Fullscript Academy

Addressing Pharmaceutical Interactions

in Clinical Practice

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Pharmaceutical Interventions:
Unintended Consequences

In 2018, Americans spent $482 billion on pharmaceutical medications. [26] *With this large expenditure, pain is alleviated, diseases are controlled, and lives are saved.*

But that's only part of the story. Pharmaceutical medications can have both a positive and negative influence on the human body. Medication interactions are one potential dangerous outcome associated with medication use. Every year, almost 450,000 adults over the age of 65 visit the emergency room as a result of adverse drug events. [26]

Considering Pharmaceutical Interactions in Clinical Practice

Addressing pharmaceutical interactions in clinical practice requires a basic understanding of pharmacokinetics and pharmacodynamics. Pharmacokinetics involves what a pharmaceutical does in the body from the standpoint of absorption, distribution, metabolism, and elimination, whereas pharmacodynamics involves an analysis of what the drug does to the body — the biochemical and physiological effects the medication has on the body. [31] These interactions illustrate a complex interplay between the medication and various body systems that is further complicated by the introduction of food, other medications, and dietary supplements that contain vitamins, minerals, herbs, and other nutrients.

> *As part of their nutrition assessment, integrative practitioners need to evaluate medications because interactions will impact patient outcomes," recommends Ashley Koff, Registered Dietitian and creator of The Better Nutrition Program. "There are different types of interactions," she says, "all of which need to be addressed as part of a personalized nutrition program.*

Pharmaceutical Medication Interactions and Potential Consequences

Practitioners should be aware of the ways in which pharmaceutical medications can interact with food and nutrients, as well as how these interactions can impact clinical outcomes. **Some of the key scenarios include:**

- Food or nutrients in the stomach or intestine can reduce pharmaceutical medication absorption by delaying digestion.
- Food or nutrients can promote pharmaceutical medication absorption.
- Food or nutrients can alter reabsorption and excretion of pharmaceutical medications from the kidneys.
- Some pharmaceutical medications can increase, decrease, or prevent nutrient absorption.
- Some pharmaceutical medications can accelerate nutrient metabolism.
- Some pharmaceutical medications can increase or decrease the urinary excretion of nutrients.

With any of these interactions, potential harmful ramifications can occur, such as:

- Altered and/or depleted nutrient status
- Pharmaceutical medication side effects
- Pharmaceutical medication toxicity
- Reduced efficacy of pharmaceutical medications [4]

One key pathway through which pharmaceutical medications are metabolized is via the cytochrome P450 (CYP) system that has enzymes located in the liver, kidneys, skin, gastrointestinal tract, and lungs. [29] Some foods, nutrients, or herbs are also metabolized by the CYP system. For example, grapefruit and some other citrus fruits can inhibit the CYP enzyme CYP3A4 in the gastrointestinal tract, enhancing the oral bioavailability of some pharmaceutical medications and potentially resulting in adverse effects. [2] This is important as CYP3A4 is responsible for the metabolism of more than half of the pharmaceutical medications presently available on the market. [10] To ensure patient safety and optimal clinical outcomes, close monitoring of potential interactions is required.

Key Pharmaceutical Medication Interactions and Side Effects

There are several types of pharmaceutical medication interactions. This guide will focus specifically on medication-food, medication-nutrient, medication-herb, medication-medication, and medication-condition interactions, as well as side effects that can negatively impact nutritional status. Note that for the remainder of this guide, the term drug will be used interchangeably with pharmaceutical medication.

