Reboxetine and Vortioxetine may increase the risk of hyponatraemia, especially in the elderly. ⁹
SSRIs and SNRIs	 Calcium Vitamin D	Increased fracture risk from as early as six weeks' use. The mechanisms are not fully understood. ^{6,10}

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Possible ⁹	Monitor serum sodium levels in patients starting antidepressant therapy, especially the elderly and those on concurrent medications affecting electrolyte balance. ⁹
A	Likely ¹⁰	Ensure appropriate calcium and vitamin D supplementation. ¹¹ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: For moderate deficiency, recommended dose of 3000–5000 IU/day for 6–12 weeks to replete stores, followed by a maintenance dose of 1000–2000 IU/day. ¹²

Drugs for diabetes

DRUG	NUTRIENT	CLINICAL EFFECT
Glucagon-like peptide (GLP-1) agonists	 Vitamin B1 (Thiamine)	Restricted food intake may result in nutritional deficiencies, including vitamin B1 deficiency. ^{13,14}
	Vitamin B12 (Cobalamin)	Once-weekly treatment may result in significant decreases in serum vitamin B12. ¹⁶
	Zinc	Once-weekly treatment may result in significant decreases in serum zinc. ¹⁶
Insulin	 Magnesium	Hypomagnesaemia occurs in up to 48% of patients with type 2 diabetes mellitus (T2DM). The cause is multifactorial but includes altered insulin metabolism. Supplementation improves insulin handling and sensitivity. ¹⁸
Metformin	Folic acid	Metformin may reduce absorption of folic acid and increase the risk of folate deficiency. Reduced levels of vitamin B12 and, to a lesser extent, folic acid can contribute to hyperhomocysteinaemia. ^{6,9}
	Vitamin B12 (Cobalamin)	Metformin may interfere with intrinsic factor secretion or uptake, affect bowel motility, or cause bacterial overgrowth, resulting in vitamin B12 malabsorption and hyperhomocysteinaemia. Reduced absorption occurs in up to 30% of people taking metformin and is dose-dependent. ^{5,6,9}
Pioglitazone	Calcium Magnesium Vitamin D	Use of pioglitazone is associated with lower bone density and increased fracture risk, particularly in women. ⁶

EVIDENCE	LIKELIHOOD	RECOMMENDATION
C	Possible ^{13,14}	Ensure adequate dietary intake and consider supplementation. ^{13,14} Recommended dose: 5-30 mg/day as a single dose or in divided doses for one month. For severe deficiency, up to 300 mg/day can be used. ¹⁵
C	Possible ¹⁶	Monitor for depletion; supplementation may be needed in some patients. ¹⁶ Recommended dose: 1000 mcg/day. ¹⁰
C	Possible ¹⁶	Monitor for depletion; supplementation may be needed in some patients. ¹⁶ Recommended dose: 16-70 mg/day. ¹⁷
A	Possible ¹⁸	Ensure adequate dietary intake and consider supplementation. ¹⁸ Recommended dose: 300-600 mg/day. ¹⁹⁻²³
A	Likely ^{6,9}	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 400 mcg - 5 mg/day. ^{9,24}
A	Likely ^{6,9}	Monitor serum vitamin B12 and homocysteine levels annually, especially in patients on long-term metformin therapy. Supplementation is often needed to correct deficiency. The risk is highest in patients taking higher doses of metformin for three years or more, particularly in older adults and vegetarians. ^{6,9} Recommended dose: 1000 mcg/day. ¹⁰
A	Possible ⁶	Monitor for depletion; supplementation may be needed in some patients. ⁶ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Magnesium: Recommended dose of 300-600 mg/day. ¹⁹⁻²³ Vitamin D: For moderate deficiency, recommended dose of 3000-5000 IU/day for 6-12 weeks repletes stores, followed by a maintenance dose of 1000-2000 IU/day. ¹²

Drugs for dyslipidaemia

DRUG	NUTRIENT	CLINICAL EFFECT
Bile acid sequestrants (Colestyramine)	Folic acid	Reduced absorption of folic acid. ^{5,9}
	Fat-soluble vitamins: A, D, E, and K	Doses >24 g/day may interfere with fat absorption, preventing absorption of fat-soluble vitamins. ^{5,9}
Statins	Coenzyme Q10 (CoQ10)	Statins can halt the synthesis of CoQ10, reducing endogenous levels. ⁹ Statins may lower CoQ10 levels in a dose-dependent manner. ⁶
	L-carnitine	Atorvastatin 10 mg/day for five months decreased L-carnitine levels in seminal fluid. ³⁰

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 400 mcg – 5 mg/day. ^{9,24}
A	Possible ⁹	Consider supplements for patients taking high doses over a long period of time. ⁹ Vitamin A: Recommended short-term dose of 10,000 IU/day. ²⁵ Vitamin E: Recommended dose of 1200 IU/day. ²⁶ Vitamin D: For moderate deficiency, recommended dose of 3000–5000 IU/day for 6–12 weeks to replete stores, followed by a maintenance dose of 1000–2000 IU/day. ¹² Vitamin K1: Recommended dose of 2.5–25 mg/day. ²⁷ Vitamin K2: Recommended dose of 90–180 mcg/day menaquinone (MK)-7. ²⁸
A	Possible ^{6,9}	Supplementation may reduce statin-related side effects. ^{6,9} The risk of CoQ10 depletion may be greater in older adults, those taking a higher dose, and those who develop statin-related myopathy. ⁶ Recommended dose: 200 mg/day. ²⁹
B	Possible ⁹	Clinical significance is unclear. ⁹ Carnitine benefits sperm count and may benefit sperm motility. ³¹ Recommended dose: 2 g/day. ³¹

