Fullscript Academy

Managing Drug-Nutrient Depletions

in Clinical Practice

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Introduction:

Filing an Important Gap

The cells and tissues in the human body require optimal levels of key nutrients in order to function properly. As a result, subclinical nutrient deficiencies can lead to poor health and chronic diseases.

There are many factors that can contribute to nutrient deficiencies, including pharmaceutical medications. Many over-the-counter (OTC) and prescription medications have been shown to negatively influence nutrient digestion, absorption, distribution, metabolism, function, catabolism, and excretion, which can lead to depletions and possible related illnesses over time.

Furthermore, identifying clinically relevant nutrient deficiencies can be challenging as there are often no overt symptoms of depletion, and many clinicians are not as knowledgeable about drug-nutrient interactions, which can lead to a delayed diagnosis. “This topic is not getting enough attention in the scientific literature which creates a knowledge gap between the problem and the solution,” said Danielle Citrolo, PharmD.

“Integrative healthcare practitioners are uniquely positioned to fill this gap,” said Dr. Citrolo, who is a Registered Pharmacist and the Director of Scientific and Regulatory Affairs with Kyowa Hakko USA, Inc., a dietary supplement manufacturer.

Dr. Citrolo’s sentiment is echoed throughout the scientific literature. The authors of a 2017 paper published in the European Journal of Nutrition concluded, “Whereas drugdrug interactions are widely recognized as clinically relevant and are included in most pharmacovigilance systems,

nutrient-drug interactions are underexplored, and their assessment is not part of the clinical routine."

In addition to drug-nutrient depletions, it's worth noting that drug-nutrient interactions in general are important to consider in clinical practice; however, this guide will focus exclusively on drug-nutrient depletions.
Learn more information about other interactions in Addressing pharmaceutical interactions in clinical practice

The Problem

The significant increase in the number of pharmaceuticals being taken by and prescribed to patients has certainly led to an increase in the potential for drug-induced nutrient depletions. In fact, according to the Centers for Disease Control and Prevention (CDC), in 2019, nearly seven in ten adults aged 40 to 79 took at least one pharmaceutical medication and one in five took at least five medications. In addition to prescription medications, the OTC medication industry earned more than $32 billion in retail sales in 2018, which means there are a significant number of medications being ingested by patients in the United States.

What's more, nutrient deficiencies already exist. Based on National Health and Nutrition Examination Survey (NHANES) data, deficiencies of key nutrients such as vitamins A, B, C, D, and E as well as magnesium, calcium, iron, potassium, and selenium are common. Drug-nutrient depletions can further contribute to existing deficiencies, leading to dangerous health ramifications.

"Over time, drug-induced nutrient depletions can mimic the very condition the drug is supposed to treat or create other new health challenges," said integrative health expert Dr. Lise Alschuler, ND, FABNO, who is Associate Director of the Fellowship in Integrative Medicine at the Andrew Weil Center for Integrative Medicine.

In addition, there is not an effective strategy in place to easily identify and correct these deficiencies. "Our medical system does not have a strong communication link between pharmacist, provider, and patient," said clinician Poorvi Shah, DO, who is also a graduate of the

integrative medicine fellowship at the Andrew Weil Center for Integrative Medicine at the University of Arizona. “As a result, drug-nutrient depletions often get missed,” she said.

Identifying patients who may be at risk of developing a drug-induced nutrient deficiency is one way to ensure potential depletions don’t get overlooked. Here are some key risk factors of which clinicians should be aware that can increase the risk of drug-induced nutrient deficiency:

- Advancing age
- Alcoholism
- Gastrointestinal disorders
- Genetically slow metabolism
- H. pylori infection
- Long-term use of the prescription(s)
- Low dietary intake (e.g., vegetarians)
- Poor diet
- Poor liver function or liver disease
- Pre-existing iron deficiency
- Renal disease
- Sedentary lifestyle
- Smoking

Dr. Shah also highlights the fact that polypharmacy, where multiple prescriptions are prescribed simultaneously, can also increase the risk of nutrient depletion.

