# Chapter 12
# Drug-Dietary Interactions: Over-the-Counter Medications, Herbs, and Dietary Supplements


**Laurence J. Kinsella, George T. Grossberg, and Neha Prakash**

## Case Vignette

A 35-year-old man presents with sudden onset of severe throbbing headache, nausea, and light sensitivity. He has no prior history of headaches and migraine. In the emergency department, his examination is normal except for mild neck stiffness and photophobia. Computed tomography (CT) of the brain was unrevealing, and lumbar puncture showed no evidence of subarachnoid hemorrhage. Magnetic resonance imaging (MRI) was performed demonstrating multiple small white matter lesions on FLAIR sequences with normal diffusion-weighted imaging. An MR angiogram demonstrated multiple segmental arterial narrowing in the branches of the middle cerebral arteries. When questioned further, he admitted to using Hydroxycut for weight loss in the last 15 days. Symptoms resolved when the supplement was stopped [1].

L. J. Kinsella, MD (✉)
Department of Neurology, SSM Neuroscience Institute, St. Louis, MO, USA

Department of Neurology, St. Louis University School of Medicine, St. Louis, MO, USA
e-mail: Laurence.Kinsella@ssmhealth.com

G. T. Grossberg, MD
Division of Geriatric Psychiatry, Department of Psychiatry & Behavioral Neuroscience, St. Louis University School of Medicine, St. Louis, MO, USA

N. Prakash, MD
Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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## Introduction

Herbal medications have been used throughout human history. Since the DHEAS Act of 1994, there has been an explosion of new products marketed to a welcoming public. Dietary supplements are far less rigorously regulated than drugs by the Federal Drug Administration (FDA). The FDA defines dietary supplement as "a product intended for ingestion that contains a 'dietary ingredient' intended to further nutritional value to supplement the diet. A 'dietary ingredient' may be one, or any combination, of the following substances: a vitamin, a mineral, an herb or other botanical" [2]. There are over 50,000 dietary supplements registered with the Office of Dietary Supplements, a division of the National Institutes of Health. The most popular include vitamin and minerals (43%), specialty supplements for weight loss and sexual health (20%), botanicals (20%), and sports (16%) [3]. Over half of American adults take dietary supplements, and about a third of older adults take over the counter medications (OTCs) [4].

Dietary supplements of interest to neurologists include the migraine remedies feverfew, riboflavin, magnesium and butterbur extract. Galantamine, a plant extract, is used in the treatment of Alzheimer's disease [3].

Without claiming to treat a disease, the dietary supplement industry may promote health and wellness benefits without the requirement of randomized controlled trials, although a number do exist [3].

Herbs may be complicated mixtures of organic and inorganic compounds, some with potentially toxic ingredients [5]. The strength and quantity of the active ingredient may differ among manufacturers. There are efforts to standardize supplement ingredients for consistency and safety [6]. As the use of herbs and over-the-counter (OTC) medications increases, so too the risk of interactions with prescribed medications. This review highlights potential side effects and drug interactions possible with OTCs, herbal medicines, and dietary supplements without undermining the potential, though often unproven, benefits when used appropriately.

In one study, 43% of patients in an outpatient practice were taking both a dietary supplement with prescribed medication. The most common products included vitamins and minerals, garlic, *Ginkgo biloba*, saw palmetto, and ginseng.

About 6% had potentially serious drug-OTC interactions [7]. This included patients taking both calcium and ciprofloxacin (reduced absorption of fluoroquinolones), potassium plus lisinopril (risk for hyperkalemia), and St John's wort plus paroxetine (increased risk of serotonin syndrome) [8].