Gastrointestinal drugs

DRUG	NUTRIENT	CLINICAL EFFECT
Antacids	Calcium	Aluminium-containing antacids may bind dietary phosphate, reducing phosphate absorption and disrupting calcium-phosphate balance. Prolonged use of high doses (e.g. aluminium hydroxide 1-3 grams four times daily) may lead to calcium depletion due to increased movement of calcium from bones into the bloodstream and compensatory increase in urinary excretion. ⁹
	Folic acid	Decreased folic acid absorption if taken concurrently. ⁵
	Iron	Decreased iron absorption if taken concurrently. ⁵
	Phosphorus	Aluminium, calcium, and magnesium contained in antacids can bind to phosphate in the gut and prevent its absorption. ^{5,9}
H2 receptor antagonists	Iron	Decreased iron absorption due to decreased gastric acid. ^{5,9}
	Vitamin B12 (Cobalamin)	H2-blockers might reduce the absorption of dietary vitamin B12 and increase the risk of deficiency. Deficiency is more likely with long-term use, with low dietary vitamin B12 intake, and in those with achlorhydria. ^{5,9}

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Likely ⁹	Avoid large doses of antacids for long periods. A supplement is needed in some patients. ⁹ Recommended dose: ≥ 1500 mg/day. ⁵
D	Unlikely ⁹	Only significant if dietary folate intake is very low. ⁹ Separate doses by two hours. ⁵ Recommended dose: 400 mcg - 5 mg/day. ^{9,24}
A	Possible ⁵	Monitor for depletion; supplementation may be needed in some patients. ⁹ Separate doses by two hours. ⁵ Recommended dose: 25 mg every two days to enhance absorption. ^{7,8}
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. Antacid and phosphate intake should be separated by at least two hours. ⁹ Recommended dose: 1000-2000 mg/day for 7-10 days to replete stores. ³²
B	Possible ⁵	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 25 mg every two days to enhance absorption. ^{7,8}
A	Possible ⁹	Monitor for depletion; a supplement is needed in some patients. ⁵ Recommended dose: 1000 mcg/day. ¹⁰

Orlistat	Fat-soluble vitamins: A, D, E, and K	Reduced absorption and blood levels of fat-soluble vitamins. ⁹ Serum vitamin D levels appear to be the most affected. ^{33,34}
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Proton Pump Inhibitors (PPIs)	Calcium	Some evidence indicates that PPIs may reduce calcium absorption and increase fracture risk. ⁶ Chronic PPI use is associated with increased fracture risk, particularly in individuals who may already be at risk of fractures, such as older adults. ⁶
	Iron	PPIs suppress gastric acid secretion. Adequate gastric acidity is essential for the absorption of iron, particularly dietary non-haem iron. Reduced gastric acidity may lead to iron depletion with prolonged PPI use in people with risk factors for developing iron deficiency. ^{5,6}
	Magnesium	PPIs increase intestinal pH and inhibit active transport of magnesium in the intestine, reducing its absorption and increasing the risk of hypomagnesaemia. ⁹
	Vitamin B12 (Cobalamin)	PPIs might reduce the absorption of dietary vitamin B12, particularly with prolonged use and in the elderly. ^{5,6,9}
	Vitamin C	PPI use is linked to lower gastric acid and serum vitamin C, particularly in those with <i>H. pylori</i> infection due to decreased intestinal bioavailability ⁶ or increased vitamin C destruction at higher pH levels. ⁹
	Zinc	PPI use may increase zinc excretion and reduce zinc absorption. ⁶

A	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Vitamin A: Recommended short-term dose of 10,000 IU/day. ²⁵ Vitamin E: Recommended dose of 1200 IU/day. ²⁶ Vitamin D: For moderate deficiency, recommended dose of 3000–5000 IU/day for 6–12 weeks to replete stores, followed by a maintenance dose of 1000–2000 IU/day. ¹² Vitamin K1: Recommended dose of 2.5–25 mg/day. ²⁷ Vitamin K2: Recommended dose of 90–180 mcg/day MK-7. ²⁸
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B	Possible ⁶	Ensure adequate intake via the diet or supplementation. ⁵ Recommended dose: ≥1500 mg/day. ⁵
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B	Possible ⁶	Monitor for depletion; supplementation may be needed in some patients. ⁶ Recommended dose: 25 mg every two days to enhance absorption. ^{7,8}
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A	Likely ^{6,9}	Magnesium supplementation alone may not reverse hypomagnesaemia until PPI therapy is discontinued. ⁶ Supplementation is recommended. ⁹ Recommended dose: 300–600 mg/day. ^{19–23}
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A	Possible ^{6,9}	Supplementation may be needed for those taking PPIs long-term. ⁵ Recommended dose: 1000 mcg/day. ¹⁰
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B	Possible ^{6,9}	Clinical significance unknown. ^{6,9} Recommended dose: 1–2 g/day for the first 2–3 days, followed by 500 mg/day for the next week, then 100 mg/day for 1–3 months. ³⁵
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B	Possible ⁶	Monitor for depletion and ensure adequate dietary intake. ⁶ Recommended dose: 16–70 mg/day. ¹⁷
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Antimicrobials


