

## Complementary, Alternative, and Integrative Rx: Safety Issues

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Findings of a recent large population survey suggest that 1 in 3 adults in this country (approximately 72 million people) uses 1 or more complementary and alternative medicine (CAM) modalities during any given year.<sup>1</sup> Many CAMs are widely regarded as safe on the basis of their established uses in traditional systems of medicine over centuries or longer and their current widespread use in the United States and other Western countries. Unfortunately, there is limited reliable information on potential risks associated with the majority of these approaches.

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All herbal medicines and other natural products contain biologically active constituents that can potentially cause adverse effects or interact with medications, other natural products, or foods. The inappropriate or unskillful use of somatic and mind-body therapies can also harm patients. Here I summarize information on tolerability, contraindications, adverse effects, and frequently encountered interactions associated with herbals and other natural products. I also briefly review safety issues encountered when somatic and mind-body therapies are used to treat or self-treat psychiatric disorders.

A significant percentage of those who receive treatment from a CAM therapist or who self-treat with herbals or other CAM modalities do so for a specific mental health problem.<sup>4</sup> As many as 60% of persons in whom a severe mood or anxiety disorder has been diagnosed use herbals or other CAM modalities concurrently with prescription medications. Few patients, however, disclose CAM use to their physician.<sup>5-7</sup> This results in potentially serious safety problems when adverse effects or interactions interfere with response to pharmacological treatment or exacerbate a preexisting

Table 1	Safety issues associated with common herbals used in mental health care
Herbal	Adverse effects
Ginkgo ( <i>Ginkgo biloba</i> )	<ul style="list-style-type: none"> <li>GI discomfort, skin allergy, dizziness, headache</li> <li>Decreases blood viscosity and antiplatelet activity; increased bleeding risk if used before surgery or childbirth</li> </ul>
Kava ( <i>Piper methystricum</i> )	<ul style="list-style-type: none"> <li>Mild GI discomfort, allergic rashes, mild headache</li> <li>Caution required in patients with hepatic risk factors; routine liver function tests suggested for patients taking kava</li> <li>Case reports of severe hepatotoxicity (necrotizing hepatitis) and liver failure associated with kava use</li> </ul>
St. John's wort ( <i>Hypericum perforatum</i> )	<ul style="list-style-type: none"> <li>Usual adverse effects include mild stomach discomfort, allergic rashes, dizziness, restlessness</li> <li>Photosensitivity reactions reported</li> <li>Rare case reports of mania induction</li> <li>Case reports of possible serotonin syndrome</li> </ul>
Valerian ( <i>Valeriana officinalis</i> )	<ul style="list-style-type: none"> <li>Morning grogginess; headache</li> <li>Impaired vigilance for a few hours after ingestion (ie residual morning sedation when used at night)</li> </ul>

medical or psychiatric disorder.

### Emerging safety standards

Until recently, the absence of rigorous federal quality and safety standards for natural products has resulted in inconsistent importing and manufacturing practices. There have been complex safety issues, including adulteration with synthetic drugs, pesticides, heavy metals, or other potentially toxic substances, and failure to meet stated contents of bioactive constituents.<sup>8,9</sup> Imported Chinese herbal medicines, for example, are commonly adulterated with steroids, phenobarbital, acetaminophen, and other drugs.<sup>10</sup>

The FDA is working on initiatives intended to improve standards of quality, safety, and evidence for

natural products. The goal is to develop and implement stringent standards of quality, efficacy, and safety of biologically active natural products that are used medicinally. Updated announcements of FDA safety warnings on herbals and other natural products can be found at [www.cfsan.fda.gov/~dms/ds-warn.html](http://www.cfsan.fda.gov/~dms/ds-warn.html).

**Herbal safety**

Most herbal supplements are generally well tolerated and have a relatively low incidence of adverse effects, especially when compared with prescription medications. However, the literature is incomplete, especially with regard to use in young children, pregnant women, women who are breastfeeding, and patients with significant liver or kidney disease, where maximum safe doses have not been clearly defined. In addition to general adverse effects, certain herbals used to treat mental health problems can potentially cause or exacerbate psychiatric symptoms.

