

Integrative Medicine

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the latest developments in integrative therapies [ALERT]

ANXIETY

Some Dietary Supplements for Anxiety

By Todd A. Born, ND

Born Naturopathic Associates, Inc., Alameda, CA; Product Manager, Allergy Research Group LLC

Dr. Born reports that he is a consultant for Nutri-Link Clinical Education.

These are stressful times, or at least there are times when many patients feel ill-equipped to manage their stressors — whether it is the economy, jobs, inclement weather, their own health or the health of loved ones, or even the health of pets. Over time, these events may take deleterious tolls. For example, numerous studies link anxiety and stress with cardiovascular disease. Not only do anxiety and stress increase disease incidence, but they also increase the risk of an adverse cardiovascular event (stroke or heart attack). Studies have shown that the prevalence of anxiety is high (approximately 70-80%) among patients who have experienced an acute cardiac event.¹ Even among the patients who have not experienced these events, the prevalence of anxiety is estimated to be between 20-25%.¹

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) discusses the various conditions within the anxiety spectrum; a full review of the diagnosis of these conditions, however, is beyond the scope of this article. Along this spectrum are panic attacks, phobias, obsessive-compulsive

disorder, post-traumatic stress disorder, and generalized anxiety and its subsets. Anxiety is even more prevalent than depression, and many times these two diagnoses go hand in hand.² Prior to any intervention, it is important to rule out organic causes such as hyperthyroidism, carcinoid syndrome, pheochromocytoma, and numerous others. Anxiety can be acute (2 days to 4 weeks) or chronic (occurs more days than not for at least 6 months). In the short term, moderate amounts of anxiety can be a beneficial part of our existence, such as alerting us to danger or perhaps even increasing our performance. But chronic or severe anxiety can take over one's life and interrupt daily activities, interrupt sleep, lead to poor dietary choices, and make one exercise less, and even to the point one just doesn't even want to go out and socialize. This can lead to serious health concerns and cause or amplify relationship issues.^{3,4}

PATHOPHYSIOLOGY

Genetic factors appear to predispose individuals to the development of generalized anxiety disorder (GAD). Data from twin studies have been inconsistent, but what has been seen is in

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the serotonin transporter gene-linked polymorphic region 5S genotype (short/short). This gene has been found to be more frequent in patients with GAD.⁶ Another theory is the variations in two subtypes of the glutamic acid decarboxylase gene, which may increase individual susceptibility to anxiety disorders, including GAD.⁷

On the topic of genetics, methylenetetrahydrofolate reductase (MTHFR) polymorphisms have clear links to mood, anxiety, and personality disorders. The MTHFR gene provides instructions for making the enzyme methylenetetrahydrofolate reductase, which plays a role in processing amino acids. MTHFR is important for a chemical reaction involving forms of the B vitamin folate (folic acid or vitamin B9). Specifically, this enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.^{8,9}

Neuroimaging and other studies suggest the symptoms of GAD are accompanied by an enhanced emotional responsiveness in fear-related brain circuits. A 2009 study using functional MRI (fMRI) showed that patients who had GAD showed greater anticipatory activity than healthy controls in the bilateral dorsal amygdala.¹⁰

Higher-than-average number of traumatic experiences and other undesirable life events in childhood have been found to increase prevalence of GAD.¹¹ GAD is more likely to occur in people with behavioral inhibition — a tendency to be timid and shy in new situations.¹²

Anxiety is multifactorial and can stem from a myriad of causes or a combination of them. Besides the aforementioned pathological conditions, caffeine, poor sleep habits, poor diet, unique nutrient deficiencies, lack of exercise, and other reasons can all play a factor.^{13,14}

ALLOPATHIC APPROACH

Conventionally, anxiety, regardless of etiology or form, tends to be managed primarily with antianxiety medications, antidepressants, sleeping medications,

and at times, counseling, cognitive behavioral therapy, or more recently mindfulness.¹⁵ With respect to the latter, there is increasing evidence of efficacy of mindfulness-based stress reduction and other behavioral health and mind-body techniques in anxiety (see article on page 61).

More patients seem to be looking into safer “alternatives” to medications. Natural does not necessarily equate to safe, but evidence-based nutraceutical interventions for anxiety disorders are available. Patients who do not tolerate the current medications may consider nutritional and herbal interventions. It can be difficult to define what is integrative medicine and what is conventional or allopathic medicine, especially as once-unconventional therapies become more and more accepted (i.e., mindfulness-based stress reduction). That said, some therapies may not be considered mainstream and still have some evidence of efficacy as adjunctive treatments, or outright substitutions for the treatments, such as pharmaceuticals, that may have significant adverse effects. Some examples of such therapies, and their dosing and important references, are listed below. Clinicians must assess their patients and decide what they believe may be most effective for each individual.

Withania somnifera (ashwagandha) is an Ayurvedic (East Indian) that has antiaging, hematopoietic, immunomodulating, anxiolytic, antidepressant, cardiovascular protection, antitumor and antineoplastic properties. Dosage is 3000-6000 mg of dried root or 300-500 mg standardized extract.^{16,17,18} A 2012 study of 64 volunteers randomized subjects to either ashwagandha or a placebo twice a day for 60 days. On day 60, significant reduction in stress scores and substantial reduction in cortisol levels were observed compared to placebo.¹⁶

L-theanine (200-400 mg daily) is an amino acid found in tea (higher amounts in green tea) that can reduce anxiety.^{19,20} L-theanine can increase levels of gamma-aminobutyric acid (GABA) and serotonin. In 2011, an 8-week

Summary Points

- Anxiety disorders affect more than 40 million U.S. adults.
- Patients with anxiety disorders who do not tolerate pharmaceutical medications may consider nutritional and/or herbal interventions.
- Nutritional/herbal interventions have the potential to interact with psychoactive pharmaceuticals, so concomitant use should be avoided.

randomized, double-blind, two-center, placebo-controlled trial sought to see if L-theanine would be effective at relieving positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder. The authors found that L-theanine was a safe and well-tolerated augmentation of antipsychotic therapy, which can “ameliorate positive, activation, and anxiety symptoms in schizophrenia and schizoaffective disorder patients.”

