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.
(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.

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-
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.

**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.

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 is often 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.5,8 Piperine reduces intestinal

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<tr>
<th>Clinical factors to consider with herb–drug interactions</th>
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<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>Changes in drug absorption</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Increased free drug levels</td>
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<tr>
<td>Pharmacokinetic changes</td>
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<tr>
<td>Changes in elimination</td>
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<tr>
<td>Pharmacodynamic interactions</td>
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**Clinical Point**

Different garlic preparations have shown diverse and highly variable results of the effects on CYP isoenzymes and metabolism.
Piperine has been shown to increase small intestine absorption surfaces and inhibit intestinal P-glycoprotein.