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LEARNING OBJECTIVES

Upon successful completion of this lesson, you should be able to:

1. identify selected drugs which negatively impact vitamin & mineral status
2. describe how selected vitamin & mineral deficiencies occur from drug therapy
3. list important considerations in the selection of vitamin and mineral supplements in the adult population
4. discuss negative consequences of over-supplementation of certain vitamins and/or minerals
5. identify key components of a multiple vitamin and mineral supplement for the older adult

To successfully complete the post-test for this lesson, you will need access to the Internet and a recent edition (e.g., 2008) of the *Compendium of Pharmaceuticals and Specialties (CPS)* for additional information.

INSTRUCTIONS

1. After carefully reading this lesson, study each question in the post-test and select the one option you believe is the best answer. Although more than one option may be considered acceptable, only one option is the best answer.
2. To pass this lesson, a grade of at least 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual pharmacists to notify them.)

ANSWERING OPTIONS

- A. For immediate results, answer online at www.pharmacygateway.ca.
- B. Mail or fax the printed answer card to (416) 764-3937. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from *Pharmacy Practice*.

Drug-induced nutrient depletion & vitamin/mineral supplementation

By Liz da Silva, RD, BHE (Dietetics)



It is commonly known that deficiencies of vitamins and minerals can occur with an inadequate dietary intake, but less appreciated is the fact there are other secondary causes including drug-induced depletion.¹ Pharmaceutical agents negatively impact nutrients through a variety of mechanisms including decreased absorption, and increased excretion and utilization. The consequences of these interactions can range from sub-clinical deficiencies to overt depletion, depending on the nutritional status and intake of the individual, as well as the type, dose and duration of pharmacological therapy. The exact incidence of drug-nutrient interactions is difficult to quantify, but certain drugs are especially problematic if used chronically by susceptible individuals.²

Counselling patients on drug-induced nutrient depletion is challenging for the community pharmacist because of the number of prescriptions dispensed and pressure from consumers to purchase vitamin and mineral supplements. Phar-

macists are in a key position to advise their clients on the relevance of nutrient depletions and how to safely prevent or correct them.

Drug-induced nutrient depletion warrants more attention than it currently receives because, although drug and food interactions are frequently recognized, drug-nutrient interactions are not. That is, when a drug interferes with an indi-

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vidual's nutritional status, it is not readily recognized, monitored or diagnosed.¹ This lesson will review selected medications in the non-pregnant adult population that rob the body of vitamins and minerals. Medications, or classes of medications, were chosen if they were within the top 100 prescriptions dispensed in 2007³ and had significant potential to deplete the body of a vitamin or mineral. Prophylaxis and treatment of drug-induced nutritional deficits are discussed, and general guidance is provided for the selection of individual and multiple vitamins and minerals in otherwise healthy people. Note that drugs discussed in this lesson are not exhaustive and others may cause a nutrient deficiency. A discussion of all recommended nutrient intakes (e.g., related to age or life stage) is beyond the scope of this article. This information is available on web-based Dietary Reference Intake (DRI) tables as described under "How To Choose A Supplement."

Medications that negatively impact vitamin & mineral status

ANTICONVULSANTS

Enzyme-inducing anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine, primidone) can reduce levels of calcium (Ca), vitamin D and folate in the body.^{4,5} The exact mechanism of how these abnormalities occur is not completely known.

The negative impact of enzyme-inducing anticonvulsants on bone metabolism has been known for over three decades and ranges from osteomalacia to overt osteoporosis. There is extensive research confirming that anticonvulsants reduce Ca and vitamin D levels and bone mineral density (BMD).⁵ The high incidence of vitamin D insufficiency (>50%)⁶ is thought to result from accelerated hepatic vitamin D catabolism.^{7,8} Despite extensive documentation of vitamin D depletion, there remains limited awareness of this problem among clinicians. For example, less than one-third of neurologists are aware of the negative impact that enzyme-inducing anticonvulsants have on these nutrients and even less (<10%) prophylactically treat their patients with vitamin D or Ca.⁹ Pharmacists, as educators of drug and nutrient interactions, can be instrumental in reversing this trend.

This class of anticonvulsants can lower serum folate to the point of inducing

megaloblastic anemia in those with a low intake of dietary folic acid.¹⁰ Supplementation on the other hand, is challenging because it can decrease seizure control in a small percentage of susceptible individuals.¹¹ Nonetheless, routine supplementation is recommended with an initial dose of 400 micrograms per day (mcg/day), which is the Recommended Daily Allowance (RDA) for folate.¹¹

Supplementation

The impact of anticonvulsants on folate is significant enough to warrant monitoring its levels. Patients taking these agents should be encouraged to meet recommended daily intakes for Ca and folate.¹² Most researchers also recommend supplemental vitamin D,⁷ but there are no generally accepted guidelines regarding the dose as the amount required to normalize vitamin D levels varies widely (400–4000 IU/day).⁵

DIURETICS

Loop diuretics (LDs) and thiazide diuretics (TDs) are known to affect total body sodium (Na) and potassium (K⁺) levels. Less appreciated is that these agents also deplete the body of Ca, magnesium (Mg) and thiamin by increasing their renal excretion.¹³⁻¹⁵

LDs and TDs have opposite effects on Ca. Chronic LD use sufficiently increases urinary Ca loss to result in bone loss.¹⁶ In contrast, long-term use of TDs results in decreased Ca excretion.