DRUG	NUTRIENT	CLINICAL EFFECT
Amphotericin B	Magnesium	Can cause a significant decrease in magnesium levels which may necessitate stopping the drug and giving intravenous electrolyte replacement. ⁹
Antibiotics	Vitamin K	Destruction of gastrointestinal microflora may lead to decreased production of vitamin K which may lead to vitamin K deficiency, prolonging clotting times, and increasing bleeding risk. This is most likely to occur with prolonged antibiotic therapy (10 days or more) in people with poor dietary vitamin K intake. ^{5,9}
Cycloserine	Folic acid	Reduced serum folate levels which may involve changes to the absorption and metabolism of folate. Rare cases of megaloblastic anaemia have occurred. ⁹
	Vitamin B3 (Niacin/Nicotinamide)	Can cause vitamin B6 deficiency, which is needed for the conversion of tryptophan to niacin, resulting in secondary niacin deficiency. ⁹
	Vitamin B6 (Pyridoxine)	Increased vitamin B6 excretion resulting in vitamin B6 deficiency. ^{5,9}
Ethambutol	Zinc	Chelates zinc and might reduce plasma and tissue levels, contributing to visual dysfunction, especially at higher doses. ^{5,9}
Isoniazid	Vitamin B3 (Niacin/Nicotinamide)	Can cause vitamin B6 deficiency, which is needed for the conversion of tryptophan to niacin, resulting in secondary niacin deficiency. Pellagra can occur in people taking isoniazid long-term. ⁹
	Vitamin B6 (Pyridoxine)	Increased vitamin B6 excretion resulting in vitamin B6 deficiency, particularly in people receiving ≥ 5 mg/kg/day. ^{5,9}

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 300-600 mg/day. ¹⁹⁻²³
A	Possible ⁹	Monitor for depletion; supplementation is needed in some patients taking antibiotics long-term. ⁹ Vitamin K1: Recommended dose of 2.5-25 mg/day. ²⁷ Vitamin K2: Recommended dose of 90-180 mcg/day MK-7. ²⁸
A	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 400 mcg - 5 mg/day. ^{9,24}
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Supplementation of 500-1000 mg/day for one week can resolve symptoms of severe niacin deficiency. ³⁶
A	Likely ^{5,9}	A supplement is needed for most patients. ⁹ Doses >50 mg/day may be needed. ⁵ 150-300 mg/day has been recommended. ⁹ Monitor for signs of excess or depletion (early signs of peripheral neuropathy, such as paraesthesia, numbness, and weakness). Ensure all sources of vitamin B6 supplementation are accounted for.
B	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁵ Recommended dose: 16-70 mg/day. ¹⁷
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Supplementation of 500-1000 mg/day for one week can resolve symptoms of severe niacin deficiency. ³⁶
A	Likely ^{5,9}	Supplementation may be needed in some patients. Monitor for signs of excess or depletion (early signs of peripheral neuropathy, such as paraesthesia, numbness, and weakness). Ensure all sources of vitamin B6 supplementation are accounted for. Recommended dose: 40-250 mg/day. ⁹


Rifampicin	Vitamin D	Increased hepatic metabolism resulting in decreased plasma levels, which can contribute to osteomalacia after prolonged therapy. ⁹
Tetracyclines	Vitamin C	Increased vitamin C excretion leading to decreased white blood cells and vitamin C status. ⁵
Trimethoprim-sulfamethoxazole	Folic acid	Inhibitory effect on dihydrofolate reductase potentially leading to folate deficiency. ^{5,9} High doses of trimethoprim (20 mg/kg/day for 2-4 weeks or 500 mg/day for several months) might precipitate megaloblastic anaemia, especially in those with other risk factors. ⁹

A	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Vitamin D: For moderate deficiency, recommended dose of 3000–5000 IU/day for 6–12 weeks to replete stores, followed by a maintenance dose of 1000–2000 IU/day. ¹²
D	Possible ⁵	Recommended dose: 1-2 g/day for the first 2-3 days, followed by 500 mg/day for the next week, then 100 mg/day for 1-3 months. ³⁵
A	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 400 mcg – 5 mg/day. ^{9,24}

Hormonal and hormonal anticancer drugs

DRUG	NUTRIENT	CLINICAL EFFECT
Aromatase inhibitors	 Calcium Vitamin D	Reduced oestrogen production leading to increased bone resorption, bone loss, and risk of fracture. ¹¹
Estrogen	Folic acid	May reduce absorption, increase excretion, or alter liver metabolism of folate, resulting in reduced serum or red blood cell folate in some women. ^{6,9}
	Magnesium	Estrogens reduce serum levels of magnesium by increasing its uptake into body tissues. This can cause hypomagnesaemia, which may contribute to thromboembolic complications associated with estrogens. ⁹
	Vitamin B6 (Pyridoxine)	Oral contraceptives may negatively impact vitamin B6 status ⁶ by interfering with vitamin B6 metabolism. ⁹

