# Herbal and Dietary Supplements for Treatment of Anxiety Disorders

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**Use of complementary and alternative medicine has increased over the past decade. A variety of studies have suggested that this use is greater in persons with symptoms or diagnoses of anxiety and depression. Data support the effectiveness of some popular herbal remedies and dietary supplements; in some of these products, particularly kava, the potential for benefit seems greater than that for harm with short-term use in patients with mild to moderate anxiety. Inositol has been found to have modest effects in patients with panic disorder or obsessive-compulsive disorder. Physicians should not encourage the use of St. John's wort, valerian, Sympathyl, or passionflower for the treatment of anxiety based on small or inconsistent effects in small studies. Although the evidence varies depending on the supplement and the anxiety disorder, physicians can collaborate with patients in developing dietary supplement strategies that minimize risks and maximize benefits.** (Am Fam Physician 2007;76:549-56. Copyright © 2007 American Academy of Family Physicians.)

Use of complementary and alternative medicine in all of its varieties, such as herbal remedies and dietary supplements, increased from 34 percent of the overall U.S. population in 1990 to 42 percent in 1997.[1] Use appears to be twice as great in persons reporting anxiety and depression than in those reporting any other problem, except for back and neck pain.[1] Based on results of two large-scale community surveys,[2,3] investigators have noted an association between both panic disorder and major depression and the use of complementary and alternative medicine.

Currently, the preferred treatment for anxiety disorders is cognitive behavior therapy and pharmacologic agents. Beta blockers or benzodiazepines are used for time-limited and predictable anxiety disorders, whereas selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, buspirone (Buspar), or monoamine oxidase inhibitors are preferred for chronic or recurrent anxiety disorders.

In recent years, studies using herbal remedies and supplements to treat mild to moderate anxiety disorders have emerged. It is important for physicians to recognize that supplements offer both benefits and risks. By doing so, they can avoid an overly dismissive attitude that discourages patients from disclosing their supplement use. At the same time, understanding the limits of available evidence allows physicians to collaborate with interested patients in developing dietary supplement strategies that minimize risks and maximize benefits.

In this article, the supplements purported to ameliorate anxiety disorders are divided into three groups: herbal supplements, nutritional supplements, and neurotransmitter and hormonal precursors. These divisions are somewhat arbitrary in that all of the products are taken orally, are available over the counter, are marketed with a variety of health claims on the Internet, and are justified by their purported ultimate effects on the neurotransmitter systems that mediate worry, stress, or fatigue symptoms in patients with anxiety disorders.

Information on supplements that claim to be useful or commonly used for anxiety disorders was obtained from several Internet sites, particularly http://www.revolutionhealth.com/drugs-treatments, http://www.healthyplace.com/Communities/Anxiety/treatment/alternative_treatment.asp, and http:/www.naturaldatabase.com. Medline via Ovid was used to search for clinical trials, guidelines, and meta-analyses that

**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

| *Clinical recommendation* | *Evidence rating* | *References* | *Comments* |
|---|---|---|---|
| Short-term use of kava is recommended for patients with mild to moderate anxiety disorders who are not using alcohol or taking other medicines metabolized by the liver, but who wish to use "natural" remedies. | A | 4, 5 | Cochrane systematic review of seven RCTs (n = 380), with findings supported by five lower-quality trials (n = 320); side effects were rare and mild; same results with only extract WS1490 trials |
| Use of inositol in a dosage of 12 to 18 g per day is a treatment option for panic disorder. | B | 24, 25 | Effectiveness similar to SSRI and better than placebo for reducing intensity and frequency of panic attacks; side-effect profile comparable to SSRI; supported by two RCTs, although both were small |
| Inositol, 12 to 18 g per day, may be used to treat obsessive-compulsive disorder but not in combination with SSRIs. | B | 26, 27 | In trials of patients with treatment-resistant OCD, inositol by itself was better than placebo in reducing OCD symptoms[26] but not in reducing anxiety scale scores; when added to SSRIs, inositol had no additional effect[27] |
| Physicians should not encourage the use of St. John's wort, valerian, Sympathyl, or passionflower for anxiety based on small or inconsistent effects in small studies. Side-effect profiles are benign. | B | 16-23 | Small, unreplicated trials with design flaws suggest some limited effectiveness |
| All other nutritional supplements have no research evidence suggesting a positive effect on anxiety disorders. Physicians should recommend other treatments. | C | — | No evidence beyond testimonials, effects on nonclinical groups, or hypothetical mechanisms of action |

*RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor; OCD = obsessive-compulsive disorder.*

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 483 or http://www.aafp.org/afpsort.xml.*