Polypharmacy and Drug-Nutrient Depletions

As mentioned previously, the CDC reports that one in five American adults presently take at least five different prescription medications, which illustrates the polypharmacy problem. Rising rates of comorbidity is increasing the prevalence of polypharmacy as 26% of all Americans and 61% of Americans over the age of 65 have been diagnosed with two or more chronic conditions.

Some research suggests that polypharmacy may actually be the cause of some of the comorbid conditions, creating a vicious cycle of metabolic pathway disruption and ensuing symptoms and illnesses that are actually the result of drug-induced nutrient depletion(s). “In some cases, correcting the nutrient deficiency may reduce the number of prescriptions the patient needs to take and help prevent the very diseases we are trying to treat,” said Dr. Alschuler. For example, diuretics prescribed for congestive heart failure can help illustrate a key issue associated with drug-nutrient depletions. “The diuretic furosemide has been shown to cause magnesium deficiency, which can further compromise heart function,” said Dr. Alschuler.

"We see this issue of polypharmacy often, especially when patients have multiple doctors involved in their treatment, change clinicians, or are in and out of hospitals," said Dr. Citrolo. "I have done many medication reconciliations in my career and in addition to being aware of depletions, duplicate prescriptions are a very common error." That's why Dr. Citrolo recommends that all integrative clinicians do a medication reconciliation each time they see a patient.

It's also important for clinicians to identify patients who may be at risk of polypharmacy. In addition to the elderly, individuals who are obese, frail, have multiple chronic health conditions, or are physically or mentally declining may have multiple drug prescriptions that should be monitored for potential depletions and interactions.

Mechanisms of Action

Understanding how pharmaceutical drugs deplete nutrients is important. **There are three primary routes that can lead to nutrient depletion:**

1. **Absorption:** Drugs can decrease, increase, or prevent absorption of key nutrients in the gut.

1. **Breakdown:** Metabolism of certain nutrients and herbs in the liver and gut can be increased, requiring a higher dietary intake that may not be achieved by the patient.

1. **Excretion:** Urinary and fecal excretion of nutrients can be either increased or decreased.

A 2016 paper published in the *EPMA Journal* identified these potential pathways that can also lead to nutrient depletion:

- Damage to mucosa and/or intestinal flora
- Formation of bile acids
- Impairment of gastrointestinal motility
- Inactivation of digestive enzymes
- Induction of micronutrient metabolizing enzymes
- Inhibition of micronutrient-intermediate metabolism enzymes
- Loss of appetite, nausea, vomiting, diarrhea, and/or constipation
- Micronutrient antagonism
- pH changes in the gut

The first step to addressing medication-nutrient depletions in clinical practice is identifying which nutrients may potentially be depleted by a specific drug class.

Nutrient Depletions Associated with Common Medications

The following table includes a list of common drug categories and nutrients that can potentially be depleted by drugs in that category.

Pharmaceutical	Class of Drug	Nutrient Depleted	Recommended Dosage	Class of Evidence
Acetaminophen/ Hydrocodone Vicodin, Norco	**Pain** Narcotic, anti-inflammatory	**Glutathione**	**N-acetyl-cysteine:** (FDA-approved protocol) **Loading phase:** 0.14 to 0.16 g/kg up to 17 doses as effervescent tablets **Maintenance dose:** 0.069 to 0.083 g/kg as effervescent tablets	**B**
Albuterol Ventolin, Proventil	**Breathing** Bronchodilator	No significant depletions confirmed	**N/A**	**N/A**
Alprazolam Xanax, Niravam	**Anxiety, panic** Benzodiazepines	No significant depletions confirmed	**N/A**	**N/A**
Amlodipine Norvasc	**Blood pressure** Calcium channel blocker	No significant depletions confirmed	**N/A**	**N/A**
Amoxicillin Amoxil, Moxatag, Larotid	**Antibiotic** Penicillin-type	**Microflora**	**Microflora:** 5 Billion CFU b.i.d. as *B. bifidum* W23, B. lactis W18, *B. longum* W51, E. faecium W54, *L. acidophilus* W37 and W55, *L. paracasei* W72, *L. plantarum* W62, *L. rhamnosus* W71, & *L. salivarius* W24 for 2 weeks during and after 1 week of 500 mg b.i.d. of amoxicillin therapy; Separate antibiotic and probiotic administration by at least 2 hours	**C**
Amoxicillin-clavulanate Augmentin, Amoclan	**Antibiotic** Penicillin-type/ beta-lactamase inhibitors	**Microflora**	**Microflora:** 5 Billion CFU q.d. as *L. paracasei* CRL-431, *B. lactis* BB-12, & *S. thermophilus* TH-4 for 1 month; or 20 billion CFU as B. BB-02, *B. lactis* Bl-04 & Bi-07, *L. acidophilus* NCFM, & *L. paracasei* LPC-37 for 3 weeks; or 25 billion CFU q.d. as *L. acidophilus* ATCC 700396 & *B. animalis ssp. lactis* ATCC SD5220 for 2 weeks; or 500 mg b.i.d. for 2 weeks as *S. boulardii* during and after 1 week of 1 g amoxicillin-clavulanate therapy	**B**