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Likely ¹¹	Ensure appropriate calcium and vitamin D supplementation. ¹¹ Calcium: ≥ 1500 mg/day. ⁵ Vitamin D: For moderate deficiency, recommended dose of 3000–5000 IU/day for 6–12 weeks to replete stores, followed by a maintenance dose of 1000–2000 IU/day. ¹²
A	Unlikely ⁹	Monitor for depletion; a supplement is needed in some patients although this is unlikely with adequate dietary folate intake. ⁹ Recommended dose: 400 mcg - 5 mg/day. ^{9,24}
B	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. Recommended dose: 300-600 mg/day. ¹⁹⁻²³
A	Possible ^{6,9}	Supplementation may be needed in some patients. Monitor for signs of excess or depletion (early signs of peripheral neuropathy, such as paraesthesia, numbness, and weakness). Ensure all sources of vitamin B6 supplementation are accounted for. Recommended dose: 100-200 mg/day. ⁵

Medroxyprogesterone acetate (MPA)	 Calcium Vitamin D	Reduced oestrogen levels leading to increased bone resorption, bone loss, and fracture risk. ¹¹
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A	Likely ¹¹	Ensure appropriate calcium and vitamin D supplementation. ¹¹ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: For moderate deficiency, recommended dose of 3000–5000 IU/day for 6–12 weeks to replete stores, followed by a maintenance dose of 1000–2000 IU/day. ¹²
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Cardiovascular drugs


DRUG	NUTRIENT	CLINICAL EFFECT
ACE inhibitors	Zinc	Long-term treatment with ACE inhibitors may increase urinary zinc excretion and lead to zinc deficiency. The risk of zinc deficiency is highest with captopril. ^{5,6}
Digoxin	Magnesium	Decreased renal reabsorption of magnesium leading to increased urinary excretion and a moderate depletion of magnesium. ⁹
Hydralazine	Vitamin B6 (Pyridoxine)	Increased vitamin B6 excretion and reduced blood levels. ^{5,9}
Loop diuretics	Calcium	Loop diuretics increase urinary calcium excretion and may reduce serum calcium levels, especially at higher doses. ^{6,9}
	Vitamin B1 (Thiamine)	High doses of diuretics can increase thiamine excretion and increase the risk of deficiency. ⁹ Increased urinary thiamine excretion and thiamine deficiency may occur in some people treated with diuretics, especially in high doses (e.g., >80 mg/day frusemide) for several months. ⁹
Thiazide diuretics	Zinc	Increased urinary zinc excretion of 50–60% may lead to decreased serum levels. Prolonged therapy may deplete tissue zinc. ⁹

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Possible ⁶	Monitor for symptoms of zinc depletion in patients on high doses of captopril for prolonged periods. ⁶ Recommended dose: 16–70 mg/day. ¹⁷
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 300–600 mg/day. ^{19–23}
C	Possible ⁹	Supplementation may be needed in some patients. Monitor for signs of excess or depletion (early signs of peripheral neuropathy, such as paraesthesia, numbness, and weakness). Ensure all sources of vitamin B6 supplementation are accounted for. Recommended dose: 100–200 mg/day. ⁵
A	Likely ⁶	Ensure adequate calcium intake, particularly for those more at risk of fractures and older people with poor calcium absorption. ⁶ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵
A	Possible ⁹	Supplementation may be needed, particularly in elderly patients with inadequate dietary intake. ⁹ Recommended dose: 200 mg/day may improve heart function in thiamine-deficient patients using high doses of diuretics. ⁹
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 16–70 mg/day. ¹⁷


Loop diuretics Thiazide diuretics	Magnesium	Loop diuretics and, to a lesser extent thiazide diuretics, interfere with magnesium reabsorption in the kidneys, increasing urinary losses and reducing serum magnesium levels. ⁹ Long-term use can significantly deplete cellular magnesium potentially leading to hypomagnesaemia. ⁶
	Potassium	Loop and thiazide diuretics increase urinary excretion of potassium, potentially leading to hypokalaemia. However, the risk of hypokalaemia may be reduced in patients taking concurrent medications that increase serum potassium levels, such as ACE inhibitors, angiotensin II receptor blockers (ARBs), or potassium-sparing diuretics. ⁹
Beta-blockers Clonidine Hydralazine Thiazides	CoQ10	Inhibition of CoQ10-enzymes of the myocardium. Hydrochlorothiazide, hydralazine, clonidine, and beta-blockers inhibit CoQ10-NADH-oxidase. ³⁹ The beta-blocker with the greatest impact is propranolol. ^{39,40}

A	Likely ⁶	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 300-600 mg/day. ¹⁹⁻²³ Magnesium levels may be restored after six months of supplementation. ⁶
A	Possible ³⁷	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 780 mg/day for prevention of hypokalaemia. 1560-3900 mg/day in 2-5 divided doses to treat hypokalaemia. ³⁸
D	Possible ⁹	Clinical significance unknown. ⁹ Recommended dose: 100-200 mg/day. ⁴¹