St John’s wort (*Hypericum perforatum*), for example, can induce mania or hypomania in susceptible persons; ephedra-containing compounds (Ma-huang) have been reported to cause psychosis<sup>11</sup>; excessive use of ginseng can result in restlessness, nervousness, and insomnia or agitation; and there are reports of extrapyramidal symptoms with kava (*Piper methysticum*) use.<sup>12</sup>

St John’s wort has uterine-stimulating effects that may result in spontaneous abortion if taken during pregnancy. In addition, it can cause a photosensitive rash and should not be used by patients who

Table 2		Safety issues associated with nonherbal natural products used to treat mental health problems
Natural product	Adverse effects	
5-Hydroxytryptophan	<ul style="list-style-type: none"> <li>At usual dosages (50 - 100 mg PO tid), mild nausea, dry mouth, stomach irritation, and drowsiness can occur</li> </ul>	
L-tryptophan	<ul style="list-style-type: none"> <li>Uncommon adverse effects include drowsiness, dry mouth, and blurred vision</li> <li>Many cases of eosinophilia-myalgia syndrome (EMS) were later confirmed to be caused by a single contaminated batch of L-tryptophan in the late 1980s; no subsequent cases of EMS have been reported</li> </ul>	
Omega-3 fatty acids	<ul style="list-style-type: none"> <li>Nausea and loose stools reported at higher doses reduced by taking oil with meals</li> <li>Mild blood-thinning activity, but no bleeding problems caused when used alone or with aspirin</li> <li>Recommend using purified pharmaceutical grade to avoid contamination from heavy metals, polychlorinated biphenyls, organochlorines</li> </ul>	
SAMe	<ul style="list-style-type: none"> <li>At high doses, more intense GI symptoms (eg, nausea, vomiting, diarrhea) and CNS symptoms (eg, mild insomnia, nervousness) reported</li> <li>Anxiety reported in depressed patients; manic episodes in bipolar patients</li> </ul>	
L-theanine	<ul style="list-style-type: none"> <li>No reports of adverse effects or interactions</li> </ul>	

are likely to experience prolonged sun exposure.

Kava may cause loss of uterine tone and should not be used by pregnant women. Women who are breastfeeding should also avoid using kava, because the active constituents (kava pyrones) pass into breast milk and may have sedating effects on a nursing infant. Kava may result in excessive sedation and worsening of vegetative symptoms when used by severely depressed patients, and it should be avoided in this population. Kava should not be used concurrently with sedative-hypnotics or alcohol, both of which may potentiate sedative and muscle relaxant effects.

Table 1 summarizes important safety issues associated with herbals that are widely used to treat or self-treat psychiatric disorders.

**Nonherbal natural products**

In addition to herbals, many natural supplements are used to treat or self-treat a range of mental health problems. These include the omega-3 essential fatty acids and the amino acids 5-hydroxytryptophan, l-tryptophan, SAMe, and l-theanine. All of these naturally occurring substances are generally well tolerated in adults and cause few serious adverse effects.

In contrast, there is incomplete safety information on the use of these and other supplements in young children, pregnant women, women who are breastfeeding, and patients with serious liver or kidney disease. In these cases, maximum safe doses have not been clearly established, and conservative dosing strategies should be used together with close monitoring for treatment-emergent adverse effects. Table 2 summarizes important safety concerns associated with nonherbal natural products used to treat mental health problems.

### **Contraindications**

Integrative treatment regimens that involve combinations of specific herbals, other natural products, and pharmacological agents are contraindicated because of associated risks of toxicity or acute exacerbations of psychiatric disorders. Ephedra, ginseng, and guarana should be avoided in bipolar and schizophrenic patients who are taking conventional mood stabilizers or antipsychotics.<sup>13</sup> These herbals can potentially cause insomnia, agitation, and worsening of psychosis or manic symptoms.

Commercial sale of ephedra in the United States was banned in 2003; nevertheless, it is still easy to obtain at Chinese medical pharmacies or by mail order. Mental health professionals should therefore ask patients who are being treated by a Chinese medical practitioner about the specific herbal formulas that are being used to ensure these do not contain ephedra. It is prudent to contact the prescribing Chinese medical practitioner when a patient cannot provide detailed information.

Ginseng can potentiate the effect of monoamine oxidase inhibitors, and it may result in a hypertensive crisis. Several case reports of interactions between ginseng and phenelzine have been reported. Guarana (*Paullinia cupana*) is a stimulant that should be avoided by bipolar and schizophrenic patients who take conventional medications because of case reports of agitation, mania, and insomnia.

Valerian may potentiate the effects of alcohol as well as the conventional sedative-hypnotics, including benzodiazepines.

Table 3 summarizes other contraindications that psychiatrists should know about when working with patients who are interested in CAMs.<sup>14,15</sup> Advise patients to avoid combinations of a specific herbal or other natural product and a specific medication when there is a reasonable basis to assume that the combination is potentially unsafe. Phenothiazines or other drugs that potentially cause photosensitivity reactions should never be used in conjunction with herbals known to cause photosensitivity, including kava and St John's wort.