Medication-Food Interactions

Medications taken orally are absorbed through the lining of the stomach or small intestines, just like food. As a result, food that is present in the digestive tract at the time a medication is taken can influence its absorption. This is an important consideration for practitioners in clinical practice as certain drug-food interactions can reduce the bioavailability of of the drug, potentially reducing the efficacy of treatment. [6] For example, soluble fibers such as pectin can delay the absorption of acetaminophen. Similarly, insoluble fibers such as bran can delay the absorption of digoxin, a medication used to treat various heart conditions. [35]

Common Medication-Food Interactions

The following table outlines other examples of medication-food interactions. [6]

Pharmaceutical Medication	Class of Drug	Food	Outcome
Celiprolol	Beta-blocker	Orange juice	Reduced absorption
Cycloserine	Antibiotic	High-fat foods	Reduced absorption
Esomeprazole	Proton pump inhibitor	High-fat foods	Reduced bioavailability
Levothyroxine	Hormone	Grapefruit juice	Delayed absorption
Theophylline	Xanthine	Caffeine	Increased drug toxicity
Various	Calcium channel blocker	Grapefruit juice	Increased bioavailability
Various	Monoamine oxidase inhibitor	Tyramine foods	Hypertensive crisis

Pharmaceutical Medication	Class of Drug	Food	Outcome
Warfarin	Anticoagulant	Charbroiled foods	Decreased activity
Warfarin	Anticoagulant	Cooked onions	Increased drug toxicity
Warfarin	Anticoagulant	High-protein diet	Raised serum albumin
Warfarin	Anticoagulant	Vitamin K vegetables	Reduced efficacy

In the table above, only two medications are noted as having interactions with grapefruit; however, as of 2013, more than 85 different medications were identified to have possible interactions with grapefruit, with 43 of those having interactions potentially resulting in serious adverse effects. [2] For example, if grapefruit juice is combined with certain statin medications, too much of the medication can remain in an individual's system, which can lead to muscle or liver damage, or even kidney failure. [33]

While avoidance of a nutrient or food may be necessary, a practitioner can personalize recommendations with proper assessment to reduce the potential for nutrient deficiencies or insufficiencies associated with medication use.

In addition to a personalized approach to patient medication monitoring and diet analysis, when and how the medication is taken is important. Many interactions, such as the previous examples given of soluble and insoluble fiber, can be avoided by taking the medication one hour before or two hours after consuming a meal. [35] Another example includes taking a probiotic supplement at least two hours after the ingestion of an antibiotic, which may prevent the reduced efficacy of the medication. [22]

> *"For example, with Warfarin, instead of avoiding vitamin K—an essential nutrient—in foods and supplements, the clinician can collaborate with the patient to standardize regular intake, monitor, and adjust to achieve optimal outcomes," says Ashley who is also Chief Nutrition Officer at BeyondBrands, a plant-based consulting agency. "Another example is caffeine, which can negatively interact with some medications, but the practitioner can also look at how the patient metabolizes caffeine to fine-tune their recommendation."*

Medication-Nutrient Interactions

According to the Council for Responsible Nutrition, 77% of Americans reported taking dietary supplements in 2019. [11] Most of the information on medication-nutrient interactions focus on nutrient depletion, which can be extensive as both over-the-counter (OTC) and prescription medications can negatively influence nutrient digestion, absorption, distribution, metabolism, function, catabolism, and excretion. [27] While most dietary supplements are considered safe, ingredients in these products can interact with certain medications. Just as with foods, some vitamins, minerals, and other nutrients can either increase or decrease the absorption of the medication, which can contribute to adverse effects. **Here are some examples:**

- Iron and zinc can reduce the intestinal absorption of quinolone antibacterials, cephalexin antibiotics, and tetracycline antibiotics, thereby reducing the medication's efficacy. [12]

- Calcium and iron supplements can decrease the absorption of levothyroxine, which may require an increase in dose of the medication. [13]

- Vitamin B6 can reduce or negate the effects of levodopa, a medication used for Parkinson's disease. [25]

- N-acetyl cysteine may reduce the efficacy of chemotherapy and radiation during active cancer treatment. [30]

Cancer treatment can be especially challenging when it comes to monitoring interactions. According to naturopathic oncologist and Editor-in-Chief of the peer reviewed open access publication, *Natural Medicine Journal*, Dr. Tina Kaczor, ND, FABNO, **"the vast majority of natural agents we use have not been tested in combination withchemotherapy and radiation so we do not know the interactions."**

She recommends that general practice integrative practitioners abstain from using natural agents that don't have direct evidence of benefit with a specific cancer medication.