Immunomodulatory and anti-inflammatory drugs

DRUG	NUTRIENT	CLINICAL EFFECT
Aspirin	Iron	Long-term aspirin use is associated with lower serum ferritin and iron deficiency. ¹⁻⁴ This may be due to gastric irritation, occult blood loss, and cytokine-mediated effects. ^{2,5}
	Vitamin B12 (Cobalamin)	Aspirin use is associated with a higher prevalence of vitamin B12 deficiency when compared with non-users and may result in a moderate risk of depletion. ⁹
Calcineurin inhibitors cyclosporin and tacrolimus	 Calcium Vitamin D	Excessive osteoclasts and bone resorption resulting in bone loss and increased fracture risk. Use in rheumatic diseases at doses below 5 mg/kg/d has not been reported to have clinically significant bone loss. ¹¹
Ciclosporin	Magnesium	Causes significant urinary magnesium loss, probably by causing renal tubular damage which reduces tubular reabsorption. Hypomagnesaemia may contribute to seizures and neurotoxicity associated with ciclosporin. ⁹

EVIDENCE	LIKELIHOOD	RECOMMENDATION
A	Likely ¹⁻⁵	Monitor for depletion; supplementation may be needed in some patients. ⁵ Older adults on long-term, low-dose aspirin therapy may be at higher risk. ⁶ Recommended dose: 25 mg every two days to enhance absorption. ^{7,8}
B	Possible ⁹	Monitor for depletion; supplementation is needed in some patients. ⁹ Recommended dose: 1000 mcg/day. ¹⁰
A	Possible ¹¹	Ensure appropriate calcium and vitamin D supplementation. ¹¹ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: For moderate deficiency, recommended dose of 3000-5000 IU/day for 6-12 weeks to replete stores, followed by a maintenance dose of 1000-2000 IU/day. ¹²
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 300-600 mg/day. ¹⁹⁻²³



Colchicine	Vitamin B12 (Cobalamin)	Reduced vitamin B12 absorption and increased risk of deficiency at doses of 1.9-3.9 mg/day. ^{5,9}
Corticosteroids	Calcium	Prolonged use of glucocorticoids can reduce bone mineral density (BMD) by decreasing bone formation, increasing bone resorption and decreasing intestinal calcium absorption. Glucocorticoids also increase fracture risk independently of BMD. The extent of bone loss and fracture risk is related to both the dose and duration of glucocorticoid therapy. ^{6,9}
	Chromium	Corticosteroids may increase urinary chromium excretion leading to chromium deficiency which may be a contributing factor to corticosteroid-induced hyperglycaemia. ⁹
	Magnesium	Long-term corticosteroid use increases urinary magnesium excretion due to bone catabolism, releasing magnesium and increasing the amount available for excretion. ⁹
	Potassium	Corticosteroids can increase urinary potassium excretion. Mineralocorticoids and some glucocorticoids cause sodium retention, resulting in compensatory renal potassium excretion and hypokalaemia. The effect is dose-related and depends on mineralocorticoid potency. ⁹
	 Vitamin D	Corticosteroids might reduce blood levels of vitamin D. Daily doses equivalent to ≥ 7.5 mg prednisone cause significant bone loss, osteoporosis, and increased fracture risk. The severity increases with duration of therapy. ⁹ Long-term inhaled corticosteroids negatively influences bone metabolism and bone mineral density. ⁶
Methotrexate	Folic acid	Methotrexate is a folate antagonist which prevents conversion of folic acid to its active form resulting in decreased serum folate levels. In patients treated with long-term, low-dose methotrexate for rheumatoid arthritis or psoriasis, folate deficiency is associated with increased risk of some side effects. ⁹

A	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 1000 mcg/day. ¹⁰
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Calcium with vitamin D is more effective than calcium alone for preventing bone loss. ⁶ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: Recommended dose of 800 IU/day. ⁹
B	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 600 mcg/day. ⁴²
B	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 300-600 mg/day. ¹⁹⁻²³
D	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 780 mg/day for prevention of hypokalaemia. 1560-3900 mg/day in 2-5 divided doses to treat hypokalaemia. ³⁸
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Calcium with vitamin D is more effective than calcium alone for preventing bone loss. ⁶ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: Recommended dose of 800 IU/day. ⁹
A	Likely ^{5,9}	A supplement is needed for most patients. ⁹ Folic acid 0.8-5 mg/day reduces side effects without reducing the efficacy of methotrexate. ⁹ Patients taking methotrexate for cancer should avoid folic acid supplements unless recommended by their oncologist. ⁹


Sulfasalazine	Folic acid	Sulfasalazine competitively inhibits absorption of folic acid and interferes with the metabolism and breakdown of dietary folate to its absorbable form, and can cause haemolysis, increasing folate requirements for new red blood cell formation. ⁹
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C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Advise patients on chronic sulfasalazine therapy to increase their dietary folate intake and to take a supplement if they have any other condition that may contribute to deficiency. ⁹ Recommended dose: 400 mcg - 5 mg/day. ^{9,24}
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Antiepileptic drugs