Loop diuretics and TDs commonly cause hypomagnesemia but potassium-sparing (K⁺-sparing) diuretics conserve Mg.¹⁷ Magnesium, in turn, is required for K⁺ to enter cells. Of those with hypokalemia, up to 40% have simultaneous hypomagnesemia. It is important for the pharmacist to be aware that refractory hypokalemia may be caused by an underlying Mg deficiency. A deficiency of K⁺ or Mg can lead to serious cardiovascular and neuromuscular complications.¹⁸

A state of Mg deficiency is frequently overlooked because serum Mg levels, which are usually used to evaluate Mg status, represent only one per cent of body stores.¹⁹ Diuretic therapy is used in several clinical conditions that affect the elderly (e.g., heart failure [HF], hypertension [HTN], edema). This group is at particular risk of developing Mg deficiency because of the high incidence of inadequate Mg dietary intake.

Although LDs and TDs decrease the body's Mg stores, a symptomatic deficiency, does not always occur. However, some researchers feel that even a sub-clinical Mg deficiency shouldn't be overlooked since it is strongly associated with increased ventricular ectopy and arrhythmias.¹⁷ In the absence of a documented deficiency however, it is prudent to withhold routine supplementation pending a renal function assessment. Renal impairment decreases Mg excretion and the resulting hypermagnesemia in those with HF treated with furosemide is associated with a worse prognosis.¹⁹

Furosemide-related thiamin depletion was first described two decades ago, but this effect is not limited to LDs. Indeed, it has been shown to occur with virtually all diuretics.²⁰ The risk of developing a deficiency increases with chronic diuretic use. A thiamin deficiency causes the condition "wet beriberi" (a disease resulting in heart failure and edema), which is reversible with thiamin supplementation. Many studies have confirmed these findings and suggest that treatment of a deficiency can improve cardiac function.^{20,21}

Thiamin is a particularly vulnerable nutrient (compared to Ca and Mg) because of its limited supply in the body.²² The institutionalized, impoverished and elderly are at higher risk of a deficiency because of their compromised dietary intake.²³

Whether diuretics induce sufficient thiamin losses to result in an overt deficiency depends upon many factors, including the dose and duration of diuretic therapy, dietary intake, use of supplements, malnutrition, patient age, chronic alcoholism and severity of heart failure.^{23,24}

Supplementation

Thiamin has been shown to improve left ventricular function,²¹ which is relevant because an increase in ejection fraction is associated with an improvement in survival in patients with HF.²⁵ Many researchers recommend routine thiamin supplementation (20–50 mg/day) for hospitalized HF patients on diuretics, or for the elderly with questionable dietary intake.¹⁴ The exact amount of thiamin required by individuals with HF is not known but it is reasonable to provide a daily supplement containing 20–50 mg to those on chronic diuretic therapy since we know they are at higher risk of developing a deficiency and there

is no known toxicity to this vitamin.^{20,26}

The routine provision of oral magnesium is not recommended without an assessment of renal function.¹⁹

GASTRIC ACID SUPPRESSIVE AGENTS

Proton pump inhibitors (PPIs) and H₂-receptor antagonists (H₂RAs) are increasingly being used for prolonged periods of time and concerns continue to be raised regarding the consequences of long-term therapy.²⁷ Certainly, from a nutritional perspective, these agents have a negative impact on the absorption of iron (Fe),²⁸ Ca,²⁹ and B₁₂.³⁰

Gastric acid is an important factor in the absorption of non-heme Fe (unlike heme Fe) because it facilitates the conversion of ferric ions to ferrous ions. Chronic acid suppression does not appear to cause Fe deficiency in subjects with normal Fe stores, but it may affect anemic individuals. In these cases, Fe therapy can fail unless the gastric acid suppressive agent is discontinued.³¹ Monitoring Fe status is recommended in groups with poor Fe dietary intake (e.g., vegetarians), and those with higher requirements (e.g., menstruating women).³²

Absorption of Ca from food sources does not appear to be affected by hypochlorhydria. Calcium carbonate salts, however, do require an acidic environment for optimal absorption. Individuals on these agents should switch to a Ca citrate salt to optimize absorption.²⁹ (See "How to Choose a Supplement")

Gastric acid suppressive agents cause malabsorption of B₁₂ by inhibiting a critical step that occurs in the stomach, namely the cleavage of B₁₂ from food-bound B₁₂.³³ Without an acidic environment, food-bound B₁₂ passes directly through the gastrointestinal tract unabsorbed. Conversely, synthetic or crystalline B₁₂ (found in foods fortified with vitamin B₁₂ or a vitamin B₁₂ supplement) is not affected by gastric pH.³³ The occurrence of B₁₂ deficiency carries significant morbidity and should not be taken lightly since it can result in irreversible neurological damage even if deficiencies are corrected. As a result, it is imperative deficiencies are both anticipated and treated promptly.³⁴

Even when not taking a PPI or H₂RA, up to 30% of adults > 50 years of age malabsorb food-bound B₁₂ due to the higher prevalence of atrophic gastritis in

this age group.^{22,35} As a result, this population is at particular risk for B₁₂ deficiency when placed on a gastric acid suppressant because they may already present with lower than normal levels of B₁₂.³⁴ Health Canada recommends that all those older than 50 years meet their vitamin B₁₂ needs mainly by consuming foods fortified with vitamin B₁₂ or a supplement containing B₁₂.³⁶