> *If a practitioner is not well-versed in oncology," she says, "the best way to 'do no harm' is to wait until the treatment is over, then do what we do so well—support and optimize recovery back to health.*

Nutrient Interactions Associated With Common Pharmaceutical Medications

The chart below primarily includes drug-nutrient interactions for which evidence from systematic reviews, meta-analyses, and randomized, double-blind, placebo-controlled human trials was available. See the white paper for a full review of literature on the nutrient interactions associated with common pharmaceutical medications.

For an explanation of the classes of evidence, please see the rating scales.

Additive	Class of Drug	Nutrient	Interaction	Class of Evidence
Acetaminophen/ Hydrocodone Vicodin, Norco	**Pain** Narcotic, anti-inflammatory	**Caffeine**	Increases analgesic effects Increases absorption Increases elimination of drug	A B C
		Alcohol	Increases risk of hepatotoxicity Induces CYP2E1	B C
Albuterol Ventolin, Proventil	**Breathing** Bronchodilator	**None**	No significant interactions confirmed.	N/A
Amlodipine Norvasc	**Blood pressure** Calcium channel blocker	**Grapefruit juice**	Inhibits CYP3A4; slightly increases plasma concentration of drug	C
Atorvastatin Lipitor	**Cholesterol** Statin	**Grapefruit juice**	Increases serum atorvastatin; Induces CYP3A4; increases plasma concentration of atorvastatin acid and atorvastatin lactone	B C
		St. John's wort	Increases LDL and total cholesterol	C
Gabapentin Neurontin, Neuraptine	**Neuropathy, pain**	**Alcohol**	Safe to use in treatment of alcohol dependency; reduces symptoms of alcohol withdrawal	A
		Cannabis	Reduces symptoms of cannabis withdrawal	B
Insulin glargine injection Lantus Solostar	**Diabetes** Insulin analogue	**Berberine**	Potential significant theoretical interaction. See the white paper for further details.	F
Levothyroxine Levothroid, Synthroid	**Thyroid** Synthetic thyroxine	**Calcium**	Decreases absorption of drug; increases in TSH	B
		Vitamin C	Increases absorption of drug; decreases in TSH	B
		Coffee	Decreases absorption of drug	C
		Grapefruit juice	Inhibits OATP1A2; slightly decreases absorption of drug	C
Lisinopril Prinivil, Zestril	**Blood pressure** ACE inhibitor	**None**	No significant interactions confirmed.	N/A

Additive	Class of Drug	Nutrient	Interaction	Class of Evidence
Metformin Glucophage XL, Gluformin	**Diabetes (biguanide)** Hepatic glucose reducer	**Berberine (300 mg)**	Improves insulin sensitivity; decreases HOMA-IR, total cholesterol, LDL	**B**
		Alcohol (>7 drinks per week)	Increases effects of drugs; increases lactic acidosis and lactate production	**C**
Metoprolol Lopressor, Toprol-XL	**Blood pressure** Beta-blocker	**None**	No significant interactions confirmed.	**N/A**
Omeprazole Prilosec, Zegerid	**Acid-reflux** Proton pump inhibitor	**St. John's wort**	Induces CYP2C19 and CYP3A4; decreases effectiveness of drug	**C**
		Grapefruit juice	Inhibits CYP3A4; inhibits metabolism of drug	**C**
Rosuvastatin Crestor	**Cholesterol** Statin	**Grapefruit juice**	Inhibits OATP2B1; reduces bioavailability of drug	**C**
		EGCG	Significantly reduces systemic exposure of drug	**C**

Note: The information provided in this chart is based on a review of literature available at the time of publication. While the content is considered to be accurate at the time of publication, new or updated research released after the publication date may impact the accuracy of the information. Please use clinical discretion when using this resource.