DRUG	NUTRIENT	CLINICAL EFFECT
Carbamazepine Phenobarbital Phenytoin	Biotin	Reduced blood levels of biotin due to decreased absorption and increased excretion. ⁹
	 Calcium Vitamin D	Accelerated inactivation of vitamin D decreasing calcium uptake, driving secondary hyperparathyroidism, and accelerating bone loss. ¹¹ Hypocalcaemia and osteomalacia have occurred, especially with prolonged or combination therapy. ⁹
	Folic acid	Reduced serum folate, occasionally leading to megaloblastic anaemia, possibly contributing to neurological side effects, and mental changes. ^{5,9}
	Vitamin B12 (Cobalamin)	May reduce vitamin B12 absorption and increase the risk of deficiency, especially with chronic use. ⁹
	Vitamin E	Reduced blood levels (9-26%) possible due to increased hepatic free radical quenching during drug metabolism. ⁹
Gabapentin	 Calcium Vitamin D	Associated with accelerated bone loss and increased risk of osteoporotic fracture. ¹¹
Oxcarbazepine	Biotin	Theoretically, oxcarbazepine may reduce blood levels of biotin due to decreased absorption and increased excretion. ⁹

EVIDENCE	LIKELIHOOD	RECOMMENDATION
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Supplementation of 500-1000 mg/day for one week can resolve symptoms of severe niacin deficiency. ³⁶
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 1-10 mg/day. ^{43,44}
A	Likely ^{9,11}	Consider routine bone mineral density and serum vitamin D (25(OH)D) monitoring, as well as vitamin D and calcium supplementation in patients on long-term treatment, particularly those at higher risk, such as elderly and institutionalised patients with limited access to sunshine. ⁹ Calcium: Recommended dose of ≥ 1500 mg/day. ⁵ Vitamin D: Recommended dose of 1000-1200 IU/day. ¹¹
A	Possible ⁸	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 1000 mcg/day. ¹⁰
B - Carbamazepine C - Phenobarbital A - Phenytoin	Possible ⁹	Encourage patients to maintain adequate dietary vitamin B12 intake, and check folate and vitamin B12 status if symptoms of anaemia develop. ⁹ Recommended dose: 1000 mg/day. ¹⁰
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 1200 IU/day. ²⁶
D	Possible ⁹	Recommended dose: 1-10 mg/day. ^{43,44}

Oxcarbazepine (continued)	Sodium	Oxcarbazepine may increase the risk of hyponatraemia by increasing the responsiveness of the renal collecting tubules to circulating antidiuretic hormone. The incidence of hyponatraemia is up to 25% in patients using oxcarbazepine, with the risk being dose-dependent. ⁹
Phenytoin	Vitamin B3 (Niacin/Nicotinamide)	Phenytoin might reduce levels of niacin and precipitate niacin deficiency, as case reports describe symptoms consistent with pellagra in people taking phenytoin alone or in combination with other anticonvulsants. ⁹
Primidone (Barbiturate)	Biotin	Reduced blood levels of biotin due to decreased absorption and increased excretion. ⁴
	Folic acid	Reduced serum folate and increased risk of folate deficiency by affecting folate absorption and metabolism. In people with low dietary intake, there is a risk of megaloblastic anaemia, possibly contributing to neurological side effects, mental changes, and cerebral atrophy. ⁹
Valproic acid Sodium valproate	 Calcium Vitamin D	Associated with accelerated bone loss and increased risk of osteoporotic fracture. ¹¹ Increases vitamin D metabolism. ⁵
	Folic acid	May reduce folate levels in some people by inhibiting intestinal absorption. ^{9,45}
	L-carnitine	May reduce blood and tissue levels of L-carnitine by interfering with its biosynthesis and increasing its excretion. L-carnitine deficiency may contribute to the development of hyperammonaemia and hepatotoxicity associated with valproate therapy. ^{5,9}
	Vitamin B3 (Niacin/Nicotinamide)	May reduce niacin levels via an unknown mechanism. ⁹

A	Possible ⁹	Monitor serum sodium concentrations after two weeks of starting or increasing the dose of oxcarbazepine, and then monthly for three months. ⁹
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Supplementation of 500-1000 mg/day for one week can resolve symptoms of severe niacin deficiency. ³⁶
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 1-10 mg/day. ^{43,44}
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 400 mcg – 5 mg/day. ^{9,24}
A	Likely ⁹	Calcium: Recommended dose of ≥1500 mg/day. ⁵ Vitamin D: Recommended dose of 2000-4000 IU/day. ¹¹
A	Likely ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Recommended dose: 400 mcg - 5 mg/day. ^{9,24}
A	Possible ⁹	Routine supplementation is not necessary for most patients who are consuming a diet adequate in L-carnitine. ⁹ If supplementation is needed, 2 g/day dose is commonly used. ³¹
C	Possible ⁹	Monitor for depletion; supplementation may be needed in some patients. ⁹ Supplementation of 500-1000 mg/day for one week can resolve symptoms of severe niacin deficiency. ³⁶