For all ages, the fact that gastric acid suppressive agents may result in clinically significant B₁₂ depletion^{30,34} is of particular concern now that H₂RAs are available in over-the-counter (OTC) formats. It is reasonable to monitor serum B₁₂ levels in individuals who are at particular risk (e.g., the elderly, those with poor dietary intake or gastrointestinal disease) and those that take these medications chronically. However, since this nutrient is inexpensive and innocuous, it is equally reasonable to simply provide a supplement for these individuals rather than wait for a deficiency to develop.³²

Supplementation

Many clinicians are unaware that oral B₁₂ therapy is as effective as the parenteral route in treating a deficiency.³⁷ Indeed, it has been the primary method of intervention for pernicious anemia in Sweden for over three decades. Pharmacists can help raise awareness of this non-invasive and inexpensive therapy. Synthetic B₁₂ is well-absorbed by passive diffusion, including those who malabsorb food-bound B₁₂.³⁸ Even individuals with pernicious anemia can absorb approximately one per cent of high-dose oral B₁₂ through passive diffusion.³⁹

In the presence of hypochlorhydria, the optimal amount of B₁₂ to prevent a deficiency is unclear, with seemingly little research to provide guidance. The current RDA (2.4 mcg/day) is likely too low, and requirements for prevention of deficiency are likely much higher.⁴⁰ As noted, this vitamin is quite safe and an upper limit has not been identified. Most multivitamin preparations contain more than the RDA, and treatment of documented deficiencies have used doses in the range of 1000 mcg/day.⁴¹

CORTICOSTEROIDS

Corticosteroids (CSs) have a high incidence of side effects, of which bone loss is one of the most serious. Corticosteroid therapy has a very rapid and negative

impact on BMD. The rate of bone loss is dose-dependent and can occur with amounts of prednisolone < 7.5 mg/day.⁴² The greatest impact is in the first year but persists throughout the course of therapy. In turn, bone loss is associated with fractures of the vertebrae, hip, pelvis, forearm and ribs. These agents are thought to exert their effect on bone in a variety of ways: suppression of bone formation, reduction in intestinal Ca absorption and increased renal Ca excretion.⁴³

Adequate vitamin D levels are essential for Ca absorption, but vitamin D does not need to be taken at the same time as the Ca supplement.²⁹ The effect of CSs on vitamin D is unknown. However, given the extremely high incidence of vitamin D insufficiency in all Canadians⁴⁴ there is no reason to think those taking a CS would not also be deficient.

Supplementation

Although there is no agreed upon standard dose for calcium and vitamin D supplementation associated with corticosteroid intake, at the very least it is reasonable to provide the recommended daily amounts for both nutrients as a preventive measure for all individuals on CS therapy.⁴⁵

METFORMIN

An association between the biguanide metformin and impaired B₁₂ absorption has been known since the 1970s. Recent studies have confirmed that malabsorption is significant enough to lead to overt deficiencies and is responsible for six per cent of all B₁₂ deficiencies.⁴⁶ The exact cause of malabsorption is unknown but the most promising theory is antagonism of B₁₂ absorption at the active transport sites in the terminal ileum.⁴⁷ A severe B₁₂ deficiency can result in peripheral nerve damage. This is particularly relevant in individuals taking biguanides as B₁₂-induced neuropathy can easily be confused with diabetic neuropathy. Misdiagnosis could lead to avoidable and permanent nerve damage.

Individuals taking metformin experience diminished B₁₂ absorption in a dose- and time-dependent manner. One gram/day of metformin almost triples the risk of B₁₂ deficiency. In a small study of a four-month duration, 30 to 60-year-olds were placed on metformin and their B₁₂ levels monitored. Diminished B₁₂ levels were observed in as little as three months from the start of therapy.⁴⁷ A separate,

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larger study (455 individuals) observed that those taking metformin for > 3 years had double the risk of those taking it for less time.⁴⁸ The depletion of B₁₂ levels significant enough to cause megaloblastic anemia has been observed and can present in five or more years.⁴⁶

Before B₁₂ depletion becomes severe enough to cause megaloblastic anemia, it can elevate homocysteine (Hcy) because it is an integral part of the Hcy metabolic pathway.⁴⁹ Homocysteine is an independent predictor of vascular disease; elevations of Hcy in the diabetic population are particularly relevant and should be avoided because the risk of vascular complications in diabetics is already 2–4 times that of non-diabetics.⁵⁰

Biguanides such as metformin have also been shown to negatively impact folate status, but the incidence and significance of these findings is unclear.⁵¹ Caution is advised regarding folate supplementation as B₁₂ deficiency is often diagnosed by the presence of megalocytosis. Concomitant folic acid can mask a B₁₂ deficiency by correcting megalocytosis, in turn allowing the underlying B₁₂ deficiency to go unchecked and irreversible damage to occur.³³

Supplementation

Supplemental B₁₂ has no known toxicity and is inexpensive. Given the morbidity associated with even a subclinical deficiency, individuals on high-dose and/or prolonged metformin therapy should be routinely monitored for a deficiency, and supplementation with B₁₂ should be considered in all cases.⁴⁸ As with gastric acid suppressants, research has yet to reveal the exact amount required to prevent this drug-induced deficiency, but doses greater than the RDA of 2.4 mcg/day are very likely needed.⁴⁰

