Complementary and alternative treatments for anxiety symptoms and disorders: Herbs and medications

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INTRODUCTION

Anxiety disorders are among the most common mental health problems in the United States. Many patients with anxiety disorders find conventional (Western) mental health care treatments to be insufficiently helpful and turn to complementary and alternative medicine (CAM) as an adjunct or substitute.

Epidemiologic studies suggest that 30 to 43 percent of patients treated in primary care for anxiety use CAM remedies as at least part of their treatment [1-3]. Clinicians would be well prepared to know about efficacy and safety of CAM treatments available for anxiety disorders.

Herbal remedies and dietary supplements used as complementary and alternative medical treatments for anxiety symptoms and disorders are described here. Complementary and alternative treatments involving physical, cognitive, or spiritual activities for anxiety symptoms and disorders are described separately. Herbal medicine and dietary supplements in general medical care are also described separately. (See "Complementary and alternative treatments for anxiety symptoms and disorders: Physical, cognitive, and spiritual interventions" and "Overview of herbal medicine and dietary supplements".)

OVERVIEW

Sixty-two percent of adults in the United States utilize some form of complementary and alternative medical treatments [3]; the most commonly used were mind-body therapies. Individuals diagnosed with a psychiatric illness are more prone to using these therapies, especially patients with elevated anxiety or anxiety disorders [4,5], in part because many who are treated psychiatrically respond only partially to treatment and have residual symptoms and impairment [6].

Among the challenges encountered with evaluating the efficacy and clinical use of herbal remedies and dietary supplements for anxiety symptoms and disorders:

- Rigorous clinical trials of pharmacotherapy for anxiety disorders have shown rates of placebo response as high as 50 percent [7]. Determinations of efficacy thus require well-designed trials in sufficiently sized samples. Instead, most trials have had small samples and other methodological limitations. Large-scale safety studies have been scarce and inconclusive. Interactions among different herbal remedies have received insufficient study.

- Consumers in the United States spend billions of dollars annually on herbal remedies and dietary supplements. This has fueled aggressive marketing campaigns, with claims of safety and efficacy for anxiety. Although often sold in pharmacies, these products are not subject to US Food and Drug Administration (FDA) regulations in the United States. Preparations can vary widely in dose and in composition of extracts and alkaloids, depending on the source.

- Many herbal remedies are largely used as a part of complex treatment strategies within Chinese, Tibetan, or Ayurveda medical systems. Evaluating their effects as a single remedy using Western testing methods and outcome measures, while useful, is incomplete. In addition, language barriers and selective databases limit access to clinical research from other countries.

Clinicians have an important role in educating patients about herbal remedies and dietary supplements. They should warn patients that the safety and efficacy of these products for anxiety symptoms and disorders is still unproven, and help them weigh the risks and benefits of using them adjunctively. Patients should be discouraged from abandoning evidence-based psychotherapies and medications for anxiety disorders. A patient's medical history should include what remedies and supplements they are taking, particularly those known to interact with other drugs or cause adverse effects.

In addition to describing complementary and alternative treatments for anxiety disorders, this topic includes obsessive-compulsive disorder (OCD), which was placed into a separate category

of disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). (See "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis" and "Obsessive-compulsive disorder in adults: Epidemiology, clinical features, and diagnosis", section on 'Assessment and diagnosis'.)

HERBAL REMEDIES

None of the herbal remedies described here has been shown in clinical trials to be clearly effective or ineffective for anxiety symptoms or disorders. Potentially serious adverse effects are described below. Safety during pregnancy is not established. Mechanisms for anxiety reduction suggest involvement of gamma aminobutyric acid (GABA) [8].

Kava-kava — Kava-kava or kava (*Piper methysticum*) has been used for medicinal, religious, and social purposes in various cultures in the South Pacific Rim. The remedy traditionally comes from the root, which is combined with water to make an emulsion. Western phytopharmaceutical producers may use other parts of the plant to make pills, eg, stems, leaves, peelings, and bark with an ethanol or acetone solvent.

The principal active ingredients of kava remedies are called kavalactones; 15 have been identified, all with psychoactive properties. The mechanism of action is not known; research suggests a modulation of GABA activity and inhibition of noradrenaline and dopamine reuptake [9,10].