Pharmaceutical	Class of Drug	Nutrient Depleted	Recommended Dosage	Class of Evidence
Atenolol Atenolol	**Blood pressure, angina, migraine** Beta-blockers	**Zinc**	**Zinc:** 20–30 mg (mild), 40–50 mg (moderate-severe) elemental zinc from Zn citrate or Zn gluconate q.d. for 6 months	**A**
		Melatonin	**Melatonin:** 2.5–5 mg q.d. 1 hour before bed during ongoing 100 mg atenolol therapy	**B**
Atorvastatin Lipitor	**Cholesterol** Statin	**Coenzyme Q10**	**CoQ10:** 50–200 mg q.d. ongoing with 10 mg atorvastatin therapy	**B**
Citalopram Celexa	**Antidepressant** Selective-serotonin reuptake inhibitors (SSRI)	**Sodium**	**Zinc:** *Emerg.: 100 ml (oral) or 3% saline (i.v.)	**A**
		Melatonin	**Melatonin:** 2 mg q.d. 1 hour before bed during ongoing 20-30 mg citalopram therapy	**C**
Fluticasone Flovent, Flonase	**Asthma, rhinitis, allergy** Glucocorticoids	No significant depletions confirmed	**N/A**	**N/A**
Furosemide Lasix, Furocot	**Blood pressure, edema** Loop diuretics	**Calcium**	**Calcium:** 500–1,000 mg of elemental Ca t.i.d. from Ca carbonate or Ca citrate and up to 2,000 mg t.i.d. as needed *Emerg.: 100-200 mg (i.v.)	**C**
		Magnesium	**Magnesium:** 300 mg q.d. as Mg citrate during > 80 mg furosemide therapy	**C**
		Pyridoxine (B6)	**Pyridoxine (B6):** 25-50 mg q.d. as pyridoxine hydrochloride	**C**
		Sodium	**Sodium:** *Emerg.: 100 ml (oral) or 3% saline (i.v.	**C**
		Thiamin (B1)	**Thiamin (B1):** 100 mg b.i.d. (i.v.) for 2 days, orally for 1 week and 200 mg long term during 80–230 mg furosemide treatment	**C**
		Vitamin C	**Vitamin C:** 200–500 mg q.d.	**C**
		Zinc	**Zinc:** 20–30 mg (mild), 40–50 mg (moderate-severe) elemental zinc from Zn citrate or Zn gluconate q.d. for 6 months	**C**
Gabapentin Neurontin, Neuraptine	**Neuropathy, pain**	**Folic acid**	**Folic acid:** 400 mcg q.d. (RDA)*	**B**