Updated: January 30, 2019 Version 1.1

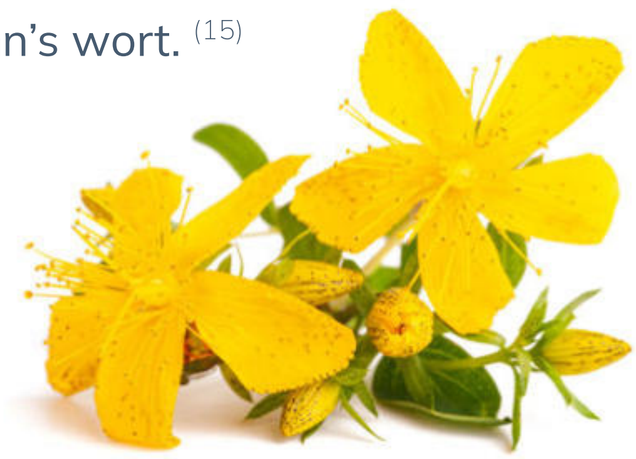
Medication-Herb Interactions

While Dr. Kaczor is concerned about medication-nutrient interactions, she says that drug-herb interactions concern her the most, especially in the field of oncology.

> *Nutrients and drugs are single agents, which can be more predictable and often better studied for interactions," says Dr. Kaczor, who is also the founder of Round Table Cancer Care.*
> *"Herbs, however, are a complex mixture of thousands of compounds that range from nourishing foodstuffs to drug-like agents in their actions.*

Herbal supplements are available as a single herb and as herbal combinations. **"Herbal combinations can add a layer of complexity to the drug-herb interaction dilemma as well because each herb has so many active constituents," says Dr. Kaczor.**

Specifically regarding oncology, according to a 2019 review, six plants, in particular, have been shown to negatively interact with chemotherapy medications, including echinacea, garlic, ginseng, grapefruit, milk thistle, and St. John's wort. [15]



Chemotherapy is not the only drug that has concerning drug-herb interactions as it relates to St. John's wort. In fact, presently there are 95 medications known to have interactions with St. John's wort, including birth control medications. [24] Oral contraceptives are one of the most commonly prescribed classes of medications, with approximately 60% of women of reproductive age currently using some form of contraceptive medication. [21]

Women's health expert and author of Beyond the Pill Dr. Jolene Brighten, ND explains that there is data suggesting that St. John's wort can reduce the efficacy of oral birth control. "That's why we typically avoid recommending St. John's wort when oral contraceptive prescriptions are the primary form of pregnancy prevention."

St. John's wort is certainly one of the most studied medication-herb interactions in scientific literature. Adverse events with St. John's wort include photosensitivity/phototoxic reactions, increased bleeding when used with anticoagulants, and breakthrough bleeding with oral contraceptives. [28]

In addition to St. John's wort, significant medication-herb interactions may also occur with silymarin and resveratrol. This is because all three of these herbs are metabolized via the CYP system, the same pathway that many pharmaceutical medications utilize, as mentioned previously. Specifically regarding the CYP system, silymarin and resveratrol can inhibit CYP3A4 activity, potentially increasing medication bioavailability and toxicity.[5]

The author of a 2012 review states that risk of adverse events associated with medication-herb interactions are low, however, that risk increases when dealing with medications that have a narrow therapeutic index. (19)

> *When there is a narrow dosage range of effectiveness, as with chemotherapy and other drugs," says Dr. Kaczor, "anything that changes the metabolism of the drug, either faster or slower, can lead to missing that narrow range completely, which can contribute to ineffective treatment or toxicity.*

While there are case reports and theoretical justification regarding some medication-herb interactions, more research in this area is needed.

"The lack of data regarding interactions between drugs and herbs is why I am most concerned with these interactions versus the other categories [drug-food, drug-nutrient]," says Dr. Kaczor.

