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Treatment Considerations for Generalized Anxiety Disorder [3]

Nutrients and herbs to change the course of this illness

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Abstract

A multipronged approach to generalized anxiety disorder (GAD) is considered the most effective and safest way to treat anxiety due to the wide range of causal factors and dysregulation of various neurotransmitters that are often involved. With a focus on correcting neurotransmitter imbalances in the limbic system, as well as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, clinicians can choose from several scientifically supported nutrients and herbs the ones that are most appropriate for each patient to modulate these pathways and change the course of this disorder.

Introduction

The National Institute of Mental Health describes generalized anxiety as a chronic pattern of constant worry and fear.[1] It is a state of apprehension and concern in the absence of a real threat. Kessler et al reported in 2010 that general anxiety disorders affect the United States population at a rate of between 13.6% and 28.8%.[2] The Centers for Disease Control and Prevention report that anxiety disorders, including GAD, are among the most common mental health issues faced by today's general population.[3] GAD is the most common anxiety disorder, and estimates show that it affects more women than men.[4]

When an individual has 3 or more anxiety symptoms for a period of 6 consecutive months on an almost daily basis, they may be diagnosed with GAD.[5] Symptoms can be placed into 2 categories: mental/emotional and somatic (see Table 1). Identifying somatic symptoms related to anxiety is a key factor in accurate diagnosis. Several studies have shown that patients with GAD in primary care present with somatic symptoms only and may not be aware of their anxiety issues.[6,7]

While this paper will focus on neurochemical imbalances of GAD and the nutrients and herbs that have been demonstrated to address dysfunction and imbalance, it is important to note that several dietary and lifestyle factors can influence the initiation and progression of this disorder and can exacerbate symptoms. Contributing factors include:

- nutrient deficiencies
- food intolerances (in particular gluten)

- reactive hypoglycemia with episodic hyperglycemia
- caffeine, drug, and alcohol use
- chronic distress
- childhood and significant adult post-traumatic stress disorder (PTSD)
- environmental factors

Comprehensive management of GAD using a multimodality approach will require exploring these contributing factors. At the same time, addressing the neurotransmitter imbalances in the limbic system and HPA axis dysfunction can be an efficacious means of managing the anxiety. These 2 pathways intersect in a significant manner, which allows the practitioner a logical basis to target underlying physiological pathways rather than merely treat symptoms.

Fear is activated in the amygdala, a key component of the limbic system. This activation causes increased levels of serotonin and increased sympathetic nervous activity with resultant increases in norepinephrine and serotonin.[8] Prolonged elevation of serotonin and norepinephrine contribute to feelings of anxiety. In addition, hyperactivity of the amygdala and hypothalamus increase corticotropic-releasing hormone (CRH). Elevated CRH is highly implicated in anxiety and depression. In fact, anxiety associated with elevated CRH is often preceded by depression.[9] This elevation of CRH is accentuated by elevated serotonin. Prolonged elevation of serotonin interferes with the HPA axis's dynamic responsiveness to stress. Chronically, this interference leads to a feed-forward situation of the HPA stress response system, which results in a flattened, and typically high, cortisol level with alterations in the cortisol circadian rhythm. This elevation of cortisol ultimately results in reduced sensitivity to negative feedback on the part of the hypothalamus and pituitary. This perpetuates the sustained elevation of CRH and resultant anxiety.[10]

Conventional medicine utilizes these pathways to impact this condition. For example, selective serotonin reuptake inhibitors (SSRIs) reduce amygdala hyper-reactivity to fear-eliciting stimuli. However, for some individuals, SSRI medications are ineffective and, in fact, aggravate anxiety. Benzodiazepines, the most commonly prescribed class of anxiolytic drugs, bind to and stimulate gamma aminobutyric acid (GABA) receptors. While effective for short-term use (2–4 weeks), the risk-benefit ratio for longer-term use of benzodiazepines is unestablished.[11] In addition, side effects can include fatigue, confusion, depression, dizziness, memory deficits, and blurred vision. Withdrawal from benzodiazepines is difficult as these medications are habituating. Withdrawal can cause acute anxiety and may lead to seizures.[12] Therefore, it is prudent to look at nutrients and herbs as complementary or alternative strategies that can impact the underlying pathophysiology of anxiety.

