Integrative Management of Anxiety

by James Lake, MD

Almost one third of US mental health care costs (approximately $50 billion) go toward the treatment of anxiety disorders.[1] Conventional pharmacological treatments for anxiety are often beneficial but have limited efficacy. A meta-analysis of high-quality studies concluded that the efficacy of conventional drug treatments for anxiety disorders varies widely depending on the core symptom being treated.[2] Frequency and severity of panic attacks tend to improve and remain improved in response to benzodiazepines; however, patients who regularly use these drugs are at significant risk for dependence and withdrawal symptoms. Elderly patients who use benzodiazepines are especially at risk for falling.

Phobias, obsessions and compulsions, and symptoms of posttraumatic stress are often poorly responsive to conventional drugs.[2] In the context of efficacy and safety issues associated with conventional treatments for anxiety, psychiatrists should know about the evidence for nonconventional therapy. In Part 1 of this article, I review research findings on the most substantiated nonpharmacological and integrative treatments for anxiety. In Part 2, I will discuss less substantiated but promising nonconventional approaches.

OVERVIEW

Positive research findings consistently support the use of kava and L-theanine in the treatment of persons with generalized anxiety. Regular relaxation, meditation, and mindfulness practices improve symptoms of generalized anxiety, and these nonpharmacological therapies may be safely combined with conventional drugs. Virtual reality graded exposure therapy (VRGET) will play a significant role in the treatment of many anxiety disorders that respond poorly to currently available treatments, such as drugs and cognitive-behavioral therapy (CBT). Numerous studies show that electroencephalographic (EEG) and electromyographic (EMG) biofeedback are as effective as regular relaxation training or mind-body practices for the treatment of moderately severe symptoms of generalized anxiety. A growing body of evidence supports the use of microcurrent stimulation of the CNS for the management of generalized anxiety.

Less-substantiated treatments for anxiety will be reviewed in Part 2 of this column and include dietary changes, supplementation with L-tryptophan or 5-hydroxytryptophan, regular exercise, massage, acupuncture (including electro-acupuncture), healing touch, and Reiki.

VITAMINS AND SUPPLEMENTS
Kava (*Piper methysticum*)

When kava is used at recommended dosages (typically 60 to 300 mg/d), patients do not experience the mental slowing or impaired cognitive functioning that is typical of many conventional anti-anxiety medications.[3] Animal studies suggest that the mechanism of action involves serotonin blockade in the amygdala by alpha-pyrones, a principal bioactive constituent of kava.

Part 1

Kava also interferes with norepinephrine reuptake and has a high binding affinity with γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptors. Kava may also modulate vagal heart tone in patients with generalized anxiety.[4]

A systematic review of 11 controlled, double-blind studies that included more than 600 patients concluded that kava was superior to placebo for the short-term management of generalized anxiety.[5] Randomized, controlled, double-blind studies support the use of kava preparations that are standardized to 70% kava lactones in divided doses of 70 to 240 mg/d for the treatment of "stress" and moderate anxiety but not for severe anxiety or agitation.[6,7] Daily use of standardized kava preparations of 100 to 200 mg was found to effectively reduce anxiety symptoms associated with menopause.[8]

Kava compares favorably with benzodiazepines and other conventional anti-anxiety drugs. The findings of a small, double-blind, controlled trial suggest that patients who have generalized anxiety who gradually increased their daily dose of kava (up to 300 mg) while tapering off a benzodiazepine did not experience worsening anxiety or benzodiazepine withdrawal.[9]

A randomized, placebo-controlled, multicenter study of 129 outpatients concluded that a standardized kava preparation (LI 150) was as effective as 2 commonly prescribed anti-anxiety agents (buspirone [BuSpar] and opipramol [Insidon], which is commonly prescribed in Germany) for the treatment of generalized anxiety.[10] Three fourths of patients in both the kava group and the conventional drug group experienced 50% or greater reductions in Hamilton Anxiety Scale scores and were classified as "treatment responders."