## Clinical Syndromes of Drug-Diet-OTC Toxicity

The presentation of herbal and OTC medication toxicity has a wide spectrum (Table 12.1). The use of excessive diphenhydramine as a sleep aid may induce somnolence and confusion, especially when combined with a beta blocker or other

**Table 12.1** Some neurologic syndromes associated with dietary supplements

| Neurologic syndrome | Medication examples |
|---|---|
| Reversible cerebral vasoconstriction syndrome | Sympathomimetic amines (khat, ephedra, ma huang, pseudoephedrine), caffeine, marijuana [9] |
| Drug-induced seizure | Khat, HCA, caffeine, diphenhydramine [10] |
| | Gingko [11] |
| Serotonin syndrome | Tryptophan [12] |
| Large fiber neuropathy | Pyridoxine (B6) [13, 14] |
| Rhabdomyolysis | Hydroxycut [15] |
| Acute renal failure | Orlistat [16] |
| Syncope from prolonged QT | Energy drinks, guarana, caffeine [17] diphenhydramine [18] |
| Intracerebral hemorrhage | Ginseng, garlic, gingko [19–21] |
| Delirium | Dextromethorphan, diphenhydramine [22] |

**Table 12.2** Dietary supplement toxicity

| Agent | Mechanism of injury | Toxicity symptoms |
|---|---|---|
| Pyridoxine (vitamin B6) | Enzyme inhibition [27] | Large fiber neuropathy, sensory ataxia [13, 14, 28] |
| Chinese herbal remedies | Heavy metal intoxication [29] | Neuropathy, encephalopathy [5, 29] |
| Metabolife | Excitotoxicity (yohimbine, guarana) | QTc prolongation, arrhythmia [30] |
| Caffeine | Excitotoxicity | Cardiac arrhythmia [30] |

inhibitor of P450 2D6. Vasoactive compounds such as pseudoephedrine (also known as ephedra and ma huang) in cough and weight loss remedies may induce stroke, seizures, or thunderclap headache. Since 2004, the FDA has banned the use of ephedra-containing compounds in dietary supplements [23].

One striking presentation of toxicity is reversible cerebral vasoconstriction syndrome (RCVS). It often presents as a thunderclap headache with or without neurological deficits. Angiography may show multifocal cerebral artery vasospasm [1, 9, 24]. RCVS has been reported secondary to vasoactive substances such as pseudoephedrine, caffeine, energy drinks, marijuana, and other naturally occurring stimulants. Another example is *khat*, a plant (*Catha edulis*) chewed in countries like Yemen. Its active ingredient is an amphetamine-like agent that may trigger cerebral vasospasm, stroke, and seizure [25, 26].

## *Dietary Supplement Toxicity*

Toxicity may be direct or secondary to an interaction with a prescribed or OTC medication. Some examples of toxicity from dietary supplements are seen Table 12.2. Pyridoxine in doses >200 mg per day for several months or >1000 mg per day for several days may induce a severe peripheral neuropathy [13, 14, 31]. Chinese herbal remedies may be laced with heavy metals [5].

## *Mechanism of the Drug-Diet Interaction*

### Over-the-Counter Medications

Increasing over-the-counter (OTC) medication use has been associated with increasing reports of toxicity and abuse (Tables 12.3 and 12.4) [40]. OTCs can be categorized as:

1. Medications for common ailments (cough syrup, analgesics, antiseptics, antifungal/antibacterials, motion sickness medications, etc.)
2. Herbal and dietary supplements
3. Weight loss supplements

Finkelstein found that one-fourth of all poisoning cases in the pediatric population seen in an ER involve improper use of OTCs [22]. Abuse and misuse of OTCs has been associated with depression [41].

Dextromethorphan is a commonly consumed cough remedy. Side effects are dose dependent and vary from mild sedation at low doses to hallucinations and