Two meta-analyses of multiple randomized trials [11-27] found kava to reduce anxiety in patients with elevated symptom levels [28,29]. As an example, a meta-analysis of seven randomized trials of 380 participants with elevated anxiety symptoms found that kava extract reduced anxiety as measured by the Hamilton Anxiety (HAM-A) scale compared with participants receiving placebo (weighted mean difference 3.9, 95% CI 0.1-7.7) [29]. Most of the trials had methodological flaws, small sample sizes, and conflicts of interest.

Side effects of kava include headaches, sedation, and sleepiness.

Numerous reports of severe hepatotoxicity and liver failure have been described in Europe and the United States, occurring within a few weeks to up to two years (average 4.5 months) following ingestion [30-36]. The US Food and Drug Administration (FDA) advised that kava should be used with caution in patients with preexisting liver disease or at risk for liver disease [37]. Hepatotoxicity and kava are discussed in further detail separately. (See "Hepatotoxicity due to herbal medications and dietary supplements", section on 'Kava-kava'.)

Valerian — Valerian root (*Valeriana officinalis*), first described by Hippocrates, has sedative and anxiolytic effects. Various compounds have been detected in valerian, including alkaloids, flavonoids, and GABA. Its mechanism of action is not known, but appears to have a relationship with valerian root affinity for the GABA receptor.

Valerian was not found to reduce anxiety compared with placebo in a single small trial. A clinical trial randomly assigned 36 patients with generalized anxiety disorder (GAD) to daily valerian, diazepam, or placebo [38]. After four weeks, there were no significant differences on the HAM-A scale or in side effects between patients treated with valerian compared with placebo.

Few adverse events have been reported as a result of valerian. Consistent with its sedative properties, valerian can cause drowsiness or dizziness. The risk of respiratory depression should be considered if valerian is proposed for use in the context of multiple sedating drugs and/or significant alcohol consumption. Valerian can cause abdominal pain in large doses.

Passion flower — Passion flower (*Passiflora incarnata*) is traditionally used as a calming herb in the Americas and Europe. Its extract is also used as flavoring in foods and beverages.

The anxiolytic effects of passion flower are milder than for kava or valerian; it is thus most common to find passion flower marketed in combination with other herbs. A combined product, Euphytose (EUP), contains passion flower, crataegus, ballota, valerian, cola, and *Paullinia*.

Two small trials of passion flower showed mixed results. As an example, a trial of 90 patients with presurgical anxiety found that patients treated with passion flower experienced less anxiety compared with patients treated with placebo [39]. EUP has not been tested in a randomized trial.

Side effects of passion flower are rare but could include drowsiness, sedation, nausea, vomiting, and dizziness.

Chamomile — Chamomile (*Matricaria recutita*) has been used for thousands of years for anxiety as well as other conditions. Research in animals has found evidence of anti-inflammatory [40], antihyperglycemic [41], antigenotoxic [42], and anticancer [43-45] properties in chamomile; these findings have not been reproduced in human studies.

Clinical trials of chamomile extract for GAD have shown mixed results:

- A clinical trial compared chamomile extract with placebo in 57 patients with mild to moderate GAD, finding the treatment to reduce anxiety on the HAM-A scale compared with the placebo group [46].

- A clinical trial of 93 patients who responded to chamomile for GAD were randomly assigned to six months of continued chamomile or placebo [47]. At the end of the trial, no difference was seen between groups in the proportion that relapsed.

Chamomile has been reported to increase anticoagulant properties of other medications and should thus be used with caution in patients whose anticoagulation status requires international normalized ratio (INR) monitoring. Adverse reactions ranging from simple dermatitis to severe anaphylaxis have also been described [48,49], but large-scale safety data have not been accumulated.

Saffron — Saffron is the dried stigmata of *Crocus sativus L*. In traditional medicine, it is used for the treatment of several conditions including cramps, depression, and asthma. It also has been studied in use for depression.

Two clinical trials, both with methodologic limitations, showed greater reductions in anxiety and depression with saffron compared with placebo:

- A clinical trial randomly assigned sixty adult patients with generalized anxiety and depression to receive a 50 mg saffron capsule or a placebo capsule twice daily for 12 weeks [50]. At the end of the trial, patients in the saffron group experienced greater reductions in anxiety and depression compared with placebo.