METHOTREXATE

Methotrexate (MTX) acts as an antimetabolite to folate. As such, it reduces the body pool of this nutrient and can cause folate deficiency-induced megalocytosis. Lower dose MTX is often prescribed for rheumatoid arthritis and psoriasis. Some of the main obstacles to MTX therapy (e.g., hepatotoxicity, gastrointestinal intolerance, alopecia) can be attenuated through folic acid supplementation without significantly affecting MTX efficacy in most (but not all) patients. An additional benefit of supple-

table 1

Tools and resources for vitamins and minerals

Name of Site	Site description & URL
National Institutes of Health Office of Dietary Supplements	Contains DRI tables and health information on supplement use and safety along with a number of useful fact sheets for patients and health professionals. For DRI tables, select “elements” and “vitamins” at the bottom of the second column. All DRI tables contain food sources, adverse effects, and information about selected nutrients for specific populations of concern. http://ods.od.nih.gov/health_information/health_information.aspx (accessed October 2008)
Natural Medicines Comprehensive Database	Evidence-based monographs on natural ingredients, vitamins & minerals, including safety, efficacy, uses and interactions. www.naturaldatabase.com (accessed October 2008) (Subscription required: approximately \$10/month)
Health Canada Food & Nutrition	First pages have definitions and explanations of different nutrient intake categories. For DRI tables adopted by Health Canada, scroll through the first several pages to “reference values for vitamins” and “reference values for elements.” www.hc-sc.gc.ca/fn-an/nutrition/reference/table/ (accessed October 2008)

DRI = Dietary Reference Intake

mentation is better MTX compliance due to reduced toxicity symptoms.^{52,53}

Supplementation

There is general agreement that folic acid should be prescribed to individuals on MTX therapy who exhibit folate deficiency-induced megalocytosis or other side effects.⁵⁴ Some clinicians feel it should be given to everyone taking this agent.⁵⁵ Additional justification for universal supplementation is based on the effect folate depletion has on raising Hcy levels. Cardiovascular disease is increasingly recognized as a major cause of mortality in individuals with rheumatoid arthritis.⁵⁶ Although there is no consensus regarding the optimal dose and frequency of folate supplementation, the most common suggestion is 5–10 mg once weekly following the MTX dose.⁵⁷

One exception to folic acid supplementation is individuals receiving MTX for cancer therapy (unless recommended by their oncologist). There is some evidence folic acid may reduce the efficacy of MTX in the treatment of lymphoblastic leukemia and theoretically, could reduce its efficacy in other cancer treatments.⁵⁸

How to choose a supplement

There are at least several reasons pharmacists need to be able to assist their clients in making safe choices regarding vitamin and mineral supplements. First,

supplement users represent a significant portion of the Canadian population (vitamin supplements are used by more than one-third of all Canadians).⁵⁹ Secondly, supplement users typically consume more than one supplement and are long-term users, which increases the potential for harm. Finally, consumers lack knowledge regarding appropriate doses and view the activity as “low risk” when in fact it is not without the potential for harm.⁵⁹

The Dietary Reference Intake (DRI) is a system of nutrition recommendations from the Institute of Medicine of the U.S. National Academy.² The DRI system, established by Canadian and U.S. scientists, provides a standard amount for all nutrients for each age and life stage group. This system replaced the Recommended Nutrient Intake system in 1998 and is endorsed by Health Canada.³⁶ Many nutrients have an established RDA, which is the level set to meet the daily needs of 97–98% of healthy individuals. When there is insufficient data to create an RDA, either an “estimated average requirement” (EAR) or “adequate intake” (AI) is used to establish daily nutrient amounts. When such research is available, the DRI also provides a “tolerable upper intake level” (UL), which is the largest amount of a nutrient one can chronically ingest without adverse health outcomes. DRI reference values are based on normal healthy individuals eating a typical mixed North American diet. Those

table 2

Nutrients of concern by age and life stage^{*81}

Population	Nutrients
<ul style="list-style-type: none"> women of reproductive age women & men > 50 years vegans those who avoid entire food groups 	<ul style="list-style-type: none"> folic acid, Fe, Ca vitamin B₁₂, Ca, vitamin D, Mg vitamin B₂, Fe, Zn depends on food group, e.g.,: <ul style="list-style-type: none"> - grains (B vitamins, folic acid, Fe) - dairy (Ca, vitamin D) - meat (Fe, vitamin B₁₂) - vegetables/fruit (vitamin C, folate, carotenoids)
<p>* Not exhaustive; other population sub-groups may need certain nutrients and the sub-groups listed here may need additional vitamins and/or minerals.</p>	

with a nutrient deficiency often need more than the UL of a particular vitamin or mineral for repletion.^{36,60} DRI tables are an indispensable resource for all pharmacists and can be accessed via the Internet. (Table 1)

Determining the need for and correct dosage of a supplement must always include a risk assessment. There are certain nutrients of particular concern and the risk of harm depends on the nutrient's UL, individual susceptibility and intake from other supplements or the diet. Nutrients with no established UL are thiamin, riboflavin, pantothenic acid, biotin and vitamin B₁₂. These are usually considered safe even when consumed in high doses.

INDIVIDUAL NUTRIENTS

Even if individuals eat well, vitamin and mineral supplements are required for subgroups of the population. For example, some individuals will require a supplement if their dietary intake cannot keep up with demand because their need is too great or physiological changes lead to inefficient nutrient utilization. Selected population sub-groups and nutrients of concern are listed in Table 2.

