

## FUNCTIONAL PSYCHIATRY FOR THE TREATMENT OF

# Anxiety



Functional psychiatry solutions for anxiety

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This ebook is a condensed explanation of various functional medicine treatments for the growing problem of stress and anxiety facing modern psychiatry. More extensive clinical information and additional educational resources for treating anxiety and stress can be found at *Psychiatry Redefined*.

You should never adjust anxiety medication without speaking with your physician. This ebook is not intended as a substitute for the medical advice of a physician. Readers shall consult a physician in matters relating to their health, and particularly with respect to any symptoms that may require diagnosis or medical attention.

## Introduction

I first started my medical training in 1981, eventually finishing a fellowship at *John Hopkins University School of Medicine* in Child and Adolescent Psychiatry and becoming an expert in psychopharmacology.

My training as a psychiatrist formed a deep-rooted appreciation for the complexity of human behavior, the neurochemistry that drives thoughts, feelings, and emotions, and the idea of a family's influence on emotional and mental wellness.

My experience taught me to put heavy importance on the relationship between patient and provider, something that has seemingly gone by the wayside in the decades since. And over the course of my career, my interest in nutrition, biochemistry and genetics led me to a more personalized approach to treating patients through Functional Psychiatry.

As a system of mental health care, Functional Psychiatry honors the connections that link the mind and body and adheres to a model of personalized medicine based on genetic and biochemical individuality.

Treatments are developed according to data derived from medical testing, analysis, and psychiatric assessment. These treatments address the underlying factors that contribute to mental health, including nutrition, inflammation, toxicity, chronic infections, hormones, neurotransmitters, and genetics. While medications can be part of Functional Psychiatry, they are rarely the sole treatment.

A Functional Psychiatry model prioritizes the treatment of nutritional deficiencies — deficiencies which I have found to be common among patients with anxiety and other mental health diagnoses. By reducing nutritional deficiencies identified through laboratory analysis, patients often improve, finding significant relief.

Over the last decade, scientific research has clearly established a relationship between nutritional deficits and brain function across every major psychiatric illness, including:

- ADHD
- Axiety
- Depression
- Eating disorders
- · Schizophrenia

Scientific evidence confirms robust associations between verifiable nutritional imbalances and the emergence and establishment of psychiatric symptoms. Mainstream treatment models in psychiatry, however, still fail to recognize nutritional imbalances as being factors in mental illness.

#### This needs to change.

In the vast majority of cases, addressing biochemistry, genetic makeup, diet, lifestyle, and relevant psychosocial variables yields far better outcomes for patients, and makes the idea of a lasting recovery an attainable goal.

For patients struggling with anxiety, there are answers and therapies beyond standard medications. Functional Psychiatry can help patients find lasting relief. This ebook is a small first step towards exploring Functional Medicine for anxiety treatment.

In Good Health,



James Greenblatt, MD Founder & Medical Director, *Psychiatry Redefined* 

# Anxiety

We have an epidemic of stress and anxiety-related disorders in the United States and throughout the world. Prior to the COVID-19 pandemic, rates of anxiety symptoms averaged around 8.9% in the world's general population. With the advent of COVID-19, anxiety rates increased dramatically to 22.6% (Schafer 2022). Youth have been similarly affected.

Before COVID, around 11.6% of youth struggled with significant anxiety throughout the world. During the first year of the pandemic rates virtually doubled to one in five children struggling with anxiety symptoms (Racine 2021).

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Even before the pandemic, among mental health conditions, anxiety disorders were the second leading cause of disability, just after depression (Xiong 2022). And anxiety disorders are not benign. Patients struggling with generalized anxiety disorder (GAD) are at increased risk of suicide, with almost three times higher levels of suicidal ideation, two and a half times higher suicide attempts and over three times higher suicide completion rates (Kanwar 2013). Considering how many individuals struggle with anxiety, these numbers are of serious concern.

Anxiety disorders also co-occur commonly with other conditions. Substance use is higher in patients struggling with anxiety disorders, which often complicates treatment and recovery (McHugh 2016). Generalized anxiety disorder is also frequently comorbid with depression, further increasing suicide risks while complicating treatment (Noyes 2001).