Pharmaceutical	Class of Drug	Nutrient Depleted	Recommended Dosage	Class of Evidence
Hydro-chlorothiazide Apo-Hydro	**Blood pressure, edema** Thiazide diuretics	**Potassium**	**Potassium:** ~780–1,560 mg (20–40 mmol) q.d. as potassium chloride or potassium magnesium citrate during 50 mg hydrochlorothiazide treatment	A
		Sodium	**Sodium:** *Emerg.: 100 ml (oral) or 3% saline (i.v.)	A
		Zinc	**Zinc:** 20–30 mg (mild), 40–50 mg (moderate-severe) elemental zinc from Zn citrate or Zn gluconate q.d. for 6 months	A
		Magnesium	**Magnesium:** 500–600 mg q.d. as Mg citrate during 25–50 mg hydrochlorothiazide therapy	B
		Chloride	**Chloride:** *Emerg.: 0.9% saline (i.v.)	C
		Folate	**Folate:** 1–5 mg q.d. as folic acid	C
Insulin glargine injection Lantus Solostar	**Diabetes** Insulin analogue	**Magnesium**	**Magnesium:** 336 mg elemental magnesium from Mg-l-lactate q.d. for 3 months during insulin therapy	B
Levothyroxine Levothroid, Synthroid	**Thyroid** Synthetic thyroxine	No significant depletions confirmed	N/A	N/A
Lisinopril Prinivil, Zestril	**Blood pressure** ACE inhibitor	**Zinc**	**Zinc:** 11 mg q.d. for men and 8 mg q.d. for women (RDA)*	A
Losartan Cozaar	**Blood pressure** Angiotensin receptor blockers	**Zinc**	**Zinc:** 20–30 mg (mild), 40–50 mg (moderate-severe) elemental zinc from Zn citrate or Zn gluconate q.d. for 6 months	A
		Calcium	**Calcium:** 500–1,000 mg of elemental Ca t.i.d. from Ca carbonate or Ca citrate and up to 2,000 mg t.i.d. as needed *Emerg.: 100–200 mg (i.v.)	C
		Chloride	**Chloride:** *Emerg.: 0.9% saline (i.v.)	C
		Magnesium	**Magnesium:** 300–600 mg q.d. as Mg citrate	C
		Sodium	**Sodium:** *Emerg.: 100ml, 3% saline (i.v.)	C

Pharmaceutical	Class of Drug	Nutrient Depleted	Recommended Dosage	Class of Evidence
Metformin Glucophage XL, Gluformin	**Diabetes (biguanide)** Hepatic glucose reducer	**Folate**	**Folate:** 5 mg q.d. for 8 weeks during metformin therapy	**B**
		Vitamin B12	**Vitamin B12:** 1,000 mcg q.d. as sublingual methylcobalamin during metformin therapy	**B**
Metoprolol Lopressor, Toprol-XL	**Metoprolol** Beta-blocker	No significant depletions confirmed; See white paper for details	N/A	N/A
Omeprazole Prilosec, Zegerid	**Acid reflux** Proton pump inhibitor	**Magnesium**	**Magnesium:** 250–300 mg q.d. as Mg citrate	**A**
		Vitamin B12	**Vitamin B12:** 1,000–2,000 mcg q.d. as sublingual methylcobalamin	**C**
		Calcium	**Calcium:** 500–1,000 mg elemental calcium t.i.d. from Ca carbonate or Ca citrate and up to 2,000 mg t.i.d. as needed	**C**
		Iron	**Iron:** 105–210 mg elemental iron q.d. from ferrous sulfate, fumarate, or gluconate	**C**
Rosuvastatin Crestor	**Cholesterol** Statin	**Coenzyme Q10**	**CoQ10:** 50–200 mg q.d. ongoing with statin therapy	**A**
Sertraline Zoloft	**Antidepressant** Selective-serotonin reuptake inhibitors (SSRI)	**Sodium**	**Sodium:** *Emerg.: 100 ml (oral) or 3% saline (i.v.)	**A**
Simvastatin Zocor	**Cholesterol** Statin	**Coenzyme Q10**	**CoQ10:** 100–150 mg q.d as ubiquinol during 20 mg simvastatin treatment	**A**
		ß-carotene	**ß-carotene:** 30 mg q.d for 5 weeks	**B**
		Vitamin E	**Vitamin E:** 670 mg (1,000 IU) q.d as d-alpha tocopherol during 10–40 mg simvastatin	**B**
		Glutathione	**Glutathione:** 500–1,000 mg liposomal GSH, or 150 mg t.i.d as sublingual GSH for 2–3 weeks	**C**

For a complete list of references for this table, please refer to the references section found at the end of this guide. For an explanation of the 12 classes of evidence, please see the Rating Scales at fullscript.com/blog/evidence-based-decision-support.