Canada's Food Guide for Healthy Eating, released in 2007, recognizes the need for supplements by certain sub-groups.⁶¹ For example, all women capable of becoming pregnant require supplemental folic acid (400 mcg/day) to decrease the risk of neural tube defects in their offspring.²² For older adults, vitamin D is one of the nutrient requirements that increases with age. The recommended daily intake for those over age 50 is 400 International Units (IU), and increases to 600 IU for those over age 70. Health Canada now recommends all adults over age 50 take a vitamin D supplement, regardless of their diet, particularly if

their sun exposure is inadequate.^{36,62}

Strict vegetarians (vegans) are also of potential concern. By definition, vegans eat only plant-based foods, avoiding all animal products including meat, poultry, fish, eggs and dairy products. In contrast, while all vegetarians avoid meat, poultry and fish, some may consume eggs and/or milk and milk products. Although more people are adopting this health practice, don't assume each is automatically nutritionally deficient. A well-planned vegetarian diet can meet nutritional needs by incorporating different foods as alternatives to different nutrients (e.g., soy or tofu as meat alternatives).⁶³

Vitamin A

Vitamin A (retinol) is the biologically active form of this vitamin and should not be confused with provitamin A carotenoids (e.g., beta-carotene), which are precursors of retinol. The UL for vitamin A was originally set at 10,000 IU/day⁶⁴ because of the risk of hepatotoxicity at higher doses. However, intakes as low as 5000 IU/day have been associated with decreased BMD, osteoporosis and increased fracture risk.^{65,66}

High dose supplementation (5000–10,000 IU) is also associated with an increased risk of mortality and should be limited to those with a clinical deficiency.⁶⁷ It is surprisingly easy to exceed the UL especially if supplements are combined (e.g., a multivitamin [MVM] plus cod liver oil). (See vitamin D)

Vitamin E

The current UL for vitamin E is 450 IU, while the RDA is considerably lower. The UL is based on the increased risk of hemorrhagic damage due to vitamin E anticoagulant activity.^{36,60} Vitamin E supplements are, however, commonly sold as

400 IU and 1000 IU capsules. A recent meta-analysis of vitamin E studies found an association between mortality and supplementation > 150 IU/day.⁶⁸ Higher vitamin E doses should therefore be avoided unless a deficiency is suspected.⁶⁸

Vitamin B₆

The UL for vitamin B₆ (pyridoxine) is set at 100 mg/day. Chronic consumption above this dose may cause sensory neuropathy.²² Individuals taking multiple supplements (e.g., a B-complex with an MVM) should be cautioned that combining supplements can easily exceed this dose.

Vitamin D

The UL for vitamin D (2,000 IU/day) was established a decade ago with limited research. Better quality and more recent evidence indicates the margin of safety is much higher (e.g., likely closer to 10,000 IU/day).⁶⁹ Since vitamin D is tied to Ca absorption, the risk of exceeding the vitamin D UL is hypercalcemia. Supplementation therefore requires medical supervision in those with sarcoidosis, tuberculosis or lymphoma.⁷⁰

The AI for vitamin D currently ranges from 200–600 IU/day,^{36,60} but higher intakes (e.g., 1000 IU/day) are already being suggested.⁶⁹ Most individuals are not able to attain these amounts through diet alone and require a supplement.⁶² For example, 250 ml (1 cup) of milk contains only 100 IU. As such, an older person requiring 600 IU/day would have to consume 1.5 liters of milk to obtain his or her daily requirement.

A precaution with vitamin D is that patients often use, or are advised to use, cod liver oil for their source of vitamin D especially through the winter months. What they may not realize is that cod liver oil also contains vitamin A, sometimes in excessive quantities. For example, some products are reported to contain an average of 15,000 IU vitamin A/20 ml.^{71,72} Conversely, some patients may confuse cod liver oil with "fish oil," which contains no vitamin A or D.⁷³

Vitamin B₁₂

Vitamin B₁₂ (cyanocobalamin) is required for myelin synthesis and repair, and normal maturation of red blood cells. The RDA for adults is 2.4 mcg/day, which includes the requirement that the majority come from fortified foods or a supple-

ment.^{22,36} This nutrient has a long half-life and it can take several years for a deficiency to develop. A clinical deficiency of B₁₂ is classically defined as megaloblastic anemia presenting with neurologic deficits, paresthesias and ataxia. However, it is now generally accepted that a clinically significant deficiency can be present in the absence of megalocytosis resulting in neurological impairment before any anemia is evident.⁷⁴

Oral vitamin B₁₂ is available in a variety of forms (tablets, granules and strips). While there are no studies to indicate which are superior in terms of absorption, most studies have been conducted with tablets. There is no UL for this nutrient, so there is little concern regarding toxicity or intolerance with oral supplementation. The doses required to treat a deficiency is described in Table 3.

Thiamin

Thiamin (vitamin B₁) is a coenzyme for several systems. It is important in the normal functioning of cardiac muscle and the prevention of beriberi. The nutrient is stored in very small quantities in the body and the RDA for adults is a mere 1.2 mg/day for men and 1.1 mg/day for women.^{36,60} A UL has not been established for this vitamin because there is no known toxicity.²²

Folate

Folic acid is the synthetic version of naturally-occurring folate. The UL for this nutrient (1000 mcg/day) is based on the risk of masking a B₁₂ deficiency. Newer research is calling into question the safety of chronic supplementation because epidemiologic evidence suggests it elevates the risk of colorectal cancer.⁷⁵ These findings need to be further explored in clinical trials. Meanwhile, folic acid supplementation (400 mcg/day) should continue to be prescribed to women able to have children⁷⁶ and to those with a documented deficiency.