**Table 1. Supplements with Clinical Trial Evidence of Effectiveness or Noneffectiveness for Treating Anxiety**

| *Type of evidence* | *Herbal supplements* | *Nutritional supplements* | *Neurotransmitter/ hormonal precursors* |
|---|---|---|---|
| Effectiveness based on meta-analysis or multiple RCTs | Kava | — | — |
| Effectiveness based on a single double-blind, placebo-controlled RCT | St. John's wort (for somatoform disorders), sympathyl (California poppy, hawthorn, elemental magnesium) | Inositol, 18 g (one RCT for panic disorder and one RCT for OCD) | 5-hydroxytryptophan (serotonin precursor; for panic disorder) |
| Weak effectiveness based on clinical/open trials | Passionflower, St. John's wort (for GAD), valerian | — | — |
| Clinical trials demonstrating noneffectiveness | Cannabis | Omega-3 fatty acids (as adjunct for treatment-resistant OCD) | — |

NOTE: *The preparations are listed in order from the most evidence of effectiveness to the least evidence.*

*RCT = randomized controlled trial; OCD = obsessive-compulsive disorder; GAD = generalized anxiety disorder.*

tested or asserted the effectiveness of these preparations in the treatment of patients with diagnosed anxiety disorders. *Table 1* includes suggested supplements that have some evidence of effectiveness for treating anxiety. Only therapies with evidence of effectiveness are discussed in this review.

Patients often justify the use of certain preparations on the basis of irrelevant or misleading evidence; to help physicians

recognize such preparations, those supplements with no clinical evidence of effectiveness in reducing anxiety are presented in *Table 2*. Clearly, the vast majority of supplements with purported anxiolytic effects have no evidence of clinical benefit.

## Herbal Supplements

### KAVA

There is substantial evidence that kava has a positive effect on the symptoms of anxiety disorders. *Table 3* summarizes the evidence on the effectiveness and safety of kava in patients with anxiety disorders.[4-12]

Kava dramatically inhibits the cytochrome P450 enzyme used by the liver to metabolize many medications, potentially altering the potency of these other medications.[13,14] Thus, it is important to be aware of the risk of drug interactions with kava. Other side effects reported with long-term use include a reversible skin rash or lesion and a yellow tint to the skin, but these reports have not been routine. Despite the absence of long-term data on safety and effectiveness,[4,13,15] the evidence shows that short-term use (i.e., up to 24 weeks) can lead to small improvements in generalized anxiety,[4] and that short-term risks do not outweigh the benefits.

For patients with mild to moderate anxiety who wish to use "natural" remedies and are not using alcohol or taking other medications that are metabolized by the liver, kava appears to be acceptable for short-term use.

### ST. JOHN'S WORT

St. John's wort is a popular supplement for treating depression but is much less popular for treating anxiety disorders. Studies specifically testing the effects of St. John's wort on patients with anxiety are extremely limited. *Table 4* summarizes the evidence for the effectiveness and safety of St. John's wort in the treatment of anxiety disorders.[16-23]

The evidence of positive effects of St. John's wort on anxiety disorders is weak. No placebo-controlled, randomized, double-blind trials have shown St. John's wort to be effective in treating generalized anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder (OCD), or phobias. The only effective trial involved patients with somatoform disorder, although the relationship between somatoform disorder and anxiety is complex. Much stronger evidence is needed before St. John's wort should be considered a treatment option for patients with diagnosable anxiety disorders.

**Although valerian has been widely used to treat anxiety, there is no evidence of an anxiolytic effect.**

### HAWTHORN AND CALIFORNIA POPPY

A single French study exists of a combination product called Sympathyl,[22] which contains 20 mg California poppy, 75 mg hawthorn, and 75 mg elemental magnesium. According to the study, Sympathyl had a very small but positive effect on anxiety. No clinical trials suggest that any of the individual components reduce anxiety in patients with anxiety disorders.

### VALERIAN

Although valerian is often cited as having anxiolytic effects and has been used for centuries by herbalists/physicians to treat nervousness, there are only two small trials involving valerian, neither of which produced clear indications of effectiveness *(Table 4*[16-23]*)*. Thus, at the present time, there

**Table 2. Supplements with No Clinical Trial Evidence of Effectiveness in Anxiety Disorders**

**Herbal supplements**

Ashwagandha *(Withania somnifera)*; Bach flower essences; bacopa; berocca; borage juice (starflower); bugleweed *(Lycopus virginicus)*; catnip; chamomile; damiana; fennel; feverfew; ginkgo; ginseng; golden root *(Rhodiola rosea)*; gotu kola; hops; kanna; lemon balm; lemongrass leaves; licorice; meadowsweet; motherwort; mullein *(Verbascum sinuatum)*; mulungu; noni *(Morinda citrifolia)*; peppermint; pine bark extract; reishi *(Ganoderma lucidum)*; Relora (magnolia/phellodendron); schisandra; scullcup (skullcap); verbena (blue vervain)