In fact, a 2015 analysis revealed that anxiety disorders appear to increase the risks for numerous other conditions, including arthritis, chronic pain, heart disease, high blood pressure, asthma and stomach ulcers (Scott 2016). Thus the costs of untreated or undertreated anxiety disorders are quite large and can cause significant morbidity for those that struggle with them.

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Recognizing and treating anxiety symptoms will have a huge impact on a patient's quality of life. While standard treatments have their place, taking a more whole person approach like that provided by Functional Psychiatry, often yields better results.

## **Standard Treatment**

Patients struggling with anxiety disorders need safe and effective treatment. Therefore, it is worth exploring what available treatments actually are effective and well-tolerated.

Mainstream psychiatry typically addresses anxiety symptoms with antidepressant medications. If these fail, it's not unusual that a psychiatrist will turn to benzodiazepines, including medications like Valium and Xanax.

Counseling, especially cognitive behavioral therapy (CBT) can also be considered for treatment, although a recent meta-analysis concluded that most pharmaceuticals have larger effects than CBT (Chen 2019).

### **Antidepressants for Anxiety**

First line medication treatment for anxiety disorders is generally an antidepressant, either a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI). And while these drugs appear to help reduce the severity of a patient's anxiety, improvements are quite modest on average.

In a recent meta-analysis, escitalopram was the medication that appeared to have the largest effect on generalized anxiety disorder symptoms. Yet, on average, escitalopram only reduced anxiety scores by 3 points on the 56 point Hamilton Anxiety Rating Scale (He 2019). While a clinically meaningful change in anxiety scores does not appear to be established, it's likely that this change may not, on average, represent a meaningful improvement in symptoms.

It is extremely common that patients prescribed antidepressant medication for anxiety have residual symptoms that are still of significant concern. If the relief provided by one medication is not adequate, the doctor may switch or add additional medications. If several antidepressants fail to provide relief, a benzodiazepine is often prescribed. In a recent meta-analysis, escitalopram was the medication that appeared to have the largest effect on generalized anxiety disorder symptoms. Yet, on average, escitalopram only reduced anxiety scores by 3 points on the 56 point Hamilton Anxiety Rating Scale.

### **Benzodiazepines for Anxiety**

Benzodiazepines and their use for treating anxiety are controversial. While the drugs were used heavily through the 1970s and 1980s, concerns for abuse, tolerance and withdrawal started to tarnish their popularity.

Currently, most sources only recommend benzodiazepines for short-term treatment of severe anxiety for a maximum of four weeks (Kennedy 2019). Yet these medications are commonly prescribed with 12.6% of the U.S. population acknowledging either use or misuse of benzodiazepines in the past year (Maust 2018). Concerningly, misuse rates reached almost 20% of those taking benzodiazepines in the survey.

Unfortunately, the side effects of benzodiazepines are not benign. With long-term treatment, benzodiazepines are associated with worsening symptoms of depression, cognitive dysfunction, falls and accidents and increased rates of death (Lim 2020, Billioti de Gage 2015, Diaz-Gutierrez 2017, Xu 2020). A recent meta-analysis of long-term use of benzodiazepines for treating anxiety found no significant difference between benzodiazepines and placebo for reducing anxiety levels (Shinfuku 2019).

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# **Functional Psychiatry for Anxiety**

Based on the modest efficacy of standard anxiety treatments, it is likely that a large percentage of patients struggle with residual anxiety symptoms even with standard treatment.

Part of the problem is the one-size-fits-all approach often taken by mental health-care providers focused almost solely on prescribing an antidepressant. This approach typically lacks an individualized understanding of the patient.

All patients are different with unique needs and challenges. A person struggling with anxiety due to severe work stress that eats fast food is different from an underweight vegan college student with a trauma history and social anxiety.

All patients are different with unique needs and challenges. A person struggling with anxiety due to severe work stress that eats fast food is different from an underweight vegan college student with a trauma history and social anxiety.

It should be obvious that these patients are different with different needs, yet their standard medical treatment will often be the same.

