Herb–drug interactions: Caution patients when changing supplements

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Ms. X, age 41, has a history of bipolar disorder and presents with extreme sleepiness, constipation with mild abdominal cramping, occasional dizziness, and "palpitations." Although usually she is quite articulate, Ms. X seems to have trouble describing her symptoms and reports that they have been worsening over 4 to 6 days. She is worried because she is making mistakes at work and repeatedly misunderstanding directions.

Ms. X has a family history of hyperlipidemia, heart disease, and diabetes, and she has been employing a healthy diet, exercise, and use of supplements for cardiovascular health since her early 20s. Her medication regimen includes lithium, 600 mg, twice a day, quetiapine, 1,200 mg/d, a multivitamin and mineral tablet once a day, a brand name garlic supplement (garlic powder, 300 mg, vitamin C, 80 mg, vitamin E, 20 IU, vitamin A, 2,640 IU) twice a day, and fish oil, 2 g/d, at bedtime. Lithium levels consistently have been 0.8 to 0.9 mEq/L for the last 3 years.

Ms. X describes no changes in her diet or prescription medications, but mentions that the brand name garlic supplement she takes was out of stock early last week, so she bought another brand of garlic supplement, consisting of oil capsules. Ms. X says, "I made sure the dose was exactly the same, since you told me not to change doses without checking with you first!" You review the bottle she brought with her and see that it contains garlic oil with "allicin equivalent to 300 mg of garlic powder" and 60 mg of vitamin C with rose hips, vitamin E, 20 IU, vitamin A, 2,200 IU, and piperine, 20 mg.

Factors of drug–supplement interactions

Because an interaction is possible doesn't always mean that a drug and an offending botanical cannot be used together. With awareness and planning, possible interactions can be safely managed (***Table 1***). Such was the case of Ms. X, who was stable on a higher-than-usual dosage of quetiapine

Practice Points

- **Severity of herb–drug interactions range from inconsequential to life-threatening.** Compared with prescription drugs, there is less research on the effects of supplements on metabolism enzymes and absorption processes.
- **Differences in product quality and ingredients can create interactions or other safety concerns** when changing brands or product formulations.
- Many statements and cautions about herb–drug interactions in tertiary resources are based on *in vitro* results; therefore, **check citations and consult several sources before making a clinical decision.**
- **Individual genetic differences can result in unpredictable effects.** Use caution when interpreting or extrapolating case reports or human studies.

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The author reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Table 1

Strategies for decreasing the risk of herb–drug interactions

Take a complete and accurate medication history by asking patients about their use of vitamins and herbs in an open and accepting manner
Obtain brand names and exact lists of ingredients and dosages. Ask patients to bring supplement containers, if possible
Check for interaction information from multiple sources; verify with recent primary literature when possible: • "No interactions known" does not mean that no interactions exist • Many herb–drug interactions listings primarily focus on the more well-known cytochrome P450 enzymes-associated interactions
Educate patients to avoid sudden changes in supplements—stopping, starting, or switching brands Stability is not guaranteed; manufacturers may change ingredients or quality at any time
Educate patients to watch for symptoms that would indicate a possible developing interaction

(average target is 600 mg/d for bipolar disorder) because of presumed moderate enzyme induction by the brand name garlic supplement. Ms. X did not want to stop taking this supplement when she started quetiapine. Although garlic is listed as a possible moderate cytochrome P450 (CYP) 3A4 inducer, there is conflicting evidence.[1] Ms. X's clinician advised her to avoid changes in dosage, because it could affect her quetiapine levels. However, the change in the botanical preparation from dried, powdered garlic to garlic oil likely removed the CYP3A4 enzyme induction, leading to a lower rate of metabolism and accumulation of the drug to toxic levels.

Box

The function of P-glycoprotein

P-glycoprotein is known as a multi-drug resistance protein because it is involved in resistance mechanisms for a number of drugs. P-glycoprotein is involved in drug transport in the gut where it functions as an efflux pump, sending toxins and other xenobiotics, such as drugs, back into the intestinal lumen. It functions similarly as a component of the blood–brain barrier. When P-glycoprotein is inhibited, bioavailability of orally administered drugs goes up and penetration across the blood–brain barrier increases; inducement of P-glycoprotein results in lower blood levels of the target drug.

Drug metabolism. Practitioners are increasingly aware that St. John's wort can significantly affect concomitantly administered drug levels by induction of the CYP isoenzyme 3A4 and more resources are listing this same possible induction for garlic.[1] However, what is less understood is the extent to which different preparations of the same plant possess different chemical profiles (***Table 2, page 40***).