- A clinical trial of 40 patients with major depression treated with either fluoxetine or sertraline were randomly assigned to receive crocin, the main ingredient of saffron, or placebo as an adjunct treatment [51]. At the end of the trial, patients receiving crocin showed greater reductions in anxiety and depression compared with placebo.

St. John's wort — St. John's wort (*Hypericum perforatum*) is widely prescribed as an antidepressant and anxiolytic remedy, especially in Europe. The mechanism of action is not known. Weak monoamine oxidase inhibiting (MAOI) properties have been suggested [52].

There is no evidence of efficacy for St. John's wort in anxiety disorders. Small trials suggest the remedy may reduce anxiety associated with other mental disorders (below). It has been tested more extensively for depression. (See "Clinical use of St. John's wort" and "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'St. John's wort'.)

- **Obsessive-compulsive disorder/social anxiety disorder** – Clinical trials of St. John's wort for obsessive-compulsive disorder (OCD) and social anxiety disorder reported negative results [53,54]. As an example, a clinical trial randomly assigned 60 patients with OCD to receive St John's wort or placebo. After 12 weeks, no difference in OCD symptom change

was seen between groups, nor in the percent of patients responding to treatment (17.9 versus 16.7 percent).

- **Anxiety** – There are no trials of St. John's wort for anxiety as a primary outcome of treatment. Reduction in associated anxiety has been reported as a secondary outcome in two clinical trials of St. John's wort, one in patients with major depression, the other in patients with somatization disorder [55,56].

The combination of St. John's wort and selective serotonin reuptake inhibitor (SSRI) antidepressants can cause serotonergic syndrome and should be avoided [57].

Other herbals — Other less well-known herbs received some study for anxiety, but generally with significant methodologic limitations or negative results:

- Keenmind (*Bacopa monnieri*) [58]
- Lemongrass (*Cymbopogon citratus*) [59]
- Rhodax (*Rhodiola rosea*) [60]
- Skullcap (*Scutellaria lateriflora)* [61]
- Silexan (lavender oil) [62]
- *Melissa officinalis* leaf extract [63,64]

Borage (*Echium amoenum*) and milk thistle (*Silybum marianum*) have shown promising results for OCD in small clinical trials [65,66].

DIETARY SUPPLEMENTS

Essential nutrients and their source — Nutrients, including vitamins, minerals, omega-3 (n-3) polyunsaturated fatty acids (PUFAs), and amino acids, are obtained through dietary intake of fruits, vegetables, nuts, and seafood. Many people are deficient in essential nutrients due to Western diets high in processed foods [67]. Nutrients are classified as "essential" when they are needed for the body's biologic processes but are not produced in adequate amounts by the body and must be obtained through dietary consumption [67]. Deficient levels of essential nutrients can result in the dysfunction of biological systems and can only be recovered by replenishment of required concentrations [67].

Specific essential nutrients

Zinc — Zinc is an essential chemical element and plays an important role in replication, transcription, and protein synthesis for DNA as well as in expression of genes, storage of hormones, and reparation of tissues in humans. Zinc has been found to influence N-methyl-D-

aspartate (NMDA) and gamma aminobutyric acid (GABA), neurotransmitter systems believed to be involved in obsessive-compulsive disorder (OCD) and in anxiety disorders [67].

- **Obsessive-compulsive disorder** – Study results have led researchers to postulate a relationship between zinc deficiency and OCD:
  - A study of blood levels of trace elements in 48 participants with OCD and 48 healthy controls found an inverse correlation between the severity of OCD symptoms and zinc levels [68]. Lower levels of iron and magnesium were seen in the OCD group, but these levels were not correlated with OCD symptom severity [68].
  - A small clinical trial found evidence of benefit of zinc supplementation of fluoxetine treatment for OCD. Twenty-three patients with OCD were randomly assigned to receive either fluoxetine (20 mg/day) and zinc (440 mg/day) or fluoxetine (20 mg/day) and placebo [69]. After eight weeks, patients in the supplemented group had lower scores on the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) compared with those in the control group.
- **Panic disorder** – A study of trace element concentrations in 54 subjects with panic disorder and 52 healthy persons suggests an association between low levels of zinc and panic disorder [70]. Blood levels of manganese, zinc, calcium, copper, and magnesium were measured in all subjects. Blood concentrations of participants with panic exhibited lower levels of zinc compared with controls; other trace element concentrations were not related to disorder status.