Calcium

Ca plays a variety of roles in the body. For example, it is vital for bones and the health and functioning of nerves and muscle tissue. There is a very high incidence of inadequate Ca intake, where only 69% of Canadian adults get the Ca they need.⁷⁷ The UL for this nutrient is 2500 mg/day based on the risk for the development of milk alkali syndrome increasing with higher doses.⁷⁸

table 3

Vitamin B₁₂ deficiency—treatment and maintenance^{22,82}

Route of administration	Initial dose	Maintenance dose (for life)
oral	1000–2000 mcg/day for 1–2 weeks	<ul style="list-style-type: none"> pernicious anemia—1 mg/day malabsorption—2.4 mcg/day
parenteral	1000 mcg/day for 1–2 weeks	1000 mcg monthly

mg = milligrams; mcg = micrograms

Supplemental Ca is available as a variety of salts. Calcium carbonate is the most cost effective (40% elemental Ca) compared with Ca citrate (21% elemental Ca). Although the carbonate is more economical and contains the most Ca, a disadvantage is that it must be taken with food for maximal absorption. Also, it is not as biologically available to individuals with hypochlorhydria. In these situations, Ca citrate is the preferred product. Citrates can be taken between meals, but are inconvenient in that more tablets are required to meet a goal dose, which may impact compliance. The maximum dose of elemental Ca from any product that should be taken at one time is 500 mg.²⁹ Calcium supplementation is contraindicated in the presence of hypercalcemia (e.g., sarcoidosis, hyperparathyroidism, hypervitaminosis D, certain types of cancer).²⁹

Magnesium

Mg is a cofactor for more than 300 enzymatic reactions. The RDA is 320 mg for women and 420 mg for men. The UL (350 mg) was established because of its cathartic effect but only refers to synthetic sources (i.e., supplements) and not to dietary sources (on which the RDA is based).⁷⁸ As indicated previously, the incidence of inadequate intake in our elder population is high, but, because it is renally excreted, supplementation should be provided cautiously to those with impaired renal function.

B-complex supplements

The composition of B-complex supplements is quite varied, but generally consists of several B vitamins (e.g., thiamin, riboflavin, niacin, pyridoxine). Some brands also contain folic acid and vitamin C. B-complex does not contain any minerals or fat-soluble vitamins.

CHOOSING A MULTIVITAMIN PRODUCT

As with individual supplements, when suggesting an MVM (a supplement with at least several vitamins and minerals) for

adults there are several things to consider: diet, age, gender, life stage, use of certain medications and supplements and chronic diseases. Different age groups have different needs and the pharmacist should refer to the DRI tables^{36,60} to determine appropriate doses and ULs. Given all the issues to consider, it is helpful to have some broad targets to minimize risk in product selection. Table 4 is one example, with considerations for those > 50 years of age.

Note that, in particular, MVMs are relatively low in Ca⁷⁹ and may be low in vitamin D. When an individual needs additional Ca, vitamin D, or any other ingredient, a single (or combination if needed and available) ingredient product(s) should be recommended. Doing so will discourage people from taking two or more MVMs to make up the desired amount. For example, some older individuals have been known to take two MVMs to meet their vitamin D requirements. This is particularly risky because the combined vitamin A content will likely exceed the UL, promoting morbidities such as hepatotoxicity and osteoporosis.⁸⁰

The pharmacist's role

The public has many misconceptions regarding vitamin and mineral supplements. For example, there is a commonly held belief that these are safe because they are “natural” substances available in a store or pharmacy. As such, there is a need for guidance in the selection of MVMs and single ingredient supplements. This direction can come from a variety of practitioners but since pharmacists are frequently at the point of purchase, they are uniquely positioned to provide advice. The importance of a pharmacist being able to guide supplement selection is highlighted by issues of both safety and efficacy. Much of the pharmacist's role in this regard has already been alluded to.

The prevalence of vitamins and mineral supplement use in Canada is high (42%),⁷⁷ with the top four being MVM prepara-

table 4

Desirable adult (> 50 years) MVM formulation*	
Nutrient	Target
Fe	≤ 8 mg/day ⁷⁹
vitamin A (retinol)	< 5000 IU ⁷⁹
vitamin D ₃ (51-70 years)	400 IU ⁶²
vitamin D ₃ (> 70 years)	600 IU ³⁶
vitamin B ₁₂	≥ 2.4 mcg/day ²²
remaining nutrients	50% to 200% RDA ⁷⁹

*adapted from reference 79; mg = milligrams; mcg = micrograms; MVM = multivitamin; IU = international unit; RDA = recommended daily allowance

tions, Ca, vitamin E and vitamin C.⁵⁹ Older women, in particular, are more likely than men to use supplements. It is also worth reiterating that supplement users commonly take more than one dose and/or more than one product, which

increases the risk of excessive intake.

The pharmacist should ask all individuals about their consumption of other supplements. If supplements are being combined, the total dosage of individual nutrients should be calculated to ensure it is below the UL and/or is enough to meet the patient's nutritional demands. When assessing patients' use, remember to ask about other classes of products—for example natural or complimentary remedies and weight loss aids—both of which may contain one or more vitamins or minerals.