Functional Psychiatry is a form of Functional Medicine that acknowledges individual differences, tests for underlying factors that can cause or contribute to symptoms and treats patients based on this individualized assessment.

Nutrient deficiencies, hormonal imbalances, toxicities, gut flora disturbances, digestive problems, genetic differences and personal history are all assessed and addressed. This leads to much better outcomes as a patient's individual idiosyncrasies are discovered and treated.

While not an exhaustive list, the following treatments, including lifestyle modifications, 5-hydroxytryptophan (5-HTP), magnesium, inositol, L-theanine and ashwagandha, can often improve anxiety symptoms. These treatments work best as a component of a personalized approach. However, they can have stand-alone benefits, as well.

If you are interested in more specific and comprehensive training and coursework for treating anxiety disorders with Functional Psychiatry, consider online courses or a training fellowship offered through *Psychiatry Redefined*.



# Lifestyle Treatment for Anxiety

While often given short shrift, lifestyle factors are crucial for addressing stress and anxiety symptoms. Factors including dietary choices, exercise and other stress-relieving techniques can help a person take control over their symptoms and minimize anxiety.

#### **Diet and Mental Health**

For depression, the research on the benefits of dietary interventions has been growing. One study treated depressed patients with either nutritional counseling from a dietician or a social support group as a control. Both groups were allowed to continue their standard depression treatment.

After 12 weeks, depression scores were reduced 40% on average with the dietary counseling, with 32% of patients achieving remission as compared to only 8% of patients in the social support group (Jacka 2017). A recent meta-analysis concluded that dietary interventions hold promise for treating and reducing depressive symptoms (Firth 2019).

A recent scoping review of diet and anxiety found a relationship between less anxiety and consumption of more fruits, vegetables and omega-3 fatty acids.

As for diet and anxiety, the data is a little less clear but still suggestive of benefits. A study on diet quality in patients with depression and anxiety found that in patients with more severe symptoms, diet quality was worse (Gibson-Smith 2018).

A recent scoping review of diet and anxiety found a relationship between less anxiety and consumption of more fruits, vegetables and omega-3 fatty acids. Reduced anxiety was also associated with healthy dietary patterns, caloric restriction, breakfast consumption, the ketogenic diet, broad-spectrum micronutrient supplementation, zinc, magnesium, selenium, probiotics, and a number of phytochemicals.

They also found that increased anxiety was associated with a "high-fat diet, inadequate tryptophan and dietary protein, high intake of sugar and refined carbohydrates, and 'unhealthy' dietary patterns (Aucoin 2021)."

The simple takeaway is that a healthy diet improves our mental and emotional wellbeing. Eating more fruits and vegetables, getting plenty of omega-3 fatty acids and quality protein should always be a part of any mental health treatment plan for anxiety.



# Exercise for Anxiety

The World Health Survey found that individuals with low physical activity levels had a 32% increased risk for anxiety disorders (Stubbs 2017). Staying more physically active is protective from developing anxiety.

As for treating anxiety with exercise, the research also shows benefits. A meta-analysis of aerobic exercise for anxiety symptoms found significant reductions in anxiety symptoms with a medium to large effect size (Aylett 2018). In general, more intense exercise was more effective than less intense exercise.

A number of Eastern styles of exercise that incorporate more mind-body techniques also offer additional options for improving mental health. Tai Chi is a practice that involves slow movements with coordinated breath and focus.

A meta-analysis of Tai Chi's effect on depression and anxiety found medium to large benefits for improving symptoms.

A meta-analysis of Tai Chi's effect on depression and anxiety found medium to large benefits for improving symptoms. Interestingly, benefits seemed greater in older, rather than younger, individuals (Zhang 2019).

Yoga is another Eastern-style practice that includes mental and physical disciplines to quiet the mind. Generally, the Westernized version of yoga involves poses or "asanas" that practitioners move through and hold during yoga practice. Research on yoga for anxiety also shows large benefits for anxiety reduction (Zoogman 2019).