Magnesium — Magnesium is obtained through dietary intake of food such as dark, leafy greens; nuts; seeds; avocado; soybeans; and bananas. It is an essential element required for biological homeostasis, glucose metabolism, as well as synthesis of proteins and is a cofactor for over 300 enzymes [67]. Case histories and preclinical studies have found evidence for associations between magnesium deficiency and anxiety and depressive behaviors, as well as improvements in these symptoms after supplementation [67,71].

Vitamin E — Vitamin E (alpha-tocopherol) is an antioxidant that is believed to have a protective effect against free oxygen radicals and lipid peroxidation (a biomarker for stress-induced oxidative cellular damage). Vitamin E has been hypothesized to exert its anxiolytic effect through protective antioxidant effects and decreasing of cortisol levels.

Findings from clinical studies include:

- Elevated levels of lipid peroxidation and elevated anxiety in 80 subjects with OCD, social anxiety disorder, panic disorder [72]

- Decreased vitamin E plasma levels and elevated malondialdehyde levels in 37 subjects with generalized anxiety disorder (GAD) compared with 20 healthy controls [72]

Antioxidant vitamins — The antioxidant vitamins A, C, and E have been studied as a group for their effect on anxiety. A study found levels of the vitamins to be lower in 40 patients with GAD and 40 patients with major depression compared with 20 healthy control patients [72].

Participants with GAD in the previous study were randomly assigned to receive either alprazolam or alprazolam plus vitamins A, C, and E daily [72]. After six weeks, participants who received vitamin supplementation had increased blood levels of the three vitamins and lower scores on the Hamilton Anxiety (HAM-A) scale compared with controls.

B vitamins — B vitamins are essential for the creation of serotonin neurotransmitters, and vitamin B deficiency has been associated with anxiety and depressive symptoms [73,74].

- **Vitamin B_6 and folate** – A study of 907 female adolescent subjects found that folate and vitamin B_6 were negatively correlated with symptoms of depression and anxiety [75].

- **Vitamin B_{12}** – A study comparing 35 subjects with OCD with 22 healthy controls found a greater proportion with vitamin B_{12} deficiency in subjects with OCD compared with controls [76]. Subjects with OCD had higher homocysteine levels, which positively correlated with Y-BOCS compulsion and Y-BOCS total scores.

Vitamin D — Vitamin D, especially vitamin D_3, plays an important role in brain plasticity, neuroimmunomodulation. It is derived from sunshine and fish with higher fat contents [77,78]. Research has suggested a possible relationship between vitamin D deficiency and vulnerability to depression and anxiety.

Clinical research findings on the relationship between vitamin D serum levels and anxiety severity have been mixed:

- A study of 80 patients with chronic hemodialysis reported an association between anxiety severity scores and plasma levels of 25-hydroxy vitamin D [79].

- In a six-week clinical trial of the effect of vitamin D supplementation on affect and cognition in young adults, no difference was found in anxiety levels between vitamin D recipients and those given placebo [80].

- A clinical trial of 322 subjects who experienced an earthquake were randomly assigned to receive vitamin D_3 or placebo as a treatment for stress and anxiety. After 18 months of treatment, there was no difference between groups in anxiety or stress symptom change [81].

Glycine — Glycine, an NMDA receptor agonist, has been shown to increase glutamatergic neurotransmission, which is known to be dysregulated in individuals with OCD [82]. Glycine has been studied as a potential adjunctive treatment for OCD. A clinical trial of 24 participants with OCD compared adjunctive daily treatment with glycine with placebo over 12 weeks. Participants receiving glycine exhibited a statistically nonsignificant trend toward lower Y-BOCS scores compared with the placebo group.

Inositol — Inositol, a naturally occurring isomer of glucose derived from the human diet, is concentrated in the brain and heart and involved in the serotonin, dopamine, and glutamate neurotransmitter systems [83,84]. Small clinical trials suggest that treatment with inositol may be efficacious for panic disorder, agoraphobia, and OCD.

- **Panic disorder** – A clinical trial with a crossover design compared adjunctive treatment with inositol to placebo over four weeks in 21 patients with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of panic disorder with and without agoraphobia [83]. Patients receiving inositol experienced a greater reduction in panic attacks compared with placebo (from 10 to 3.7 versus 10 to 6.3 panic attacks) and a decrease in the severity of agoraphobia.