**Table 12.3** Ten examples of potential drug-OTC interactions

| OTC | Rx drug | Interaction |
|---|---|---|
| Diphenhydramine | Metoprolol | Bradycardia |
| | SSRI/SNRI | Serotonin syndrome |
| Pseudoephedrine | SSRI/SNRI | Serotonin syndrome |
| Acetaminophen | Alcohol | Increased toxic acetaminophen metabolites, increased alcohol levels [32] |
| Caffeine | Alcohol | Inhibitor of CYP1A2, raising caffeine levels [30] |
| Aspirin | Valproate | Displaces VPA, raising levels [33] |
| Omeprazole | Ciprofloxacin | Reduced Cipro levels, CYP1A2 vs malabsorption [34] |
| Fexofenadine | Ketoconazole | Increased fexofenadine levels [35] |
| Dextromethorphan | Quinidine | Increased serum concentrations due to 2D6 inhibition, now FDA approved for pseudobulbar affect (NUEDEXTA) [36] |
| Loperamide | Quinidine | CNS depression due to PGP inhibition within blood-brain barrier [37] |

**Table 12.4** Mechanisms of drug-diet interactions

| Example | Adverse event | Mechanism |
|---|---|---|
| Diphenhydramine and alcohol | Additive sedative properties | Pharmacodynamic interaction |
| Fluvoxamine and caffeine | Increased caffeine levels [38] | P450 1A2 enzyme inhibition [30] |
| Amitriptyline and St John's wort | Low amitriptyline levels [39] | P450 3A4 enzyme induction |
| Statins and grapefruit juice | Myalgias, statin myopathy | Inhibits first-pass metabolism of 3A4 enzyme |
| Warfarin and spinach | Reduced INR, increase thrombotic risk | Incomplete vitamin K inhibition |

ataxia and coma at higher doses. In a review of adolescent overdose, 25% are OTC medications, and half were due to dextromethorphan [22]. Other common agents of overdose include diphenhydramine [42], aspirin, acetominophen, motion sickness agents such as dramamine, and pseudoephedrine.

## Weight Loss Supplements

Weight loss supplements are popular and are a dominant player in the dietary supplement industry. A quick review of Amazon shows hundreds of products marketed to the public [43]. Some of the most widely used supplements and their ingredients are listed in Table 12.5. Hydroxycut is among the most popular weight loss supplements. Prior to 2004, it contained both ephedra and caffeine. It has had several reformulations due to reports of toxicity and was pulled off the market in 2009 following an FDA warning [55]. Current versions contain up to 400 mg of caffeine. Hydroxycut has been linked with liver toxicity [44, 45], seizures [46], RCVS [1], mania [47], and rhabdomyolysis [48].

Hydroxycitric acid (HCA) is the active ingredient of *Garcinia cambogia extract (MOA)*, a fruit rind of *Garcinia gummi-gutta*, and is most commonly used in weight loss supplements. It is purported to regulate serotonin levels, promote lipid oxidation, and inhibit lipid synthesis [56]. Although HCA has potential beneficial effects, drug interactions and adverse effects do occur. Serotonin syndrome has been

**Table 12.5** Weight loss supplements and toxicity

| Weight loss supplement brand | Ingredients | Active ingredient known | Toxicity reported |
|---|---|---|---|
| Pure *Garcinia cambogia* extract 95% HCA | *Garcinia cambogia* extract (HCA), potassium, calcium, chromium | Hydroxycitric acid (HCA) | Liver toxicity [44, 45], seizures [46], RCVS [1], mania [47], and rhabdomyolysis [48] |
| Hydroxycut | 230–340 mg caffeine, green coffee extract, yohimbe, L-theanine, *Coleus forskohlii* | Green coffee bean extract | Manic episodes [49] |
| | | | Serotonin syndrome with escitalopram [50] |
| | | | QTc prolongation with yohimbine [30] |
| Alli orlistat FDA approved | Orlistat (60 Mg). Inactive ingredients: FD&C Blue No. 2, edible ink, gelatin, iron oxide, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium starch glycolate, talc, titanium dioxide | Orlistat | Hepatotoxic [51] and nephrotoxic [16] |
| | | | Deficiency of fat-soluble vitamins [52] |
| | | | Inhibits absorption of some medications [53] |
| NatureWise CLA 1250 | Safflower oil: 80% conjugated linoleic acid (CLA) | Conjugated linoleic acid (CLA) | Hepatic steatosis in animal studies [54] |

reported in a woman on escitalopram and *Garcinia* for weight loss [50]. *Garcinia* has also been associated with manic episodes [49].