Of course, reduced efficacy and adverse events can also take place with medication-medication interactions.

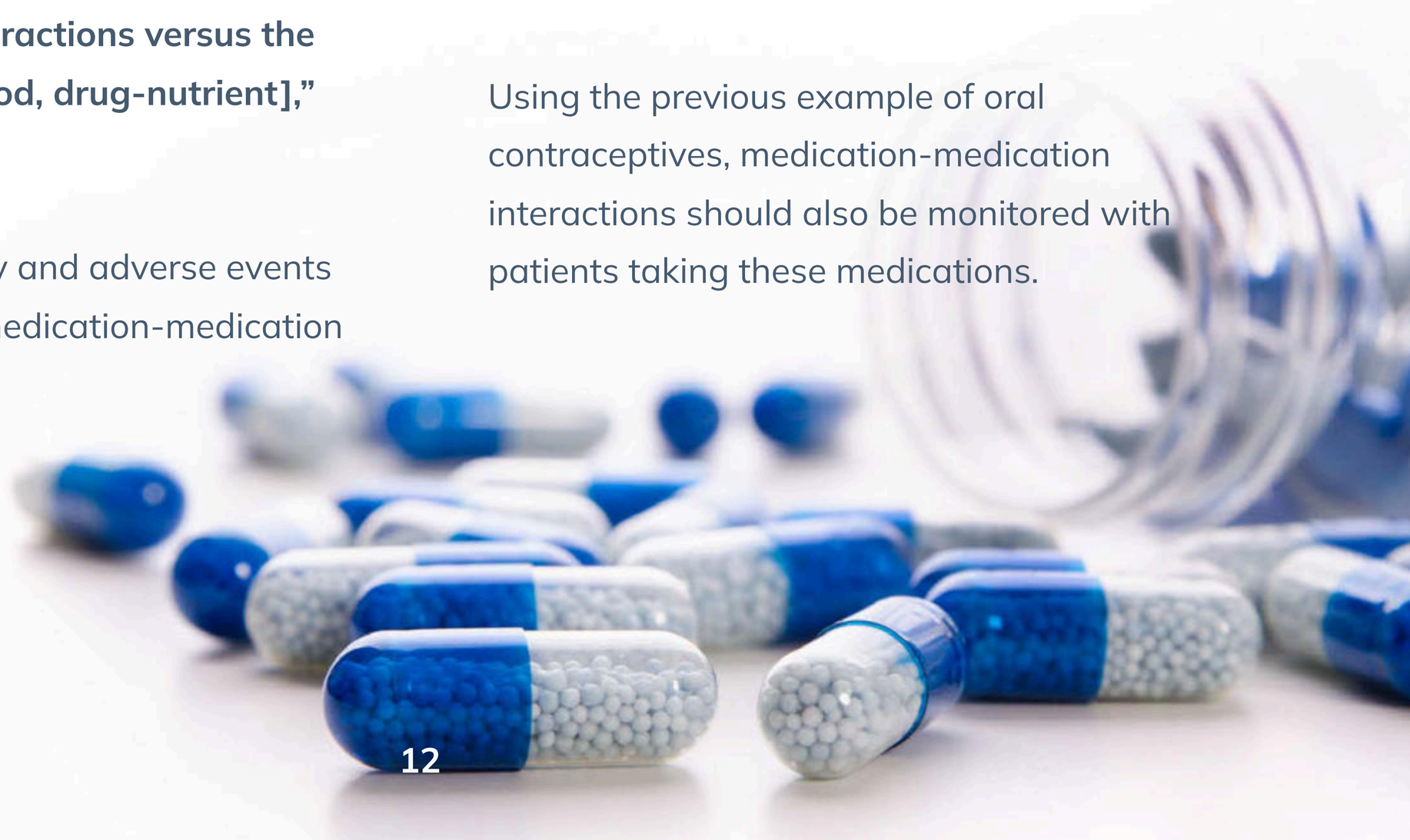
Medication-Medication Interactions

In the United States, medication-medication interactions can be serious and expensive. Each year they cause approximately 2.8% of all hospitalizations, accounting for more than 245,000 visits and a total cost of $1.3 billion. (7) As mentioned previously with other types of interactions, in addition to reducing the therapeutic effects of a medication, medication-medication interactions can have serious and potentially life-threatening adverse effects, such as gastrointestinal bleeding and hyperkalemia.(8)