**Nutritional supplements**

Adrenal extracts; carbohydrate-rich diet; garum armoricum (great bluefish); ginger; L-theanine (green tea); macrobiotic diet; milk peptides (New Life Tryptozen); oats; perilla oil (perilla frutescens); vitamins $B_3$, $B_6$, $B_{12}$, and C

**Neurotransmitter and hormonal precursors**

Amino acids (L-phenylalanine/phenylalanine [norepinephrine precursor], L-arginine, L-lysine, L-glutamine, L-leucine); melatonin; pregnenolone; phytoestrogens (soy or Mexican yam); tyrosine (norepinephrine precursor); SAMe (S-adenosyl-L-methionine)

is no clinical evidence of an anxiolytic effect of valerian when compared with placebo in patients with anxiety disorder.

#### PASSIONFLOWER

A single randomized double-blind trial compared 45 drops of passionflower tincture per day to 30 mg per day of oxazepam (Serax; brand no longer available in the United States) for 30 days.[23] Investigators noted a marked reduction in anxiety score in both groups, but without a placebo group it was unclear whether other aspects of the milieu could have caused the effects.

### Nutritional Supplements

Despite the number of nutritional supplements purported on the Internet to treat anxiety, only inositol, part of the vitamin B complex (B8) and an intracellular second messenger, has evidence suggesting superiority to placebo and even comparability with the SSRI fluvoxamine (Luvox; brand no longer available in the United States). *Table 5* summarizes the evidence supporting the effectiveness and safety of inositol in managing anxiety disorders.[24-27]

Inositol appears to have a positive effect on patients with panic disorder; however, its effect on patients with OCD is less clear. Physicians should inform patients that the limited data that exist to date suggest partial responses with a side-effect profile that may be comparable with that of SSRIs.

### Neurotransmitter or Hormonal Precursors

The anxiolytic neurotransmitter or hormonal precursors with some evidence of effectiveness are shown in *Table 1*. The vast majority of neurotransmitter or hormonal precursors that claim to be useful

**Table 3. Evidence Regarding the Effectiveness and Safety of Kava in Anxiety Disorders**

| *Design* | *Description* | *Comments* |
|---|---|---|
| Meta-analyses on GAD | A Cochrane systematic review identified 12 RCTs of effects of kava on patients with GAD[4]; the meta-analysis included seven trials that met quality criteria (n = 380); kava significantly reduced Hamilton Anxiety Scale scores, although the weighted mean difference between kava and placebo was only 3.9 scale points; the other five trials (n = 320) showed similar tendencies; a replication meta-analysis involving only those RCTs that used extract WS1490 replicated and extended these results[5] | Kava was consistently better than placebo in producing small reductions in anxiety symptoms; side effects noticed across all studies were "mild, transient, and infrequent"[4]; the authors concluded that kava taken for one to 24 weeks was safe and mildly effective; the replication[5] allowed more comparisons between patient subgroups and suggested most improvement effects in women and patients younger than 53 years |
| RCTs on GAD | Recent small RCTs involving patients with GAD (n = 64) showed no significant effect of kava,[6] with treatments typically lasting four weeks | Trial durations were short, and sample size was small; although studies of eight weeks' duration[7] have shown effectiveness, a 25-week study[8] showed that therapeutic effects started in the eighth week |
| RCT on safety | Recent examinations of adverse event reports with kava[9] and improved understanding of the pharmacologic substances in kava[10] show that its safety compares favorably with FDA-approved treatments for anxiety disorders | Researchers concluded that liver toxicity is rare and idiosyncratic, with the majority of reported cases resulting from the combination of kava with other hepato-active agents; the benefits of kava seem to outweigh its risks[10] |
| Case reports on safety | Cases of liver toxicity have been reported, some requiring organ transplants; kava preparations withdrawn from the market in many countries; the FDA issued an advisory[11]; later, research suggested that nonstandard inclusion of the kava plant's bark in kava preparations increased toxicity level[12] | Unclear if dosing, preexisting liver damage, or toxic combinations with other hepato-active agents were causative |

*GAD = generalized anxiety disorder; RCT = randomized controlled trial; FDA = U.S. Food and Drug Administration.*