In addition to the medications found in the table, chemotherapy is another broad category with several associated depletions. According to Dr. Alschuler, who is a naturopathic oncologist, any patient with cancer who is receiving chemotherapy is at risk of developing several nutrient depletions. “The most common nutrient depletions I observe are general antioxidant depletions including glutathione, selenium, and depending on the diet, carotenoids,” she said.

“Magnesium and calcium can also be depleted, and some patients can develop anemia as a result of B vitamin deficiencies, either B12, B6, or folate,” she added.

While direct drug-nutrient influences are important, it’s also critical to understand the impact prescription and OTC drugs can have on the gut microbiome.

Disruption of the Gut Microbiome

When healthcare practitioners think of gut disruption and protecting the gut microbiome from certain drugs, they often think of antibiotics. It’s certainly true that antibiotic prescriptions can deplete good bacteria and disrupt the gut environment; however, other drug categories can also have this effect.

In addition to antibiotics, proton-pump inhibitors (PPIs) and statins can negatively affect the composition of the gut microbiome.

Psychotropic drugs, such as SSRIs for the treatment of depression, are metabolized in the gut and have been shown to have antimicrobial activity, which can deplete good bacteria.

A 2019 intervention study showed that metformin, a medication commonly prescribed to treat diabetes, disrupts the gut microbiome.

NSAIDs have also been shown to disrupt microbial balance in the gut especially when combined with PPIs, antidepressants, or laxatives.

In fact, in 2019, researchers from the Netherlands found that one-half of the commonly prescribed drugs they evaluated, which included 18 different popular drug categories, had a disruptive and profound impact on the gut microbiome.

Many of these drugs disrupt the gut microbiome indirectly by influencing gut pH and directly by depleting certain commensal bacteria. Research also shows that the risk of gut microbiome dysfunction and imbalance increases when more than one drug is taken at a time.

This connection between pharmaceutical drugs and the gut is important because research is clearly showing that the health of the gut microbiome significantly impacts overall health on a systemic level. Protecting the balance of this internal bacterial ecosystem is an important clinical goal.

"Gut health is key to the health and wellbeing of a patient, so I explore a patient's gut health not only from a food perspective, but also a drug perspective—past, present, and future," said Dr. Shah. "This can shed significant light on the status of the gut and future risk of disease."

It's crucial that practitioners ask about current and past medication use as both have the potential to contribute to underlying nutrient deficiencies.

The Important Role of the Integrative Health Provider

"The issue of drug-nutrient depletion is very important for clinicians," said Dr. Alschuler. "While we all realize certain medications are necessary and can be extremely helpful, we also appreciate the fact that they can come with certain risks." Understanding and addressing those risks will help integrative healthcare practitioners more effectively serve the health needs of all of their patients.

In addition to identifying all medications a patient is currently taking and their potential health implications, doing regular medication reconciliations, and optimizing gut health, there are two other key roles for the integrative practitioner:

1. Reduce the risk of developing a drug-induced nutrient deficiency

1. Correct identified underlying nutrient deficiencies

"Drug-nutrient depletions are far more common than clinicians may expect," said Dr. Shah. "Many patients are also unaware that drugs can cause nutrient deficiencies, so it's important for practitioners to discuss this issue with their patients."

Determining a baseline status of key nutrients is important, especially for patients who have utilized pharmaceuticals in the past or present. A comprehensive dietary assessment combined with laboratory testing will help determine baseline nutrient status.

Evaluating Nutrient Status

Vitamins and minerals influence health on countless levels. Here are some examples of key nutrients and the roles they play in the human body:

- B vitamins are critical to the central nervous system; they influence cellular energy, antioxidant activity, neuroprotection, and myelin and neurotransmitter synthesis.

- In addition to regulating calcium and phosphorus homeostasis, vitamin D influences immune regulation, cardiovascular health, skin and muscle function, cellular growth control, and several other biological processes in the body.

- Magnesium is an essential mineral that is a required cofactor to perform more than 300 different enzymatic reactions in the body, making it critical to numerous metabolic functions.

- Vitamin A is essential to many physiological processes in the body, including reproduction, growth and development, and immune system activity.