Kava is generally well tolerated, even at doses significantly above typical therapeutic doses. Uncommon adverse effects include GI upset, rash, headache, and dizziness.[11] In recent decades, there have been reports of kava inebriation,[12] although this social phenomenon has not been observed in Europe, where kava preparations are used medicinally to treat anxiety. Kava does not potentiate the effects of alcohol consumption in humans. Rare case reports suggest that kava may cross-react with benzodiazepines, increasing their sedating effects.[13] Reports of hepatitis[14] and fulminant liver failure have led to restrictions in the sale of kava products in many European countries and to a warning issued by the FDA.[15] These cases were rare, however, and independent experts have concluded that most reported cases of liver failure were associated with a processing error that resulted in toxic levels of alkaloids in a single batch of kava.[16,17]

In view of these safety issues, patients should be advised against taking kava[18] when there is a question of alcohol abuse or concurrent use of conventional sedative-hypnotics. One case report suggests that kava may interfere with anti-parkinsonian drugs.[19]

L-Theanine (gamma-ethyl-amino-L-glutamic acid)

Green tea is used as a restorative in traditional Chinese medicine and contains many bioactive constituents, including the amino acid L-theanine. The anti-anxiety effect of L-theanine is achieved through enhanced alpha brain wave activity and increased synthesis of GABA.[20,21] Greater GABA levels, in turn, increase the brain's levels of dopamine and reduce serotonin levels, resulting in general feelings of calm and well-being.[22] Changes in brain electrical activity, as measured with EEG, are dose-dependent and are similar to the beneficial EEG changes observed in meditation, including increased alpha waves in the occipital and parietal regions.[23] A calming effect is usually noted within 30 to 40 minutes after L-theanine is taken at doses of 50 to 200 mg, and typically lasts 8 to 10 hours. Moderate anxiety symptoms often improve in patients taking 200 mg once or twice daily. More severe anxiety symptoms may require dosages of 600 to 800 mg/d, taken in divided doses of 100 to 200 mg.

Unlike benzodiazepines and other conventional anti-anxiety treatments, L-theanine does not result in increased drowsiness, slowed reflexes, or impaired concentration. There is no risk of tolerance or dependence developing, and there have been no reports of serious adverse effects or interactions with other natural products or conventional drugs.

SOMATIC AND MIND-BODY APPROACHES
Applied relaxation comparable to cognitive therapy

Applied relaxation is a generic term for somatic or mind-body exercises used to diminish generalized anxiety. Relaxation techniques include sustained deep breathing,[24] progressive muscle relaxation, guided imagery, and systematic desensitization. Several models have

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been proposed to explain the anxiety-reducing effects of mind-body practices, including Benson's relaxation response and Selye's general adaptation syndrome. One model posits that anxiety is associated with muscle tension and is reduced by behaviors or cognitions that diminish tension and autonomic arousal. The effectiveness of relaxation as a treatment of various anxiety symptoms has been extensively reviewed.[25]

Guided imagery is widely used as a self-directed treatment of generalized anxiety. Applied relaxation techniques are often practiced together with mental imagery, meditation, or mindfulness training. Imagery can be individualized to the specific anxiety symptoms of each patient and is known to have beneficial effects on the immune system, physiological stress responses, and cognitive-emotional functioning in general.[26] The consistent practice of mental imagery effectively reduces many kinds of anxiety symptoms, including generalized anxiety, feelings of panic, and traumatic memories.[27,28] Imagery and relaxation techniques are often used together to induce hypnotic trance states, resulting in a dramatic reduction in symptoms of generalized anxiety.[29]

In a 5-month prospective study, patients with general anxiety randomized to a relaxation group versus a group treated with conventional antidepressants and relaxation experienced equivalent and significant improvements in state anxiety levels by the end of the trial.[30] In a small controlled trial, 36 anxious adult outpatients randomized to 12 weekly sessions of applied relaxation or conventional cognitive therapy experienced significant and comparable reductions in anxiety.[31]

Combining relaxation with guided imagery is probably more effective than either approach alone. In an open trial, 60 women who reported anxiety and postpartum depression experienced significant reductions in both anxiety and depressed mood using a combined relaxation-guided imagery protocol during the first 4 weeks after childbirth.[32] In contrast to the largely beneficial effects of relaxation on general anxiety symptoms, panic attacks are sometimes reported during applied relaxation exercises by those who have panic disorder.[33]