There are a number of key neurotransmitters in the amygdala that when imbalanced can be connected to issues of anxiety. While this is a complex dynamic interaction, in general, people with GAD have hyperactive neuronal activity producing the various symptoms previous mentioned.

Correcting Neurochemical Issues with Nutrients and Herbs

Many options are available to healthcare practitioners who wish to employ alternatives to conventionally prescribed anxiolytics for the treatment of GAD. Amino acids and botanicals that correct key neurotransmitter imbalances, namely that reduce inappropriately elevated levels of serotonin and norepinephrine, may reduce GAD. In addition, decreased oxytocin has been linked to a worsening of anxiety issues.[13] Oxytocin reduces amygdala activity and in so doing has an anxiolytic effect. A therapeutic goal with GAD is, therefore, to increase

oxytocin.[14]

Chronic dysregulation and activation of the HPA axis is associated with anxiety. This HPA dysregulation can cause an elevation in CRH, which, as mentioned above, has been linked to increased anxiety.[15] Elevated CRH is also linked to increased serotonin and stimulation of the amygdala, which causes a reduction in oxytocin levels. When CRH is normalized, oxytocin is increased, and elevated serotonin is reduced. The combined effect is significantly anxiolytic.

GABA, glycine, magnesium, glutathione and N-acetyl cysteine (NAC) are nutrients that inhibit excitatory neurotransmitters. Ensuring proper amounts of amino acid levels is critical, especially arginine and lysine. Smriga et al demonstrated in a double-blind, randomized, clinical trial that lysine and arginine supplementation reduced anxiety in both men and women compared to placebo.[16]

L-theanine, an amino acid found in tea (*Camellia sinensis*), has been shown in several studies to increase dopamine and serotonin production and GABA activity.[17] L-theanine also generates alpha waves in the central nervous system, resulting in a relaxed yet alert state. Lu et al also demonstrated that L-theanine can create a relaxed state[18] while Lyon et al showed that L-theanine helped boys diagnosed with attention-deficit hyperactivity disorder to sleep better.[19]

Specific vitamins and minerals have been shown to reduce anxiety. A double-blind, randomized, controlled trial by Carroll et al found that men who took a multivitamin and mineral formula had significant reductions in anxiety compared to placebo.[20] In their double-blind, randomized, controlled crossover trial, Souza et al showed that magnesium plus vitamin B6 reduced premenstrual anxiety and GAD in women.[21]

Omega-3 fatty acids positively impact anxiety disorders on many levels including reducing corticol hyper-excitability and norepinephrine levels, as well as increasing dopamine binding, improving stress tolerance, and providing direct anxiolytic effects. Kiecolt-Glaser et al found in their double-blind, randomized, clinical trial that omega-3 fatty acid supplementation reduced anxiety in medical students.[22]

Several studies have shown that supplemental phosphatidylserine reduces anxiety measures by decreasing CRH and blunting cortisol levels.[23,24]

The anxiolytic effects of the volatile oil of lavender (*Lavender angustifolia*) have been the subject of many randomized clinical trials. Perry et al reviewed 15 randomized clinical trials and concluded that oral lavender supplements may have a therapeutic effect.[25] In a well-designed randomized clinical trial, Woelk et al compared an oral lavender extract (Silexan 1265) to lorazepam for the treatment of GAD and found that 40% of the lavender group went into remission compared to 27% of the lorazepam group.[26] When compared to placebo, Kasper et al found that this same lavender oil extract significantly decreased anxiety ($P<0.01$) and had a superior percentage of responders (76.9 vs 49.1%; $P<0.001$) and remitters (60.6 vs 42.6% $P=0.009$).[27] Uehleke et al had similar results using lavender oil for restlessness caused by sub-threshold anxiety in adults with chronic fatigue, post-traumatic stress disorder, or somatization disorder.[28]