Some medication-medication combinations that can cause significant adverse effects include:

- Celecoxib with methotrexate
- Clopidogrel and aspirin
- Diclofenac with methotrexate
- Diclofenac with glimepiride
- Digoxin with spironolactone
- Fenofibrate with omeprazole
- Losartan with diclofenac
- Omeprazole with losartan (14)

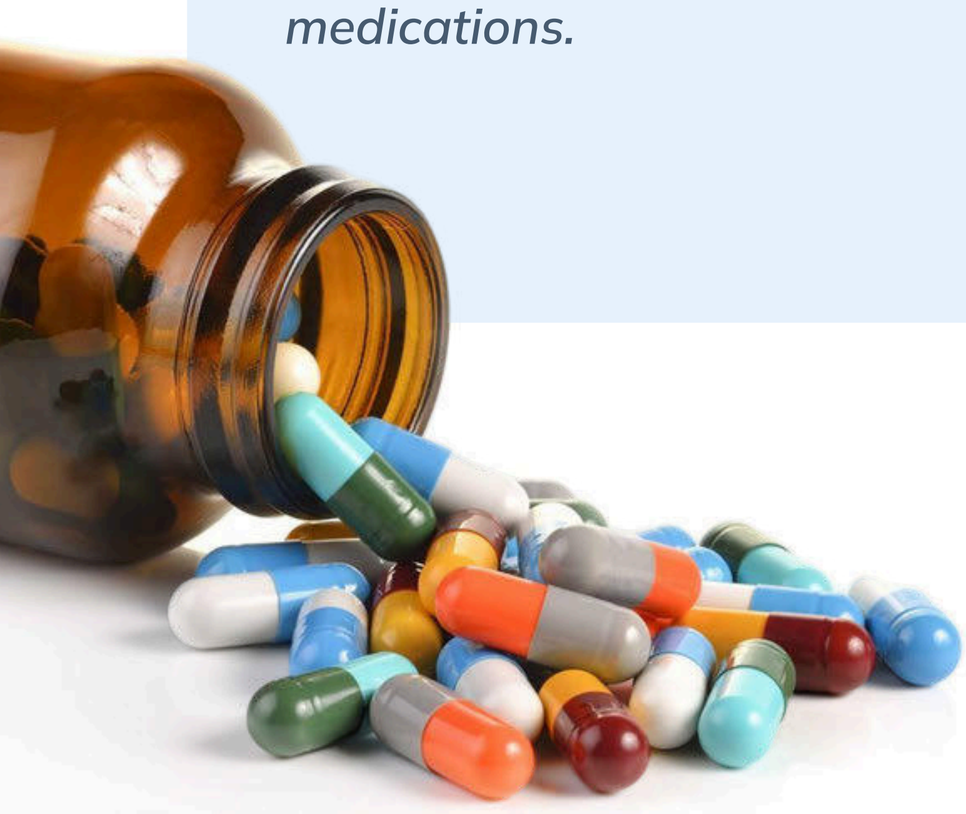
Using the previous example of oral contraceptives, medication-medication interactions should also be monitored with patients taking these medications.



One of the most significant causes of medication-medication interactions is polypharmacy, when more than one medication is prescribed at the same time. The Centers for Disease Control and Prevention estimates that one in five American adults are presently taking at least five different prescription medications. [16]

Another aspect that can influence drug interactions is the health status of the patient.