The web sites listed in Table 1 can provide the pharmacist with reliable information regarding vitamins and minerals. For efficiency, the DRI tables can be printed so they are readily available for counseling individual patients about vitamins and minerals.

Summary

There is no doubt certain drugs can and do deplete the body of vitamins and minerals. Some medications have anti-nutrient effects that are significant enough to cause a deficiency. As with drug-drug interac-

tions, the significance of drug-nutrient interactions varies and the challenge is to identify those that can cause harm.

In order to best guide an individual's need for, and appropriate doses of, a vitamin or mineral supplement, pharmacists must not only familiarize themselves with the drugs that cause these occurrences, but also the recommended daily intake and UL for each nutrient. The use of tools such as Health Canada's and the Office of Dietary Supplements' DRI tables is critical for the latter.

The pharmacist's awareness of potential drug-induced deficiencies during the course of dispensing prescription medications (or providing advice on OTC agents), will help limit the occurrence of deficiencies. In turn, awareness of appropriate intakes and which nutrients have a UL will facilitate reduction in the potential for patient harm. ^{CP}

References available at www.pharmacygateway.ca (Go to Continuing Education, CE Archives, Pharmacy Practice Continuing Education Lessons, November 2008, Drug-induced nutrient depletion & vitamin/mineral supplementation.)

Questions

To answer online, go to www.pharmacygateway.ca, CE section, CE Online, Pharmacy Practice

Note: You will need one or both of the DRI tables described in Table 1 of the text to answer some of the following questions. The CPS may also be required.

1 Which of the following situations warrant(s) a prophylactic vitamin supplement?

- a) chronic use of furosemide for HF in a malnourished individual
- b) chronic use of omeprazole for gastric esophageal reflux disease
- c) 10-day course of prednisone 5 mg for an asthma flare-up
- d) both a) and b)
- e) all of the above

2 When determining the total of individual supplements for a patient taking more than one product, the pharmacist can safely save time by assessing only the content of the fat-soluble vitamins A, E, D and K.

- a) true
- b) false

3 What effect does phenytoin have on the body's requirement for calcium and vitamin D?

- a) It increases the requirement of both.
- b) It decreases the requirement of both.
- c) It has no effect on either.
- d) It increases the requirement of calcium and decreases the requirement of vitamin D.
- e) It decreases the requirement of calcium and increases the requirement of vitamin D.

4 Given the following choices, which MVM is preferred for a 79-year-old male taking a PPI?

- a) Product A - thiamin (5 mg), folic acid (400 mcg), vitamin C (100 mg), vitamin B₁₂ (1.5 mcg), calcium (125 mg), vitamin D (400 IU), Zn (13 mg), Fe (19 mg), Mg (45 mg)
- b) Product B - thiamin (2 mg), folic acid (100 mcg), vitamin C (80 mg), vitamin B₁₂ (25 mcg), calcium (120 mg), vitamin D (600 IU), Zn (8 mg), Fe (5mg), Mg (45 mg)
- c) Product C - thiamin (3 mg), folic acid (200 mcg), vitamin C (120 mg), calcium (85 mg), vitamin D (800 IU), Zn (10 mg), Fe (4 mg), Mg (45 mg)

5 A factor not associated with a risk of thiamin deficiency is:

- a) the individual's nutritional status
- b) the dose and duration of diuretic therapy
- c) chronic alcoholism
- d) hypomagnesemia

6 Appropriate management of a 68-year-old individual requiring chronic use of an H₂RA includes:

- a) recommend a vitamin B₁₂ supplement
- b) recommend a folic acid supplement
- c) recommend an increase in dietary B₁₂ from animal protein
- d) both a) and b)
- e) all of the above

7 A 30-year-old female with Type 2 diabetes is taking metformin. She read on the Internet that metformin may cause a vitamin B₁₂ deficiency and would like advice selecting a supplement. Which of the following is the most appropriate product?

- a) B-complex: thiamin (2.5 mg), riboflavin (5 mg), niacin (50 mg), pyridoxine (150 mg), B₁₂ (500 mcg), vitamin C (100 mg)
- b) MVM: thiamin (3 mg), vitamin B₁₂ (25 mcg), folic acid (400 mcg), vitamin C (120 mg), calcium (85 mg), vitamin D (800 IU), Zn (10 mg), Fe (15 mg), Mg (45 mg)
- c) Super MVM: thiamin (1 mg), vitamin B₁₂ (25 mcg), folic acid (50 mcg), vitamin C (500 mg), calcium (65 mg), vitamin D (50 IU), zinc (50 mg), Fe (5 mg), Mg (25 mg), selenium (500 mcg), vitamin A (6000 IU), beta-carotene (10,000 IU)

8 Men and women > 65 years of age both require at least 800 IU of vitamin E each day.

- a) true
- b) false

9 Which of the following individuals is/are at risk for developing a deficiency of one or more vitamins or minerals?

- a) a 45-year-old otherwise healthy male with a 5% intentional weight loss over the past six months
- b) a 27-year-old woman who has been a practising vegan for the past four years
- c) an 80-year-old housebound man who is taking no vitamin supplements and whose weight is stable

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- d) both b) and c)
e) all of the above

10 A 60-year-old male is being treated with MTX for severe psoriasis. About three weeks ago, he started a “mega vitamin/mineral supplement,” and has noticed his “skin seems worse.” What is/are possible explanations for this change?