Drug-Nutrient Depletions Guide

NUTRIENT SUMMARY

NUTRIENT	KEY ACTIONS	DEFICIENCY SIGNS AND SYMPTOMS
Biotin	<ul style="list-style-type: none"> • Hair, skin, and nail health⁴⁶ • Healthy fetal development⁴⁷ • Nutrient metabolism⁴⁸ 	<ul style="list-style-type: none"> • Brittle nails⁴⁸ • Skin rash⁴⁸ • Neurological impairment⁴⁸ • Thinning hair⁴⁸
Calcium	<ul style="list-style-type: none"> • Bone and teeth mineralisation⁴⁸ • Cardiovascular function⁴⁸ • Muscle contraction and relaxation⁴⁸ • Nerve conduction⁴⁸ 	<ul style="list-style-type: none"> • Poor bone health⁴⁷ • Muscle twitches, cramping, numbness, or tingling⁴⁸
Chromium	<ul style="list-style-type: none"> • Improves insulin sensitivity⁴⁸ 	<ul style="list-style-type: none"> • Impaired glucose tolerance⁴⁸
Coenzyme Q10 (CoQ10)	<ul style="list-style-type: none"> • Antioxidant activity⁴⁹ • Cardiovascular health⁴⁹ • Cognitive health⁵⁰ • Energy production⁴⁹ • Fertility^{51,52} • Immune system support⁴⁹ 	<ul style="list-style-type: none"> • Fatigue⁵³ • Increased risk of health conditions such as cardiovascular disorders, diabetes mellitus, neurodegenerative disorders, and muscular dystrophy⁵³ • Reduced fertility^{51,52}
Folic acid	<ul style="list-style-type: none"> • Healthy fetal development⁴⁸ • Red blood cell formation⁴⁸ • Synthesis of genetic material⁴⁸ 	<ul style="list-style-type: none"> • Fatigue⁴⁸ • Mouth ulcers⁴⁸ • Muscle weakness⁴⁸ • Neural tube defects⁴⁸
Iron	<ul style="list-style-type: none"> • Energy production⁵⁴ • Immune system support⁵⁴ • Oxygen transport and storage⁵⁴ 	<ul style="list-style-type: none"> • Dizziness⁵⁵ • Fatigue⁵⁵ • Headaches⁵⁵ • Pale skin⁵⁵ • Shortness of breath⁵⁵ • Thin, brittle, and flat spoon shaped nails⁵⁶

NUTRIENT	KEY ACTIONS	DEFICIENCY SIGNS AND SYMPTOMS
L-carnitine	<ul style="list-style-type: none"> • Energy production⁵⁷ • Fatty acid metabolism⁵⁷ 	<ul style="list-style-type: none"> • Fatigue⁵⁷ • Irregular heartbeat⁵⁷ • Muscle weakness⁵⁷
Magnesium	<ul style="list-style-type: none"> • Blood pressure regulation⁵⁸ • Blood glucose control⁵⁸ • Energy production⁵⁸ • Muscle function⁵⁸ • Nerve conduction⁵⁸ 	<ul style="list-style-type: none"> • Abnormal heart rhythms⁵⁸ • Fatigue⁵⁸ • Loss of appetite⁵⁸ • Muscle twitches, cramping, numbness, or tingling⁵⁸ • Nausea, vomiting⁵⁸
Phosphorus	<ul style="list-style-type: none"> • Energy production⁵⁹ • Formation of bones and teeth⁵⁹ • Supports cell function⁵⁹ • Supports homeostasis⁵⁹ 	<ul style="list-style-type: none"> • Confusion⁵⁹ • Fatigue⁵⁹ • Frequent infections⁵⁹ • Muscle weakness⁵⁹ • Poor bone health⁵⁹
Potassium	<ul style="list-style-type: none"> • Cardiovascular system support including blood pressure regulation and stroke prevention⁶⁰ • Nerve and muscle function⁶⁰ 	<ul style="list-style-type: none"> • Constipation⁶⁰ • Muscle cramps⁶⁰ • Weakness and fatigue⁶⁰
Sodium	<ul style="list-style-type: none"> • Blood pressure regulation⁴⁸ • Fluid and electrolyte balance⁴⁸ • Healthy cellular function⁴⁸ • Nerve and muscle function⁴⁸ 	<ul style="list-style-type: none"> • Confusion⁴⁸ • Headache⁴⁸
Vitamin A	<ul style="list-style-type: none"> • Immune system support⁴⁸ • Maintaining healthy vision⁴⁸ • Reproductive health and growth⁴⁸ • Skin and bone health⁴⁸ 	<ul style="list-style-type: none"> • Frequent infections⁴⁸ • Rough, elevated, coned-shaped papules⁴⁸ • Poor vision, especially night blindness⁴⁸