GABA (100-200 mg up to three times daily) has natural relaxant effects.²¹ A 2006 study used EEG-measured alpha waves on 13 subjects given either water, L-theanine, or GABA. After 60 minutes of administration, GABA significantly increased alpha waves and decreased beta waves compared to water or L-theanine.²² In the second part of the study, eight acrophobic subjects received either GABA or placebo. All subjects crossed a suspended bridge. Immunoglobulin A (IgA) saliva levels were monitored during bridge crossing. The placebo group showed a marked decrease in their IgA levels, while the GABA group showed significantly higher levels.²²

Inositol (12-18 g per day) was found to be equivalent or better than fluvoxamine.^{23,24} In a double-blind, randomized, controlled trial (RCT), Palatnik et al found that the number of panic attacks in the inositol group reduced by an average of four episodes compared to 2.4 from fluvoxamine over a 1-month period. Nausea and tiredness were more common with fluvoxamine, whereas inositol was well tolerated.²³

Omega-3 essential fatty acids reduce inflammation and anxiety at 2500 mg daily.²⁵ In a 12-week, double-blind RCT, 68 medical students had blood drawn at baseline and under stressful conditions (before an exam). Lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF- α), and interleukin 6

(IL-6) were measured. The subjects were given either 2085 mg EPA/348 mg DHA or placebo. LPS and TNF- α decreased, IL-6 increased, while secondary analyses that used the plasma n-6:n-3 ratio in the treatment group showed that decreasing n-6:n-3 ratios led to lower anxiety. The authors concluded, “The reduction in anxiety symptoms associated with n-3 supplementation provides the first evidence that n-3 may have potential anxiolytic benefits for individuals without an anxiety disorder diagnosis.”

Piper methisticum (kava kava) can be given 150-400 mg in divided doses of standardized extract (70% kavalactones).^{26,27} A 2003, 8-week, double-blind RCT involving 129 patients showed that kava kava LI150 is well tolerated and is as effective as buspirone and opipramol in the acute treatment of outpatients with GAD.²⁶ Due to concerns about hepatotoxicity, most experts recommend monitoring liver enzymes at baseline and every 6 months if using kava kava long term. It should be avoided in people with preexisting liver disease.

Passiflora incarnata (passion flower) at 45 drops per day of a tincture (1:8 in 45% alcohol) was found to be just as effective as oxazepam.²⁸ A double-blind RCT involving 36 outpatients found passion flower extract to be equivalent to oxazepam in GAD. The passion flower was well tolerated, while the participants who took oxazepam experienced significantly more problems relating to impairment of job performance.²⁸

Silexan is a lavender oil capsule (80 mg daily) used as an alternative to benzodiazepines.²⁹ A 2010 multicenter, double-blind RCT looked into the efficacy of a 6-week intake of silexan vs lorazepam.

Anxiety Facts⁵

- Anxiety disorders are the most common mental illness in the United States, affecting 40 million U.S. adults age 18 and older (18% of U.S. population).
- Anxiety disorders cost the United States more than \$42 billion a year, almost one-third of the country's \$148 billion total mental health bill.
- More than \$22.84 billion of those costs are associated with the repeated use of health care services; people with anxiety disorders seek relief for symptoms that mimic physical illnesses.
- People with an anxiety disorder are three to five times more likely to go to the doctor and six times more likely to be hospitalized for psychiatric disorders than those who do not suffer from anxiety disorders.
- Anxiety disorders develop from a complex set of risk factors, including genetics, brain chemistry, personality, and life events.

The primary target variable was the change in the Hamilton Anxiety Rating Scale (HAM-A). The mean of the HAM-A-total score decreased clearly and to a similar extent in both groups. Silexan showed no sedative effects, has no potential for drug abuse, and, therefore, may be considered an alternative to benzodiazepines for GAD.

Rhodiola rosea (100-400 mg daily), known for its adaptogenic properties, decreases anxiety and enables better adaptation to stress response.^{30,31} Use with caution in patients with bipolar disorder.

ADVERSE EFFECTS AND INTERACTIONS WITH ALLOPATHIC THERAPEUTICS

All of the aforementioned interventions have the potential to interact with psychoactive pharmaceuticals, including additive effects with anxiolytics, so concomitant use should be avoided or done cautiously. In addition, GABA and L-theanine may theoretically potentiate antihypertensives, so caution is advised.^{32,33}

Precautions should be taken with certain conventional treatments, including selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors, which block reabsorption (reuptake) of the neurotransmitter serotonin in the brain and block the absorption (reuptake) of the neurotransmitters serotonin and norepinephrine in the brain, respectively.^{34,35} Nutrients like tryptophan, 5-hydroxytryptophan, and s-adenosylmethionine can increase the amount of serotonin, and combined with the medication may cause serotonin syndrome (SS) in susceptible people. SS can range in severity from mild to life-threatening. Most cases of SS are mild and resolve with prompt recognition and supportive care.^{36,37,38}

CONCLUSION

It has been observed that the greatest success at anxiety resolution is with a combination of the “recommendations,” along with counseling and stress reduction techniques. The brilliance of integrative medicine is to take the patient’s whole picture into account and determine an individualized treatment plan and strategy based upon the evidence-based treatment recommendations. ■

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