- **Obsessive-compulsive disorder** – A clinical trial with a crossover design compared adjunctive inositol with placebo in 13 patients with OCD over six weeks [85]. Patients receiving inositol had lower scores on the Y-BOCS at the end of the period compared with controls.

Omega-3 (n-3) polyunsaturated fatty acids — n-3 PUFA, which is found in fish oil, reduced anxiety in small clinical trials, but has not been studied for anxiety disorders.

Systematic reviews and meta-analysis have shown conflicting results in the treatment of anxiety symptoms. While one meta-analysis of 19 trials and over 2000 participants showed improvements in severity of anxiety symptoms with n-3 PUFAs, a larger meta-analysis of 31 trials including over 41,000 participants showed that n-3 PUFAs has little or no effect in preventing anxiety symptoms [86,87].

n-3 PUFA protects neurotransmission from glucocorticoids, which are released during the body's stress response [88]. It is postulated that this protective effect, particularly on excitatory

glutamatergic neurotransmitter systems, underlies a potential therapeutic benefit of n-3 PUFA on anxiety.

L-lysine and l-arginine — The essential amino acids L-lysine (Lys) and L-arginine (Arg) have been shown to reduce anxiety and stress hormone reactions in individuals with high levels of anxiety [89]. A clinical trial of 107 healthy volunteers were randomly assigned to receive L-lysine and L-arginine or placebo daily [90]. After one week, participants assigned to the L-lysine/L-arginine group had lower levels of state and trait anxiety compared with the placebo group.

HOMEOPATHY

Homeopathy, developed by a German clinician at the end of the 18th century, involves the administration of highly diluted doses of substances to treat illnesses [91,92]. Meta-analyses of 25 clinical trials of homeopathy for anxiety in samples drawn from diverse populations reported significant methodologic limitations and inconclusive results [91,92].

Homeopathy is described in greater detail separately. (See "Homeopathy".)

AROMATHERAPY

Aromatherapy, the practice of administering isolated volatile oils from plants via inhalation, massage, or internal use, has been utilized in the treatment of anxiety. A systematic review of 16 clinical trials examining the anxiolytic effects of aromatherapy for individuals with anxiety symptoms reported uncertain benefits due to methodologic limitations of the trials [93].

SUMMARY AND RECOMMENDATIONS

- **Overview** – Clinical trials of herbal remedies and dietary supplements in anxiety symptoms and disorders have generally had small sample sizes and other methodologic limitations. Large-scale safety studies have been scarce and inconclusive. Interactions among different herbal remedies have received insufficient study. (See 'Overview' above.)

  We help our patients weigh the risks and benefits of using these products. We include remedies and supplements they are taking, particularly those known to interact with other drugs or cause adverse effects, as part of the medical history. (See 'Overview' above.)

- **Herbal remedies** – None of the herbal remedies tested for anxiety disorders in clinical trials have been shown to be clearly effective or clearly ineffective. Trials suggest that kava

and chamomile may reduce anxiety in people with generalized anxiety disorder (GAD). Findings from trials of valerian, passion flower, and St. John's wort are either mixed or negative. (See 'Herbal remedies' above.)

- **Adverse effects** – Serious adverse effects of herbal remedies tested in anxiety disorders include hepatotoxicity associated with kava and an anticoagulant effect with chamomile. We encourage patients not to underestimate the potential risks of herbal remedies. (See 'Herbal remedies' above.)

- **Dietary supplements** – Small clinical trials of some substances have shown promising results, but at best provide weak supporting evidence; none can be recommended for use at present:

  - Zinc for obsessive-compulsive disorder (OCD) and panic disorder
  - Antioxidant vitamins for GAD
  - Inositol for panic disorder, agoraphobia, and OCD
  - n-3 PUFAs for anxiety
  - L-lysine/L-arginine for anxiety associated with cortisol deficiency

- **Homeopathy** – Homeopathy has not been shown to be efficacious for anxiety disorders or for anxiety symptoms in medically ill patients. Systematic reviews of the use of aromatherapy in the treatment of anxiety disorders have reported unclear benefits. (See 'Homeopathy' above and 'Aromatherapy' above and "Homeopathy".)

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