NUTRIENT	KEY ACTIONS	DEFICIENCY SIGNS AND SYMPTOMS
Vitamin B1 (Thiamine)	<ul style="list-style-type: none"> • Energy metabolism⁴⁸ • Muscle function⁴⁸ • Nervous system function⁴⁸ 	<ul style="list-style-type: none"> • Apathy⁴⁸ • Confusion⁴⁸ • Enlarged heart⁴⁸ • Irritability⁴⁸ • Muscle weakness⁴⁸ • Poor short-term memory⁴⁸ • Weight loss⁴⁸
Vitamin B12 (Cobalamin)	<ul style="list-style-type: none"> • Cognitive health⁴⁸ • Metabolic health⁴⁸ • Nervous system function⁴⁸ • Red blood cell production⁴⁸ 	<ul style="list-style-type: none"> • Anaemia⁴⁸ • Constipation⁴⁸ • Fatigue⁴⁸ • Loss of appetite⁴⁸ • Tingling, numbness, and burning in the hands or feet⁴⁸ • Sore tongue⁴⁸
Vitamin B3 (Niacin/ Nicotinamide)	<ul style="list-style-type: none"> • Cellular signalling⁴⁸ • Energy metabolism⁴⁸ 	<ul style="list-style-type: none"> • Abdominal pain⁴⁸ • Bilateral rash on areas exposed to sunlight⁴⁸ • Depression⁴⁸ • Diarrhoea⁴⁸ • Fatigue⁴⁸ • Glossitis (swollen tongue)⁴⁸ • Headache⁴⁸ • Memory loss⁴⁸ • Vomiting⁴⁸
Vitamin B6 (Pyridoxine)	<ul style="list-style-type: none"> • Cellular signalling⁶¹ • Energy metabolism⁶¹ • Nerve function⁶¹ • Neurotransmitter synthesis⁶¹ 	<ul style="list-style-type: none"> • Confusion⁶¹ • Depression⁶¹ • Dermatitis with cheilosis (scaling on the lips and cracks at the corners of the mouth)⁶¹ • Fatigue⁶¹ • Glossitis (swollen tongue)⁶¹ • Irritability⁶¹ • Poor immune function⁶¹ • Peripheral neuropathy - paraesthesia, numbness, and weakness (also a sign of toxicity).⁶²

NUTRIENT	KEY ACTIONS	DEFICIENCY SIGNS AND SYMPTOMS
Vitamin D	<ul style="list-style-type: none"> • Calcium and phosphorus regulation to support bone mineralisation⁶³ • Glucose metabolism⁶³ • Immune system support⁶³ • Mood⁶² • Regulates blood pressure and vascular cell growth to support cardiovascular health⁶³ 	<ul style="list-style-type: none"> • Frequent infections⁶⁴ • Poor bone health and increased risk of osteoporosis and osteomalacia⁴⁸
Vitamin E	<ul style="list-style-type: none"> • Cardiovascular support⁶⁵ • Eye health⁶⁶ • Immune system support^{65,67} • Skin health⁶⁸ 	<ul style="list-style-type: none"> • Decreased night vision⁶⁵ • Frequent infections⁶⁷ • Lack of muscle coordination⁶⁵ • Retinopathy⁶⁶
Vitamin K	<ul style="list-style-type: none"> • Maintaining healthy bone mineralisation⁶⁹ • Maintaining normal blood coagulation⁶⁹ 	<ul style="list-style-type: none"> • Blood taking longer to clot⁶⁹ • Poor bone health, including osteopaenia or osteoporosis⁶⁹
Zinc	<ul style="list-style-type: none"> • Immune system support⁷⁰ • Skin health⁷¹ • Supports normal growth and development during pregnancy, childhood, and adolescence⁷² • Wound healing⁷¹ 	<ul style="list-style-type: none"> • Cognitive impairment⁷⁰ • Frequent infections⁷⁰ • Poor growth⁷⁰ • Reductions in sense of taste⁷² • Rough skin⁷⁰ • Slow wound healing⁷¹ • Weight loss⁷⁰

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Note:

Blackmores has made every effort to ensure that the information in this guide is accurate and up-to-date but this does not guarantee that every possible interaction is included. Blackmores cannot be held responsible for any future changes that may occur in this constantly expanding area of study. The information in this guide is for informational purposes only and is not intended as a substitute for professional advice. Healthcare professionals who consult this document are cautioned that any medical or product-related decision is the sole responsibility of the healthcare professional. Blackmores advises that healthcare professionals should ask patients about both complementary medicine and drug use. Should an adverse event occur, send a 'blue card' adverse reaction reporting form to the TGA or go online to aems.tga.gov.au and inform the manufacturer of both the complementary medicine and the medication.

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About This Guide

This guide outlines the potential nutrient depletions associated with over 40 individual drugs across 10 drug classes and includes guidance on more than 80 nutrient depletions. It serves as an essential resource for healthcare professionals helping them to:



Comprehensive, evidence-based resource for integrative patient care

This guide is a comprehensive, evidence-based resource that offers clear insights into drug-induced nutrient depletions by providing the level of evidence and the likelihood of nutrient depletions linked to specific drugs. The guide empowers healthcare professionals to adopt an integrative approach to patient care, considering all aspects of a patient's health.



Enhance patient safety and care

With clear explanations and practical recommendations, the guide supports proactive monitoring, early identification of nutrient depletions and timely interventions. This proactive approach supports the quality use of medicines and enhances patient safety by ensuring that potential risks are considered and effectively managed.



Support patient-centred clinical practice

Effective communication with patients about nutrient depletions and their management is essential for promoting adherence and achieving optimal health outcomes. The guide assists healthcare providers in communicating complex information in an accessible manner, helping patients understand the importance of monitoring nutrient levels and adhering to supplementation or dietary recommendations.

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