Back to Nature

Evidence-based nutraceutical medicines are gaining interest within the pharma market – particularly for targeting the widespread prevalence of anxiety disorders. Combined with other forms of integrative treatments, these nutritional formulations can allow for personalised and effective treatment plans

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There are times when many patients feel ill-equipped to manage their stress – whether it stems from the economy, jobs, extreme weather, their own health, or that of loved ones or pets. Over time, these events may take deleterious tolls on the body; numerous studies link anxiety and stress with cardiovascular disease, for example. Not only does stress increase disease incidence, but it also heightens the risk of an adverse cardiovascular event, such as a 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, and 20-25% among patients who have not (1).

The *Diagnostic and Statistical Manual of Mental Disorders* discusses the various conditions within the anxiety spectrum. Along this spectrum are panic attacks, phobias, obsessive-compulsive disorder (OCD), post-traumatic stress disorder, and generalised anxiety and its subsets. Anxiety is even more widespread than depression and, in many cases, 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, or pheochromocytoma, as well as numerous others.

Anxiety can be acute (generally speaking, this will refer to a period lasting from two days to four weeks) or chronic (occurs more days than not for at least six months). In the short term, moderate amounts of anxiety can be a beneficial part of our existence – for example, alerting us to danger, or even increasing our performance. But chronic or severe anxiety can take over one's life and interrupt daily activities, disturb sleep, encourage poor dietary choices, lead to a reduction in exercise, and restrict social interactions. This can lead to serious health concerns and will often cause or amplify relationship issues (3-4).

Pathophysiology

Genetic factors appear to predispose individuals to the development of generalised anxiety disorder (GAD). Data from twin studies have been inconsistent, but what has been observed is that the serotonin transporter gene-linked polymorphic region SS genotype (short/short) appears more common in patients with GAD (6). Another theory involves the variations in two subtypes of the glutamic acid decarboxylase gene, which may increase individual susceptibility to anxiety disorders (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 MTHFR enzyme, which plays a role in processing amino acids, and is important for a chemical reaction involving forms of the vitamin B 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 magnetic resonance imaging showed that patients who had GAD showed greater anticipatory activity than healthy controls in the bilateral dorsal amygdala (10).

Meanwhile, a higher than average number of traumatic experiences and other undesirable life events in childhood have also been found to increase prevalence of GAD (11). GAD is more likely to occur in people with behavioural inhibition – a tendency to

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be timid and shy in new situations (12). Furthermore, anxiety is multifactorial and can stem from myriad causes, or a combination of them. Besides the aforementioned pathological conditions, caffeine, poor sleep habits, a bad diet, unique nutrient deficiencies, lack of exercise and numerous other factors can all play a part (13,14).

Allopathic Approach

Conventionally, anxiety – regardless of etiology or form – tends to be managed primarily with anti-anxiety medications, antidepressants, sleeping medications and, at times, counselling, cognitive behavioural therapy or mindfulness (15). With respect to the latter, there is increasing evidence of the efficacy of mindfulness-based stress reduction and other behavioural health and mind-body techniques on anxiety.

More patients seem to be looking into safer alternatives to medication. Natural does not necessarily equate to safe, but evidence-based nutraceutical interventions for anxiety disorders are available. Patients who do not tolerate their current pharmaceutical medicines may consider nutritional and herbal options. It can be difficult to define what is integrative medicine, and what is conventional or allopathic medicine, especially as once-unconventional therapies have become increasingly accepted. That said, some therapies which may not be considered mainstream still have some evidence of efficacy as adjunctive treatments – or as outright substitutions – such as pharmaceuticals, although they may have significant adverse effects. Some examples of such therapies, and their dosing and important references, are listed below.