Clinical studies with different garlic preparations—dried powder, aqueous extracts, deodorized preparations, oils—have demonstrated diverse and highly variable results in tests of effects on CYP isoenzymes and other metabolism activities.[2] There also is contradictory evidence between *in vitro* and *in vivo* studies, with 1 *in vitro* study of garlic extract demonstrating marked CYP3A4 effects up to 30%, while another study using a water-soluble, aged garlic extract noted little or no effects.[3]

Other studies also have demonstrated opposite results.[2] A clinical trial in healthy participants found no difference in the pharmacokinetic parameters of the CYP3A4 substrate drug midazolam before and after administration of a garlic oil supplement.[4] However, inhibition of CYP2E1 was likely, demonstrated by a 22% increase in levels of the skeletal muscle relaxant chlorzoxazone.[4] A study of garlic on ritona-

Clinical Point

Because an interaction is possible doesn't mean that a drug and an offending botanical cannot be used together

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Table 2

Clinical factors to consider with herb–drug interactions

Effect	Causes	Examples
Changes in drug absorption	Physical interference with drug by blocking or binding	Psyllium, flax seed, marsh mallow, chitosan
	Inhibition of intestinal P-glycoprotein	Piperine, ginkgo, milk thistle, ginseng
	Increases in intestinal motility or diarrhea	Aloe, cascara sagrada, European buckthorn
Increased free drug levels	Displacement of protein-bound drugs	Willow, meadowsweet
Pharmacokinetic changes	Inhibition or induction of cytochrome P450 enzymes	St. John's wort, echinacea, ginkgo, garlic, grapefruit, goldenseal, resveratrol
Changes in elimination	Increased diuresis or fluid retention	Dandelion, yerba maté, stinging nettle, cowhage
Pharmacodynamic interactions	Supplement has either similar or opposing effects to target drug	Anticonvulsants: ginkgo (may lower seizure threshold) Antihypertensives: yohimbe (could increase blood pressure) CNS depressants: valerian (GABA agonist)

Clinical Point

Different garlic preparations have shown diverse and highly variable results of the effects on CYP isoenzymes and metabolism

vir pharmacokinetics demonstrated large intra-subject variations, leading researchers to speculate that the garlic extract used could be both inducing and inhibiting CYP3A4, as well as having effects on drug absorption via P-glycoprotein (***Box, page 39***). This brings up another possible interaction because Ms. X substituted a different brand and form of garlic.[5]

Drug absorption. Small differences in amounts of vitamins in the supplement are unlikely to be clinically significant, but the addition of piperine could be affecting quetiapine absorption. Piperine, a constituent of black pepper and long pepper, is used in Ayurvedic medicine for:

- pain
- influenza
- rheumatoid arthritis
- asthma
- loss of appetite
- stimulating peristalsis.[6]

Animal studies have demonstrated anti-inflammatory, anticonvulsant, anticarcinogenic, and antioxidant effects, as well as stimulation of digestion via digestive enzyme secretion and increased gastromotility.[3,6]

Because piperine is known to increase intestinal absorption by various mechanisms, it often is added to botanical medicines to increase bioavailability of active components. BioPerine is a 95% piperine extract marketed to be included in vitamin and herbal supplements for that purpose.[3] This allows use of lower dosages to achieve outcomes, which, for expensive botanicals, could be a cost savings for the manufacturer. Studies examining piperine's influence on drug absorption have demonstrated significant increases in carbamazepine, rifampin, phenytoin, nevirapine, and many other drugs.[7,8] These increases are caused by several mechanisms, but the 2 most important may be inhibition of intestinal P-glycoprotein and increases in small intestine absorption surfaces (***Table 2***).[6-9]

In addition to increased absorption, piperine seems to be a non-specific general inhibitor of CYP isoenzymes; IV phenytoin levels also were higher among test participants.[6,8] Piperine reduces intestinal

glucuronidation via uridine 5′-diphospho-glucuronosyltransferase inhibition, and the small or moderate effects on lithium levels seem to be the result of diuretic activities.[3,7]

Patients often are motivated to control at least 1 aspect of their medical treatment, such as the supplements they choose to take. Being open to patient use of non-harmful or low-risk supplements, even when they are unlikely to have any medicinal benefit, helps preserve a relationship in which patients are more likely to consider your recommendation to avoid a harmful or high-risk supplement.

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Related Resources

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Drug Brand Names

Carbamazepine • Tegretol, Carbatrol
Chlorzoxazone • Lorzone, Parafon
Lithium • Eskalith, Lithobid
Midazolam • Versed
Nevirapine • Viramune
Phenytoin • Dilantin
Quetiapine • Seroquel
Rifampin • Rifadin
Ritonavir • Norvir

Clinical Point

Piperine has been shown to increase small intestine absorption surfaces and inhibit intestinal P-glycoprotein