Yoga
Open studies and anecdotal evidence provide a strong argument for the therapeutic benefits of regular yoga practice among persons with generalized anxiety. The regular and skillful practice of specific yogic postures or breathing

methods results in sustained changes in brain activity and possibly in beneficial changes in neurotransmitter activity that manifest as a subjective state of alert calmness. Training in a particular style called Sudarshan Kriya yoga involves a specialized breathing technique that reportedly decreases serum cortisol levels, the major stress hormone in humans.[34] Patients with any anxiety disorder diagnosis improved significantly when they combined a daily yoga practice with relaxation and mindfulness training.[35] Yoga reduces anxiety in patients with hypertension and epilepsy,[36,37] and probably reduces test anxiety.[38] There is some evidence that regular yoga practice reduces the need for conventional drugs in generally anxious patients.[37] Findings of a small controlled study showed that the regular practice of a specific Kundalini yoga left-nostril breathing technique significantly reduced symptom severity in patients with obsessive-compulsive disorder.[39]

Meditation and mindfulness training
Meditation practices are used in many cultures to reduce anxiety and maintain optimal psychological and spiritual health. Beneficial physiological effects of meditation include decreased oxygen consumption, respiratory rate, and blood pressure, as well as EEG changes associated with decreased autonomic arousal.[40] Mindfulness-based stress reduction (MBSR) is an integrative approach pioneered by Kabat-Zinn[41] that has been validated as highly effective in reducing the physical, emotional, and cognitive consequences of chronic stress. MBSR incorporates elements of different Eastern meditation practices and Western psychology.

Research findings show that the consistent practice of mindfulness meditation, in which the patient practices detached self-observation, significantly reduces generalized anxiety and other anxiety symptoms.[35,42] Ninety-three percent of patients (N = 322) who started a 10-week MBSR program successfully completed it, and the majority reported significantly decreased physical and emotional distress, improved quality of life, a greater sense of general well-being, increased optimism, and increased feelings of control.[43] Patients

with irritable bowel syndrome (IBS), a frequent concomitant of generalized anxiety, experienced significantly fewer symptoms of both IBS and anxiety when they engaged in 2 brief (15-minute) daily sessions of mindfulness meditation.[44] The cultivation of self-awareness through mindfulness training assists anxious patients in avoiding potentially stressful situations and engaging in more effective coping when stress is unavoidable.[45]

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Virtual reality graded exposure therapy
Controlled studies confirm that VRGET is more effective than conventional imaginal exposure therapy (ie, the use of mental imagery to provoke a feared object or situation) and has comparable efficacy to in vivo exposure therapy.[46,47] Anxious or phobic patients are frequently unable to tolerate conventional exposure therapy and remain chronically impaired because they never become desensitized to a feared object or situation. As in imaginal exposure and in vivo therapy, VRGET has the goal of desensitizing the patient to a situation or object that would normally cause anxiety or panic.

Research findings support the use of VRGET as a treatment for many anxiety disorders, including specific phobias, generalized anxiety, panic disorder with agoraphobia,[48] and posttraumatic stress disorder (PTSD).[49] In a controlled study, VRGET and conventional CBT were equally effective in the treatment of panic disorder with agoraphobia; however, patients who underwent VRGET required 33% fewer sessions.[50]

Case reports and controlled studies have demonstrated the efficacy of VRGET for many specific phobias, including fear of flying,[51,52] heights, animals, and driving.[53-55] In one controlled study (N = 45), 65% of anxious adults who had a specific anxiety disorder according to *DSM-IV* criteria reported significant reductions in 4 of 5 anxiety measures.[56] VRGET is as effective as conventional exposure therapy for fear of flying, and is more cost-effective because both patient and therapist avoid the expense and time commitments required for in vivo desensitization.[51,53,54] In a preliminary study, persons who overcame fear of flying using VRGET combined with biofeed-

back (including respirations, galvanic skin response [GSR], and heart rate) were able to fly without the use of conventional medications or alcohol 3 months posttreatment.[52]

VRGET is also beneficial in traumatized patients in whom PTSD has been diagnosed. A virtual environment that simulates the devastation following the September 11, 2001, attacks on the World Trade Towers has been successfully used to treat individuals with severe PTSD.[57]

Emerging evidence suggests that combining VRGET with D-cycloserine, a partial NMDA agonist, results in greater improvement in acrophobic symptoms compared with treatment with VRGET alone. Findings from animal studies and a randomized clinical trial suggest that D-cycloserine functions as a cognitive enhancer by stimulating NMDA receptors, and may facilitate extinction of conditioned fear in patients with phobia.[58] Twenty-eight patients with a *DSM-IV* diagnosis of acrophobia were randomized to receive either 500 mg of D-cycloserine or placebo in combination with 2 sessions of VRGET in a virtual glass elevator environment. Patients receiving D-cycloserine experienced significantly greater improvement in phobic symptoms than matched patients being treated with VRGET alone.[59] This difference was noticeable 1 week following treatment and was maintained at 3-month follow-up.