Kava and valerian potentiate the sedating effects of benzodiazepines, and therefore should not be used in combination with this drug class. Reasonable exceptions to this caveat can be made for:

- The patient who uses a benzodiazepine at bedtime only for sleep may be able to take kava during the day.
- The patient who is being closely monitored during a gradual tapering of a daytime benzodiazepine regimen while titrating kava to manage withdrawal effects or recurring anxiety.

Psychiatrists who recommend herbals and other natural products should always provide patients with information about specific products that are approved by the United States Pharmacopeia for the disorder that is being treated and that are highly rated by third-party reviewers. It is prudent to document informed consent in the patient's chart whenever herbals or other natural products are recommended. Reputable third-party reviewers—such as ConsumerLab, the National Nutritional Foods Association (NSF), and NSF International—have Web sites that provide safety reviews, product quality ratings, and reports of product recalls and warnings.



Table 3

**Contraindications to use of herbals and other natural products in patients with psychiatric disorders**

- Avoid concurrent use of any herbal tincture (which can contain up to 75% alcohol) and alcohol, conventional anxiolytics, or hypnotics.
- Avoid ginseng-containing formulas in patients with chronic insomnia, “nervousness,” or hysterical symptoms and in schizophrenic patients with predominantly positive symptoms. (Excessive doses can cause insomnia or agitation.)
- Avoid concurrent use of phenothiazines and herbs with antimuscarinic activity (which can decrease plasma phenothiazine level).
- Avoid concurrent use of St John’s wort or ginseng-containing products and monoamine oxidase inhibitors (MAOIs); these products can potentiate MAOI effects, possibly leading to hypertensive crisis.
- Avoid ginseng in patients taking caffeine or other stimulants (eg, guarana) and in patients taking hormonal therapies. Avoid guarana-containing products in schizophrenic patients or others taking hypnotics or anxiolytics.
- Special safety issues must be addressed when a patient is considering combining Chinese herbal medicines with conventional pharmacological agents. In view of limited available safety information, it is generally reasonable to avoid combining Chinese herbals and Western synthetic drugs unless there are compelling reasons to do otherwise.<sup>18,19</sup>

**Somatic, mind-body, and energy modalities**

In addition to herbals and other biological CAM modalities, acupuncture, yoga, qigong, and other somatic, mind-body, or energetic modalities are widely used to treat or self-treat psychiatric disorders in North America and Western Europe. Alternative somatic, mind-body, and energetic modalities have good safety profiles and relatively few contraindications or serious complications—especially when administered by a qualified CAM practitioner.

Massage can result in transient exacerbation of pain syndromes if too forceful. Massage of the abdomen, legs, and feet should be avoided during the first trimester of pregnancy. Chiropractic manipulation is generally safe; however, minor uncommon adverse effects can include transient local discomfort after therapy, headache, and fatigue.

Acupuncture is generally safe when performed by a trained Chinese medical practitioner. Infrequent adverse effects of acupuncture include transient pain, tiredness, bruising, fainting, and vomiting. Rare serious complications include pneumothorax and nerve damage. Infection from contaminated needles is extremely rare in the United States.

EEG biofeedback (or “neurotherapy”) and other forms of biofeedback involve weak electrical currents. Exercise caution when using this approach in patients who have heart conditions, pacemakers, or implanted defibrillators or electrical devices.

Homeopathic remedies contain extremely diluted amounts of active biological agents and as such are extremely safe. There are rare case reports of brief “healing crises” associated with transient worsening of symptoms with homeopathic remedies. Rare cases of transient psychosis or agitation have been reported during qigong practice by patients who have personality disorders or schizophrenia. Although yoga is generally safe, some advanced postures may result in injury to inexperienced practitioners.

### **Due diligence**

It is important to be prudent when referring patients to CAM practitioners. Identifying a qualified CAM practitioner can pose challenges, especially for CAM specialty areas for which there are few or no requirements for minimum standards of professional training or credentialing.<sup>3,16</sup> While most CAM practitioners are competent and caring professionals, some are poorly trained or do not have the specialized skills necessary to work with serious psychiatric disorders, and there is often little or no oversight of their clinical work.<sup>3,16</sup> Herbalists, naturopaths, and homeopaths, for example, have widely varying training backgrounds and clinical experience ranging from no formal training to rigorous training programs followed by years of required supervision and credentialing by a professional board. Completion of a rigorous training program and verification of credentials and licensure are important steps in this process. CAM practitioners should be chosen after careful deliberation. Finally, even when qualified CAM practitioners are available, many patients elect to self-treat with 1 or more CAM therapies in the absence of appropriate professional consultation.<sup>17</sup>

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