*Information from references 4 through 12.*

**Table 4. Evidence Regarding the Effectiveness and Safety of St. John's Wort, Valerian, Sympathyl, and Passionflower in Anxiety Disorders**

| *Design* | *Description* | *Comments* |
|---|---|---|
| RCT with St. John's wort in OCD | Compared 30 patients with OCD taking LI 160 extract (range: 300 to 1,800 mg) and 30 patients with OCD taking placebo for 12 weeks[16]; St. John's wort had no effect on reducing Yale-Brown Obsessive-Compulsive Scale total or subscale scores | Agitation side effect more common with St. John's wort |
| Open, uncontrolled study of St. John's wort in OCD | Significant reductions in the Yale-Brown Obsessive-Compulsive Scale score in 12 patients with OCD starting one week into the study and continuing throughout the 12-week trial[17]; the compound used was a 450-mg, extended-release formulation of 0.3% *Hypericum* taken two times a week | The small number of patients and lack of comparison to placebo make this evidence weak; few side effects reported |
| RCT with St. John's wort in social phobias | Compared flexible doses of LI 160 extract (range: 300 to 1,800 mg twice a day) and placebo in 40 patients with social phobias[18]; St. John's wort had no effect in reducing anxiety scores | Side effects no worse than placebo |
| RCT with St. John's wort in somatoform disorders | St. John's wort was used to treat somatoform disorders using reductions in the Hamilton Anxiety Scale somatic anxiety subscale score as the primary outcome measure[19]; after patients with significant depressive symptoms were excluded, 150 patients were randomized to St. John's wort or placebo; dosage of the LI 160 extract was 300 mg twice a day<br>Results showed a strong positive effect of St. John's wort, compared with placebo, in reducing somatic anxiety, psychic anxiety, overall anxiety scores, and physician and patient ratings of somatoform disorder symptoms | Somatoform disorders have complex relationship with anxiety disorders |
| Open trial with St. John's wort plus valerian in anxiety and depression | Valerian was used in combination with St. John's wort to treat patients with comorbid anxiety and depression; the combination was better than St. John's wort alone at reducing anxiety scores[20] | Suggestive improvement of St. John's wort with addition of valerian; very few side effects |
| RCT with valerian versus diazepam (Valium) and placebo in GAD | Randomized, double-blind, placebo-controlled comparison of valerian with diazepam in GAD, 12 patients per group for four weeks[21]; no differences between valerian and placebo, or between diazepam and placebo | Too underpowered to demonstrate differences in effectiveness; no differences in side effects |
| RCT with Sympathyl versus placebo; two tablets twice a day in GAD | Double-blind randomized trial conducted among patients with mild to moderate GAD in 22 general practices in Paris, France[22]; Sympathyl (n = 130) and placebo (n = 134) groups were relatively large; after three months the Sympathyl group showed a 10.6-point decline in the Hamilton Anxiety Scale score, whereas the placebo group showed an 8.9-point decline | Statistically significant advantage for Sympathyl compared with placebo, but size of difference (1.7 scale points) very small |
| RCT of passionflower versus oxazepam (Serax; brand no longer available in the United States) in GAD | Each group had 18 patients with GAD[23]; both groups started with mean Hamilton Anxiety Scale scores of 20 and ended with significant reductions to 6; the groups also had the same level of side effects | Both groups equally positive but small study with no placebo group; results unclear |

*RCT = randomized controlled trial; OCD = obsessive-compulsive disorder; GAD = generalized anxiety disorder.*

*Information from references 16 through 23.*

for treating anxiety disorders have no evidence supporting clinical utility. Only 5-hydroxytryptophan appeared to show clinical effectiveness among the precursor preparations. *Table 6* summarizes the available evidence relevant to the effectiveness and safety of 5-hydroxytryptophan.[28,29]

Although there is some indication that 5-hydroxytryptophan can reduce anxiety symptoms among patients with anxiety disorders, the evidence is weak. Also, it has been known to cause eosinophilia-myalgia syndrome, a significantly dangerous side effect. Therefore, the risk/benefit ratio does not favor physician support of patients choosing this medication because it is "natural."

## Key Recommendations for Physicians

Because use of herbal remedies is increasing, it is important for family physicians to ask their patients about such use. Encouraging data support the effectiveness of some of these products, particularly kava and, to a lesser degree, inositol. Although none of these supplements or products are free of adverse effects, the potential for benefit seems greater than the risk of harm.