VRGET will become more available as technology costs continue to decrease, and it will probably become a widely used and cost-effective approach for outpatient treatment of panic attacks, PTSD, agoraphobia, social phobia, and other specific phobias. Several basic VRGET tools are available over the Internet, permitting mental health professionals to guide patients in the use of these computer-based advanced exposure protocols through real-time videoconferencing anywhere high-speed Internet access is available.[60] In the near future, the integrative management of phobias, panic attacks, and other severe anxiety syndromes will combine VRGET, biofeedback, and pharmacological treatment in outpatient settings. Patients with severe phobia will also have the option of gaining access to Web-based VRGET tools via high-speed Internet connections.

Patients who are considering using VRGET should be aware of infrequent but significant safety issues. Fewer than 4% of persons experience transient symptoms of disorientation, nausea, dizziness, headache, and blurred vision when in a virtual environment. "Simulator sleepiness" is a feeling of generalized fatigue that occurs infrequently. Intense sensory stimulation during

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VRGET can trigger migraine, seizures, or gait abnormalities in persons who are prone to these medical conditions, and VRGET is therefore contraindicated in these populations. Anxious patients who are actively abusing alcohol or narcotics should not use VRGET. Patients who have disorders of the vestibular system should be advised against trying VRGET. Patients with psychosis should not use VRGET because immersion in a virtual environment can exacerbate delusions and potentially worsen reality testing.[61]

EMG, GSR, and EEG biofeedback training

Biofeedback has nonspecific beneficial effects on many anxiety symptoms. EMG, GSR, and EEG biofeedback training are effective treatments for generalized anxiety.[62-64] Patients with chronic anxiety trained in EEG or EMG biofeedback achieve symptom reduction similar to those taking conventional anti-anxiety medications.[65,66] The long-term benefits of EEG biofeedback for anxious patients have not been clearly established. One study evaluated 2 EEG biofeedback machines on patients complaining of anxiety and "burnout" in an addiction treatment center.[67] Although patients experienced immediate reductions in state anxiety during biofeedback training, long-term effects on burnout were not maintained following discontinuation of treatment.

Microcurrent electrical stimulation

Microcurrent electrical stimulation, also called "cranial-electrotherapy stimulation" (CES), is an effective treatment for generalized anxiety. Quantitative EEG studies have confirmed beneficial changes in brain electrical activity when this approach is used.[68] A meta-analysis of double-blind, controlled trials comparing CES with a sham treatment (ie, electrodes applied, but with no current) concluded that measures of generalized anxiety improved in 7 of 8 studies, and the magnitude of improvement reached statistical significance in 4 of these.[69] A larger review encompassing 34 sham-controlled trials conducted between 1963 and 1996 concluded that regular CES treatments resulted in short-term symptomatic relief of generalized anxiety symptoms mediated by direct effects on autonomic brain centers.[70]

In a 10-week open trial of daily, self-administered CES therapy in 182 individuals with *DSM-III* anxiety disorders, 73% of patients reported significant reductions in anxiety that were maintained at 6-month follow-up.[71] Significantly, conventional drugs had failed in 25% of patients in the study, and 58% had received no previous treatment of any kind for their anxiety symptoms. In general, patients who receive at least 4 to 6 CES treatments experience more sustained reductions in anxiety than patients who receive fewer treatments. The results of a small, double-blind, sham-controlled study (N = 20) suggest that a single CES treatment in patients who report generalized stress results in beneficial changes in autonomic arousal that are sustained at least 1 week following treatment, as measured by decreases in EMG and heart rate.[72]

Patients with one or more phobias reported significant reductions in state anxiety when exposure to the anxiety-inducing stimulus was followed by 30 minutes of CES treatment.[73] Comparable anxiety reduction was achieved with CES and conventional anti-anxiety medications, suggesting that CES may be an effective approach for patients with phobia who wish to discontinue conventional drugs.

Dr Lake is in private practice in Monterey, Calif, and is on the clinical faculty in the department of psychiatry and behavioral sciences at Stanford University Hospital. He chairs the American Psychiatric Association Caucus on Complementary, Alternative, and Integrative Care (www.APACAM.org) and is author of the Textbook of Integrative Mental Health Care *(Thieme, 2006).*

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