- a) His supplement may contain a large amount of folic acid which is decreasing the efficacy of MTX.
b) His supplement may be increasing the amount of available MTX leading to a drug-related dermatological reaction.
c) His supplement may contain large amounts of vitamin A which, when combined with MTX, can increase the risk of skin cancer.
d) Both a) and c).
e) Both b) and c).

11 Pernicious anemia may be treated with either oral or parenteral B₁₂.

- a) true b) false

12 Which of the following is/are an appropriate form(s) for a 65-year-old to meet his or her vitamin D requirements?

- a) cod liver oil supplement d) either a) or c)
b) fish oil supplement e) any of the above
c) vitamin D supplement

13 L.S. is a 43-year-old female who only takes carbamazepine for epilepsy. Which of the following is/are true with respect to her potential nutrient requirements?

- a) She is at risk for osteomalacia due to a high incidence of calcium and vitamin D deficiency in patients taking carbamazepine.
b) Carbamazepine can increase her folate levels, putting her at risk for decreased seizure control.
c) Carbamazepine-induced vitamin B₆ deficiency can put L.S. at risk for neuromuscular complications.
d) Both a) and b).
e) All of the above.

14 Which of the following is/are an important consideration(s) in the selection of a MVM for an otherwise healthy 74-year-old man?

- a) It should have at least 15 mg of Fe.
b) It should contain a maximum of 400 IU of vitamin D.
c) It should contain more than 5000 IU of vitamin A.
d) Both a) and b).
e) None of the above.

A.M. is an 82-year-old female with a medical history of heart failure, chronic obstructive pulmonary disease (COPD) and osteoporosis. She was recently discharged from a one-month hospital stay for fluid overload. Her medication profile includes: furosemide, alendronate, docusate and cimetidine. She is taking the following supplements: MVM, B-Complex and calcium citrate (300 mg elemental calcium/tablet BID).

15 A.M. started on a course of corticosteroid therapy that is expected to last several months. Which of the following statements is true?

- a) Corticosteroids increase the need for calcium, and given her other medications and conditions, A.M. likely requires more calcium than she currently takes.
b) The corticosteroid will probably help A.M.'s osteoporosis as it increases BMD.
c) A.M.'s vitamin D intake should be assessed as corticosteroids are known to directly deplete this vitamin.
d) Corticosteroids conserve pyridoxine so her MVM and B-Complex should be assessed to prevent going over the UL.
e) None of the above.

16 A.M. incorrectly always takes both of her Ca supplement doses at bedtime. Which of the following recommendations would enhance her absorption of this nutrient?

- a) Switch her current calcium to a Ca carbonate product.
b) Divide the calcium into no more than 500 mg/dose over the course of the day.
c) Take her current calcium supplement with a meal.
d) Check all supplements to ensure her vitamin D intake is not so high that it would decrease Ca absorption.
e) All of the above.

17 Which of A.M.'s medications increase her risk of developing wet beriberi?

- a) alendronate d) cimetidine
b) docusate e) none of the above
c) furosemide

18 Which of the following are additional potential drug-related problems in A.M.?

- a) She is taking two drugs known to increase the risk of hypomagnesemia.
b) A.M.'s age and medication profile suggest she is at increased risk for hypokalemia.
c) A.M. should automatically be placed on magnesium and potassium to prevent refractory hypokalemia.
d) Both b) and c).
e) All of the above.

19 A patient complains of fatigue, numbness and tingling in her extremities, and altered control of bodily movement. A deficiency in which of the following is most likely to explain these symptoms?

- a) calcium d) vitamin B₆
b) vitamin A e) none of the above
c) vitamin B₁₂

20 DRI tables provide information about both gender- and age-specific vitamin and mineral doses. According to those from the National Institutes of Health Office of Dietary Supplements, which of the following is/are correct?

- a) The RDA for zinc in an otherwise healthy 30-year-old female is 8 mg/day and the UL is 40 mg/day. Requirements are likely to be higher in those who are strict vegetarians.
b) The UL for vitamin C for a 50-year-old male is 2000 mg/day. Going over the UL increases the chances of GI distress, kidney stones and excess iron absorption.
c) The RDA for niacin in a 25-year-old pregnant woman is 18 mg/day (compared to 14 mg/day in a non-pregnant woman of the same age) while the UL is 35 mg/day.
d) Both a) and b).
e) All of the above.

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THIS MONTH

Drug-induced nutrient depletion & vitamin/mineral supplementation

AUTHOR

Liz da Silva's expertise on the topic of micronutriture comes as a result of publishing on the topic and authoring an e-course on vitamin B₁₂. She has lectured at many conferences and most recently at the international conference of the American Society of Parenteral and Enteral Nutrition (ASPEN). Additionally, as the chairperson of the FHA Pharmacy & Therapeutics Nutrition Subcommittee, she has established standards for pharmacy to use in vitamin and mineral selection. And finally, her work in the community and acute care setting has made her aware of some of the challenges faced by both the public and the community pharmacist on the topic of micronutriture.

All lessons are reviewed by a minimum of six pharmacists for accuracy, currency and relevance to current pharmacy practice.

This lesson is valid until October 20, 2011. Information about drug-induced nutrient depletion & vitamin/mineral supplementation may change over the course of this time. Readers are responsible for determining the most current aspects of this topic.

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