Ashwagandha (*Withania somnifera*) is an adaptogenic herb that has also been shown to increase dopamine receptors in the brain while the reducing the anxiety-producing effects of

norepinephrine. Several studies have shown that Ashwagandha has anxiolytic effects.[29] Another interesting clinical trial by Cooley et al compared naturopathic care that featured Ashwagandha supplementation to standardized psychotherapy. In this randomized clinical trial, there was significantly greater improvement of anxiety parameters in the naturopathic care group compared to the psychotherapy group.[30]

Two of the active constituents of magnolia (*Magnolia officinalis*), honokiol and magnolol, enhance neutrotransmitter activity and reduce anxiety. Preliminary animal data shows honokiol compared favorably to benzodiazepines without the side effects.[31] Kalman et al demonstrated reduced anxiety in postmenopausal women with above average anxiety scores who took a combination of standardized honokiol and berberine. Compared to placebo, the treatment group reported a significant reduction in perceived anxiety (P=0.043).[32]

Black cohosh (*Actaea racemosa*) is a botanical primarily used to treat menopausal symptoms; however, some data exists to warrant consideration in cases of anxiety. Geller and Studee evaluated 4 randomized clinical trials that utilized black cohosh for mood and anxiety with 1 trial that combined black cohosh with St. John's wort. All 4 studies found reduced anxiety compared to placebo, and 1 of the studies showed reduction equivalent to standard hormone replacement therapy.[33]

Finally, the botanical kava (*Piper methysticum*) can be considered for patients experiencing GAD. This botanical has been shown to be efficacious for the treatment of anxiety disorders; however, it is not widely prescribed due to concerns regarding hepatotoxicity that arose from a published case study, but which have not been observed in controlled clinical trials. These concerns are likely the result of herb/drug interactions and/or poor quality extracts, rather than the botanical itself. Sarris et al evaluated the safety profile of kava compared to placebo and found no significant differences across the groups in liver function tests, nor were there any significant adverse reactions that could be attributed to the kava.[34] In this study, kava was also shown to increase libido in women correlated with reduced anxiety.

Conclusion

Successful therapeutic intervention requires that any underlying neurotransmitter or hormonal imbalances be addressed. Of course, the most effective approach would include dietary and lifestyle changes such as increased physical activity, increased consumption of fruits, vegetables, and omega-3 rich foods. Such dietary and lifestyle recommendations are beyond the scope of this paper.

Working in concert with appropriate diet and lifestyle changes, certain nutrients and herbs can assist with symptom management and help to address the key neurochemical pathways that contribute to and exacerbate generalized anxiety. While more rigorous clinical data will help further validate the use of these nutrients and herbs, their preliminary efficacy and safety profile compared to pharmaceutical agents presently being used makes them candidates for first-line treatment consideration.

Table 1: Anxiey Symptoms

Mental/Emotional Symptoms
- Fear

- Decreased libido
- Decreased emotionality
- Irritability
- Restlessness, inability to relax
- Difficulty concentrating

Somatic Symptoms

- Arrhythmia
- Dyspnea
- Nausea
- Sweating
- Tremor
- Increased urination
- Increased appetite
- Diarrhea
- Vertigo
- Increased pain sensitivity

Table 2: Author's suggested dosage ranges

Natural Therapy	Suggested Daily Dosages
Magnesium (as citrate, malate, glycinateor fumarate)	200–400 mg
Pyridoxine (vitamin B6)	50 mg
GABA	500–750 mg
Glycine	500–2,000 mg
Glutathione	250–500 mg
N-acetyl-cysteine	600–1,200 mg
Lysine	1,000–2,500 mg
Arginine	1,000–2,500 mg
L-theanine	200–400 mg
Omega-3 fatty acids	2,000–3,000 mg
Phosphatidylserine	400–800 mg
Lavender essential oil extract (Silexan WS 1265)	80–160 mg
Withania somnifera (ashwagandha)	500–600 mg (standardized extract to 1.5% withanolides)
Honokiol	100–400 mg
Black cohosh (*Actea racemosa*)	40–80 mg (standardized extract to 5%–8% triterpene glycosides)

Kava (*Piper methysticum)*	200–250 mg kava lactones

About the Author

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