> *While all antibiotics do not make oral contraceptives ineffective, the antibiotic rifampin does interact and will reduce the efficacy of birth control medications," says Dr. Brighten, who is the Chief Medical Officer at Rubus Health in Portland, OR and Oakland, CA. "Anticonvulsants, seizure medications, and HIV drugs have also been shown to make birth control medications less effective. In general, drugs that increase liver enzyme activity, such as rifampin and phenobarbital, can reduce the efficacy of birth control medications.*



Medication-Condition Interactions

"Drug-condition interactions can sometimes be overlooked by practitioners," says Dr. Brighten. "For example, oral contraception is contraindicated in women with migraines with aura, cardiovascular disease, or high blood pressure."

Prescribing an inappropriate medication due to a related condition can lead to increased healthcare utilization, as well as an increased risk of mortality, morbidity, and adverse events. [23] In fact, in one study involving 600 patients 65 years or older, patients with drug-condition interactions were about twice as likely to report an adverse event to a medication compared to those without this type of interaction. [17]

Medication-condition interactions can also occur with OTC medications. In one study, the most common drug-condition interaction occurred in patients with a history of peptic ulcers who were also taking aspirin or NSAIDs. [18] Another example is with gout as gout medications can increase the risk of heart failure. [9]

In addition to direct interactions that can negatively influence clinical outcomes, medications can also cause side effects that can impact a patient's nutritional status, reducing overall wellness and quality of life.