Ashwagandha

Withania somnifera (or ashwagandha) is an Ayurvedic that has anti-ageing, haematopoietic, immune-modulating, anxiolytic, antidepressant, cardiovascular protection, anti-tumour and anti-neoplastic properties. Recommended dosage is 3,000-6,000mg of dried root or 300-500mg standardised extract (16-18). In a 2012 study, 64 randomised test subjects were given either ashwagandha or a placebo twice a day for 60 days. On day 60, a significant reduction in stress scores and cortisol levels were observed compared to the placebo (16).

Green Tea

L-theanine (200-400mg daily) is an amino acid found in tea – with higher amounts in green tea – that can reduce anxiety and increase levels of gamma-aminobutyric acid (GABA) and serotonin (19-20). In 2011, an eight-week randomised, double-blind, two-centre, placebo-controlled trial aimed to discover if L-theanine would be effective at relieving some of the symptoms of schizophrenic test subjects. The authors found that the nutrient 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

The regulating agent GABA (100-200mg up to three times daily) can itself offer natural relaxant effects (21). A 2006 study used electroencephalography-measured alpha waves on 13 subjects, who were 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 a placebo. All subjects were asked to cross a suspended bridge, during which immunoglobulin A (IgA) saliva levels were monitored. The placebo group showed a marked decrease in their IgA levels, while the GABA group's were significantly higher.

Inositol

The pharmaceutical fluvoxamine is commonly used to treat depression and OCD. However, evidence suggests that the vitamin-based alternative inositol (12-18g per day) can provide equivalent or better results when compared to fluvoxamine (23-24). In a double-blind, randomised 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 one-month period. Nausea and tiredness were more common with fluvoxamine, whereas inositol was well-tolerated (23).

Omega-3

Essential fatty acid omega-3 has been shown to reduce inflammation and anxiety at 2,500mg daily (25). In a 12-week, double-blind trial, 68 medical students had blood drawn at baseline and under stressful conditions (before an exam). Lipopolysaccharide (LPS), tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) were measured. The subjects were given either 2,085mg eicosapentaenoic acid combined with 348mg docosahexaenoic acid, or a placebo. While LPS and TNF-α decreased with the nutrient, IL-6 was seen to increase, and 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."

Kava Kava

Piper methisticum (kava kava) can be given at 150-400mg in divided doses of standardised extract (70% kavalactones) (26-27). A 2003 eight-week, double-blind RCT involving 129 patients indicated 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 six months if using kava kava long term. It should be avoided in people with pre-existing liver disease.

Passion Flower

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 anti-anxiety drug 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 oxacepam experienced significantly

more problems relating to impairment of job performance (28).

Lavender Oil

Silexan is a lavender oil capsule (80mg daily) used as an alternative to benzodiazepines – a type of sedative (29). A 2010 multi-centre, double-blind study looked into the efficacy of a six-week intake of silexan versus lorazepam. 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 and has no potential for drug abuse; it may, therefore, be considered an alternative to benzodiazepines for GAD.

Rhodiola Rosea

The herb *Rhodiola rosea* (100-400mg daily), known for its adaptogenic properties, has been shown to decrease anxiety and enable better adaptation to stress response (30-31). However, it should be used with caution in patients with bipolar disorder.

Adverse Effects

All nutraceutical interventions have the potential to interact with psychoactive pharmaceuticals – including additive effects with anxiolytics – so concomitant use should either be avoided or actioned cautiously. In addition, GABA and L-theanine may theoretically potentiate antihypertensives, so close monitoring 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 of the neurotransmitter serotonin in the brain and block the absorption 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 main medication, may cause serotonin syndrome (SS) in susceptible people. SS can range in severity from mild to life-threatening – although most cases are of a low level – and will resolve with prompt recognition and supportive care (36-38).

Anxiety Resolution

Successful anxiety resolution appears to be based on a combination of relevant medications – whether pharmaceutical or nutraceutical – along with counselling and stress reduction techniques. The brilliance of integrative medicine is that it takes the patient's whole picture into account, and can determine an individualised treatment plan and strategy formed from the evidence-based treatment recommendations.

Note

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