Another weight loss supplement, *orlistat*, is an over-the-counter, semisynthetic lipase inhibitor. It blocks gastric and pancreatic lipase, leading to a 30% reduction in absorption of dietary triglycerides [57]. Orlistat may reduce levels of cyclosporine [53], leading to loss of immunosuppression. It may cause hepatotoxic [51] and nephrotoxic [16] effects. Because of its mechanism of action, it has the potential to cause deficiency of fat-soluble vitamins [52]. Conjugated linoleic acid has been associated with hepatic steatosis in animal studies [54].

### Other Herbal and Dietary Supplements

What follows is a list of dietary supplements that have been associated with direct toxicity or drug-diet interactions. The supporting literature is often weak and based upon case reports (Tables 12.6 and 12.7). More rigorous clinical studies of some previously suspect dietary supplements such as garlic, gingko, ginger, and cranberry show no significant interactions at recommended doses; however, megadosing may be associated with greater toxicity. The most important dietary supplement to cause clinically relevant interactions with prescription drugs is St John's wort [58, 59].

*St John's wort* has been used successfully for mild to moderate depression [66]. When taken together with an SSRI or SNRI, it may increase the risk of serotonin syndrome due to additive serotonergic effects [8]. It may lower the efficacy of various medications by its action as an inducer of P450 enzymes, especially CYP3A4, leading to lowered plasma levels (Table 12.7). Drug interactions have been seen with alprazolam, amitriptyline, cyclosporine, fexofenadine, indinavir, methadone, simvastatin, tacrolimus, warfarin, and oral contraceptives [59, 64]. St John's wort does not appear to interact with carbamazepine, dextromethorphan, mycophenolic acid, or pravastatin [8].

Hypoglycemia is more likely when St John's wort is used with oral hypoglycemic agents such as glipizide and rosiglitazone. It may induce delirium with loperamide, possibly due to its effects on P-glycoprotein [67]. St John's wort has been reported to trigger mania in bipolar patients [68] and psychosis in schizophrenia [69].

*Garlic* is commonly utilized for its purported cardiovascular benefits and antiplatelet and antineoplastic activities [70]. It may have modest antihypertensive effects [71]; however, caution is advised when using along with other antihypertensives as it may further lower blood pressure. Garlic has been reported to inhibit platelet aggregation [19], and concurrent use with ASA and clopidogrel has been associated with an increased bleeding tendency [20, 72] although this effect is contested [59].

*Gingko biloba* is a commonly used medicinal plant for memory enhancement, claudication, tinnitus, and vertigo. Like other herbs, there are case reports of increased risk of bleeding when used along with anticoagulant or antiplatelet therapies [73]. However, more rigorous studies have not confirmed a clinically important interaction [59, 39, 74].

**Table 12.6** Case reports of drug-dietary supplement interactions

| Dietary supplement | Purported mechanism of action/indication | Toxicity/interaction |
|---|---|---|
| Black cohosh | Menopausal symptoms | Case reports of hypotension with HCTZ, lisinopril, diltiazem not confirmed in clinical trials, likely safe [58] |
| Cranberry juice | Acidifies urine, reduce bacterial adherence | Case reports of warfarin and antiplatelet interaction not confirmed by controlled trials [59] |
| Garlic | HTN, atherosclerosis | Case reports of warfarin and antiplatelet interaction not confirmed by controlled trials [59] |
| *Ginkgo biloba* | Increase blood flow; memory promotor | Case reports of warfarin and antiplatelet interaction not confirmed by controlled trials [59] |
| Ginseng | Memory promotor | Possible bleeding risk with antiplatelet agents [60] |
| Goldenseal | Anticancer properties | May inhibit action of drugs metabolized by CYP2D6 and 3A4 [61] |
| Saw palmetto | Reduce Sx of prostatic hypertrophy | Single case report of warfarin interaction, likely safe [59, 62] |
| Soy | Relief of menopausal symptoms | Possible promotor of estrogen-sensitive tumor growth [63] |
| St John's wort | Depression, anxiety | Potent CYP3A4 inducer |
| | | Reduces BCP, simvastatin, warfarin, alprazolam. Delirium with loperamide |
| | | Serotonin syndrome with SSRI, buspirone [8, 64] |