And yet, many patients aren't getting enough of these and other critical nutrients, which puts them at risk of developing chronic illness(es). According to the United States government, "about half of all American adults have one or more preventable, diet-related chronic disease." Getting optimal amounts of key nutrients through diet and dietary supplements is critical in helping to prevent diet-related chronic illnesses. That's why the government establishes Recommended Dietary Allowances (RDAs) and Dietary Reference Intakes (DRIs), which are nutrient requirement levels sufficient to meet the needs of nearly all healthy individuals. When an RDA cannot be firmly established, an Adequate Intake (AI) level is created.

However, RDAs and/or AIs have not been established for all of the key nutrients required by the body to function properly. "One example of an important nutrient without an RDA is glutathione," said Dr. Alschuler. "While the majority of glutathione is produced endogenously, it can become conditionally essential in situations that produce extreme or prolonged oxidative stress, such as chemotherapy, surgery, or other physical trauma or illness."

She explained that there is not a clinically pragmatic way to measure glutathione status directly, so the clinician can use indirect methods to measure oxidative damage, such as blood or urine 8-hydroxy2'-deoxyguanosine, or lipid peroxides, including malondialdehyde.

Glutathione is also an important example because levels decline with age and can be further depleted by taking the OTC medication acetaminophen (e.g., Tylenol). "Although taking acetaminophen is considered to be generally safe in the medical community, when taken daily over a long period of time, it can deplete glutathione levels, especially in the elderly who may already be deficient," said Dr. Citrolo.

There is also no established RDA for CoQ10, and yet this nutrient is an important antioxidant that plays a vital role in adenosine triphosphate (ATP) production and cellular bioenergetics, especially in tissues with high metabolic needs such as the heart. This is problematic for patients prescribed statin drugs because these drugs have been shown to reduce plasma levels of CoQ10 by anywhere from 16 to 54%, which increases the risk of statin-induced myopathy and poor cardiovascular health.

In addition to a lack of RDA or AI, another challenge is that some healthcare professionals feel the established RDAs or AIs for some nutrients are too low. A prime example is vitamin D, which is a common deficiency, but the RDA is only 600 IU daily for people aged one to 70, which may not be enough to help

reduce the risk of vitamin D deficiency and the corresponding illnesses associated with that depletion.

Despite the challenges, testing nutrient levels remains an important step in determining insufficiency or deficiency. Many labs in the integrative medicine industry provide reliable blood and urine testing services to evaluate the status of a wide range of nutrients.

"Some of the tests I order frequently include red blood cell magnesium, red blood cell zinc, serum B12 and methylmalonic acid as a more sensitive indicator of B12 status, serum folate, whole blood selenium, and a fatty acids profile," said Dr. Alschuler.

Every practitioner has their own preferred methods of testing and their preferred lab(s) they use to measure nutrient status. When testing is combined with a thorough intake and ongoing symptom monitoring, druginduced nutrient deficiencies can be prevented, identified, and corrected.

Developing a Personalized Proactive Patient Plan

In the age of personalized medicine, addressing drug-nutrient depletion is an ideal opportunity for integrative practitioners to develop a proactive plan for their patients who are taking medications or have taken them in the past. Clinicians can use a three-step approach to help address potential nutrient depletions:

1. Identify high-risk patients.

1. Protect nutrient status through diet and dietary supplements.

1. Correct deficiencies with diet and dietary supplements.

"I start with a detailed intake of the patient's diet, medications, and lifestyle," said Dr. Shah. "I look for any signs and symptoms that can help me determine potential insufficiencies and I combine all of this information with testing to create a comprehensive treatment plan."
Dr. Shah also feels it's important to get a historical picture of past medication use. "I find that patients will remember the medications they are currently taking, but they may forget to mention drugs that they have taken in the past," she said.

In addition to Dr. Shah's strategy, Dr. Citrolo believes clinicians should work closely with a registered pharmacist. "As a pharmacist, I'm biased, but I recommend practitioners have a clinical pharmacist in their practice or develop a solid working relationship with the local pharmacist," she said. "A good pharmacist can really make a difference to a clinical practice, especially when it comes to the issue of drug-induced nutrient depletions."

The Bottom Line

The integrative health practitioner has a unique perspective. They can help patients who are presently taking medications or those who have taken OTC and/or prescription drugs in the past. They can keenly identify patients at risk, protect nutrient status, and correct any underlying deficiencies that may be present.

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