The existing data show that the popular supplements St. John's wort, valerian, and omega-3 fatty acids have little therapeutic value for anxiety disorders, and their use should be discouraged in favor of more effective treatments. In addition, many

**Table 5. Evidence Supporting the Effectiveness and Safety of Inositol in Anxiety Disorders**

| *Design* | *Description* | *Comments* |
|---|---|---|
| RCT crossover with placebo in panic disorder | Twenty-one patients with panic disorder were randomly assigned to 6 g of inositol or placebo twice a day for four weeks and then switched to the other substance[24]; during week 4, the mean number of panic attacks was 3.7 in the inositol group compared with 6.3 in the placebo group | Panic attack frequency and intensity were significantly reduced in the inositol group |
| RCT crossover with SSRI in panic disorder | Inositol was compared with fluvoxamine (Luvox) in 20 patients with panic disorder[25]; each crossover phase lasted four weeks (dosage: inositol, 18 g per day, or fluvoxamine, 150 mg per day); the four-week intervals were separated by a one-week placebo washout period; overall, both drugs reduced panic attack frequency and intensity, anxiety scale scores, and clinical global improvement scores; no meaningful clinical differences were noted between the two drugs | The absence of a placebo condition is troubling but, taken together with the previous trial, inositol appears to reduce panic disorder symptoms in the short term; over a one-month interval, inositol showed effectiveness similar to that of established SSRI medications for panic disorder |
| RCT crossover with placebo in OCD | The same research team compared inositol and placebo for the treatment of OCD[26]; 13 patients with OCD who had failed SSRI or clomipramine (Anafranil) treatments or who could not tolerate their side effects used 18 g per day of inositol or placebo for consecutive six-week treatment intervals; inositol produced significant reductions in Yale-Brown Obsessive-Compulsive Scale scores (4.6) compared with the placebo condition (0.3); reductions in Hamilton Anxiety Scale scores were not significantly different | Inositol appears to be highly effective in reducing OCD symptoms but not in reducing anxiety scale scores; participants with OCD had failed previous treatment, so findings may not be typical of patients with OCD in general |
| RCT crossover with placebo in OCD | Inositol added to SSRI treatments for OCD[27]; 13 patients with OCD who had not responded adequately to fluoxetine (Prozac), fluvoxamine, or clomipramine for at least eight weeks were given consecutive six-week trials on 18 g per day of inositol or placebo, in addition to the SSRI medication; inositol provided no additional benefit | The two studies on treatment-resistant OCD suggest inositol adds no benefit to SSRI therapy but may have positive effects on its own; none of these short studies produced side effects from inositol that would suggest risk greater than that of SSRIs |

*RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor; OCD = obsessive-compulsive disorder.*

*Information from references 24 through 27.*

**Table 6. Evidence Supporting the Effectiveness and Safety of 5-Hydroxytryptophan in Anxiety Disorders**

| *Design* | *Description* | *Comments* |
|---|---|---|
| RCT in panic disorder | Patients with panic disorder (n = 24) exposed to a panic-inducing carbon dioxide challenge were given a single dose of 5-hydroxytryptophan (200 mg) or placebo before exposure[28]; patients with panic disorder showed a significantly lower occurrence of panic symptoms; patients without panic disorder did not show any significant effects of the carbon dioxide challenge | This small trial compared patient responses to an artificial panic-inducing challenge; it is not clear if the panic prevention effect would transfer to real-world situations |
| RCT on mixed anxiety disorders | Double-blind placebo-controlled trial on 45 mixed anxiety disorders, mostly panic attacks with agoraphobia, compared 5-hydroxytryptophan with clomipramine (Anafranil) and placebo for eight weeks[29]; the clomipramine and 5-hydroxytryptophan were titrated from 25 mg a day to a maximum of 150 mg per day; the clomipramine group showed significant reductions in Hamilton Anxiety Scale scores compared with placebo, whereas the 5-hydroxytryptophan group showed modest, nonsignificant improvements | No clinically meaningful effect of 5-hydroxytryptophan on reducing anxiety scale scores |
| Case reports on safety | In the past, multiple cases of eosinophilia-myalgia syndrome were reported among L-tryptophan users; this serious, incurable, potentially fatal neurologic condition motivated the temporary withdrawal of serotonin precursors from the market; the pattern of cases suggested they came from a single brand of contaminated L-tryptophan | L-tryptophan products are back on the market; there is current speculation that any brand of L-tryptophan or L-hydroxytryptophan can elicit this serious side effect in overdose |

*RCT = randomized controlled trial.*

*Information from references 28 and 29.*

preparationsthat might be used by patients to reduce anxiety lack evidence of effectiveness with anxiety disorders. The availability of natural treatments that are supported by clinical evidence and the recognition of those that are not will help physicians collaborate with patients using or seeking natural remedies to maximize the potential for benefit and minimize the potential for harm.

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