**Table 12.7** Other drug-diet interactions

| Dietary product | Rx drug | Interaction |
|---|---|---|
| Grapefruit juice | Statins | Myalgias, rhabdomyolysis |
| | Ca channel blocker | Hypotension, bradycardia |
| | Chemotherapy | Reduced efficacy |
| | Fexofenadine | Reduce efficacy (OATP inhibition) [65] |
| Caffeine | SSRI | Irritability, tremor |
| Hard cheese | MAOIs, selegiline | Serotonin syndrome |
| St John's wort | Cyclosporine | Lowers plasma levels by PGP and 3A4 induction [35] |
| St John's wort | Indinavir | Lowers plasma levels by PGP and 3A4 induction [35] |
| St John's wort | Cyclosporine | Lowers plasma levels by PGP and 3A4 induction [35] |

The significance of herb-drug interactions in elderly patients receiving warfarin or in patients taking higher than recommended doses or combinations of herbal medicines is not yet established. Various case reports have shown seizure inducing properties of gingko, likely attributed to the 4′-methoxypyridoxine or B6 antivitamin [11]. There is a case report of fatal seizures when combined with valproate and phenytoin [75].

*Ginseng* has two active ingredients: ginsenosides and eleutherosides, known for its antioxidant and anti-inflammatory effects. It is well tolerated with low side-effect

profile; however, with prolonged use, hypertension, nervousness, sleeplessness, skin eruptions, and morning diarrhea may occur; euphoric and agitated states have been reported. Early reports of decreased warfarin efficacy and manic-like episodes when used with MAO-inhibitors like phenelzine [76] have not been confirmed in later studies [39].

*Saw palmetto* is marketed as a herbal remedy for benign prostate hypertrophy. It is considered to be a relatively safe herbal medicine; however, case reports of pancreatitis and heart block suggest caution when used in megadoses [77, 78]. Early reports of coagulopathy associated with saw palmetto [79] have not been confirmed in larger clinical studies [39].

## False-Positive Urine Drug Testing

Urine drug screening (UDS) is commonly used in a variety of settings, including the workplace, in athletics, criminal settings, and healthcare. Easy access to urine samples makes them ideal for UDS – usually via immunoassay. However, false positives and negatives can occur – often resulting in adverse consequences. For definitive results, gas chromatography-mass spectrometry needs to be utilized.

The Department of Health and Human Services' Guidelines for UDS in the workplace include testing for five substances: amphetamines, cannabinoids, cocaine, opiates, and phencyclidine [80]. In the healthcare settings, UDS for benzodiazepines, alcohol, and tricyclic antidepressants is also common. UDS may be confounded by substituting, diluting, or adulterating urine [81, 82].

Examples of "false positives" in UDS include:

- Using "hemp milk" (sold at health food stores) as a cause of false-positive UDS for cannabinoids.
- Consuming poppy seed pastries may give positive UDS for opiates.
- Dextromethorphan (in OTC cough syrup) may be false positive for opiates.
- Venlafaxine may result in false positive for methamphetamine [83].

## Conclusion

People crave autonomy in healthcare and will often reach for the pharmacy aisle before calling a doctor. Patients may be putting themselves at risk for toxicity and drug interactions with the expanding use of herbal medications, OTCs, and dietary supplements. Clinicians need to be aware of potential drug interactions between prescribed and nonprescribed substances. It is important to take a thorough medication history that includes dietary habits, OTCs, supplements, and herbal remedies to predict and prevent potential interactions.

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