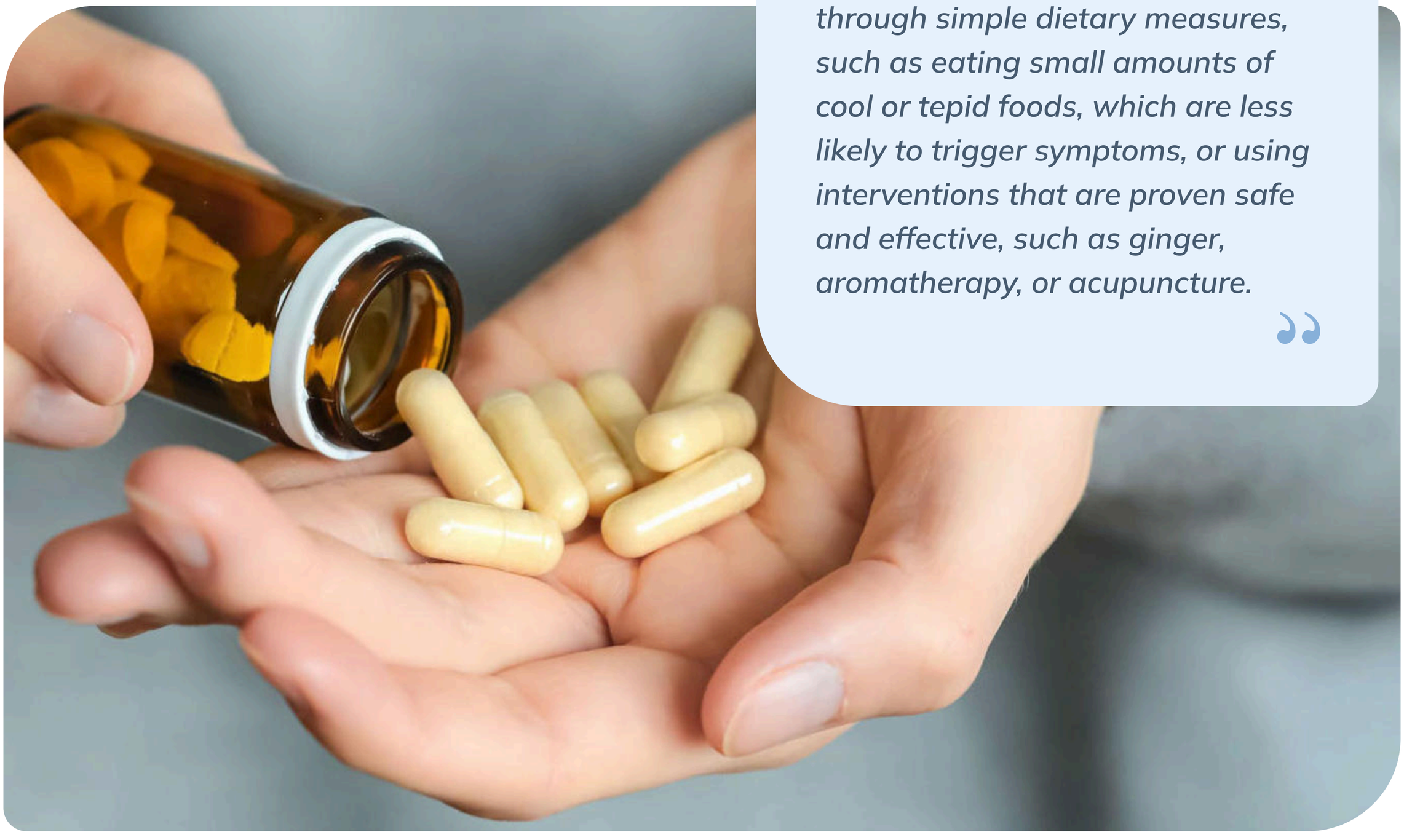
Medication-Nutrition Side Effects

Certain drug side effects can negatively impact nutritional status. For example, antibiotics can cause diarrhea, constipation, or abdominal pain. [3] A 2020 study featured in the journal Menopause found that antidepressants, beta-blockers, and insulin were all associated with weight gain in postmenopausal women. [32]

As for weight loss, there are many medications that can contribute to anorexia, including amantadine, digoxin, fluoxetine, levodopa, lithium, metformin, penicillamine, topiramate, and nortriptyline. [34] It is estimated that one- half of people diagnosed with cancer are at risk of developing cachexia, which is anorexia combined with progressive loss of muscle mass. [1]

As with chemotherapy, there are other examples of ways to avoid or reduce medication side effects. Oftentimes, adhering to prescription guidelines will help. It's important that the patient finishes the medication, does not skip doses or take more than prescribed, and takes the medication at the required time of day. [20] Encouraging patients to closely follow prescription guidelines is an important role for the integrative health practitioner.

> *Chemotherapy, by definition, is almost always a toxic compound, so it's not surprising that the body often responds to it with symptoms of nausea and loss of appetite," explains Dr. Kaczor.*
> *"The integrative practitioner may suggest lessening these symptoms through simple dietary measures, such as eating small amounts of cool or tepid foods, which are less likely to trigger symptoms, or using interventions that are proven safe and effective, such as ginger, aromatherapy, or acupuncture.*



The Bottom Line

“Medication interactions impact patient outcomes, so it’s important that practitioners have a comprehensive assessment system that they use not just at the initial visit but throughout the entire time a practitioner is working with that patient,” says Ashley Koff. “This will also help patients understand the interrelationship that medications have on their overall health program.”

There is a broad scope of medication interactions to consider, including with food, nutrients, herbs, other medications, and existing conditions. In addition, being aware of and managing the side effects caused by certain medications is equally important.

> *Physicians should cross reference prescriptions with any supplements the patient may be taking,” recommends Dr. Brighten. She says if a practitioner is not licensed to prescribe medications, it may be unlikely they’ve received sufficient pharmacology training to thoroughly evaluate drug interactions. “In this case, the practitioner may want to contact the prescribing clinician prior to recommending herbs, nutrients, or other interventions,” she says. “That’s really the best way to ensure the safety of those patients who are taking prescription medications.*

For both the practitioner and the patient, the first step towards addressing interactions is awareness. A proactive plan can then be created to help reduce the risk of adverse events and increase the chance of successful clinical outcomes. If you are a patient, please consult with your practitioner if you have concerns about interactions.

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