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# Meditation and Mindfulness for Anxiety

Meditation can be thought of as the act of consciously holding your focus on something. Mindfulness is a type of meditation that emphasizes a non-judgmental focus on the present moment, including thoughts, feelings and sensations.

A meta-analysis of anxious college students treated with mindfulness meditation found large effect sizes for reducing anxiety levels

While the data is stronger for benefits in depression, the research also appears to suggest at least modest benefits for reducing anxiety (Saeed 2019). And some studies suggest stronger effects for different populations. A meta-analysis of anxious college students treated with mindfulness meditation found large effect sizes for reducing anxiety levels (Bamber 2019). On average, studies included just around 100 minutes of meditation practice per week or just under 15 minutes per day.



# Nutrients & Anxiety

When it comes to treating anxiety, a number of nutrients stand out. Two of the nutrients below both focus on improving serotonin function: 5-HTP and inositol. The other nutrient, magnesium, is one of the most common deficiencies I encounter with patients. While these three nutrients can play a role in anxiety, other nutrients may also be key to treatment. For a more complete discussion on anxiety treatment, consider additional coursework or training through *Psychiatry Redefined*.

# 5-Hydroxytryptophan (5-HTP)

5-Hydroxytryptophan or 5-HTP is an amino acid derived from tryptophan. It is the direct precursor to serotonin and comes with several advantages. While tryptophan can be metabolized away from serotonin, 5-HTP can only be used for serotonin production. In addition, delivery of tryptophan across the blood brain barrier is limited, whereas 5-HTP crosses quickly (Lynn-Bullock 2004). As such, supplementation with 5-HTP is a more direct way to increase serotonin levels in the brain.

## By rapidly increasing serotonin production, treating conditions known to be serotoninresponsive with 5-HTP becomes practical.

By rapidly increasing serotonin production, treatment of conditions known to be serotonin-responsive with 5-HTP becomes practical.

A trial in patients with fibromyalgia also found significant improvements in anxiety with 5-HTP supplementation. Self ratings of anxiety dropped approximately 40% as compared to 11% in the placebo group (Caruso 1990).

A combination of inhaled carbon dioxide and oxygen has been shown to safely induce a panic state in panic



(tryptopahn molecular structure)

When subjects with panic disorder were administered 5-HTP prior to the carbon dioxide challenge, anxiety and panic attacks were significantly reduced.

disorder patients. Interestingly, when subjects with panic disorder were administered 5-HTP prior to the carbon dioxide challenge, anxiety and panic attacks were significantly reduced (Schruers 2002). The evidence shows a rapid reduction in panic attack initiation with 5-HTP.

A recent trial examined the combination of fluoxetine and 5-HTP as compared to fluoxetine and placebo for obsessive compulsive disorder. Symptoms improved by 37% with adjunctive 5-HTP as compared to 25% without (Yousefzadeh 2020).

When dosing 5-HTP you typically start at 50 mg and work your way up slowly to minimize gastrointestinal side effects based on the patient's response. The maximum dose is typically 200 mg. If a person is on a medication that already raises serotonin, caution should be exercised as the combination of 5-HTP with SSRIs or SNRIs can lead to serotonin syndrome. Serotonin syndrome, when severe, is a medical emergency that can be life threatening.

While 5-HTP works as a precursor for serotonin, another key factor that shores up serotonin function is inositol, crucial to the functioning of the phosphatidylinositol second messenger system.

## **Inositol**

Inositol is a simple sugar alcohol that is found in large quantities throughout the brain. Due to its structure, inositol can exist in nine different forms, although myo-inositol is the most abundant and active. Inositol, when combined with phosphates and fatty acids, is utilized in the phosphatidylinositol second messenger system.

This system plays a key role in multiple neurotransmitter signaling pathways. When a cell surface receptor receives a signal, the signal needs to be relayed through a secondary messenger system inside the cell to activate a response.

Inositol-containing compounds play a critical part in facilitating the reception, processing and response of certain neurotransmitters, including serotonin, dopamine, glutamate, acetylcholine and others (Camfield 2011).

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Evidence suggests that increasing inositol levels through supplementation may help to facilitate neurotransmitter function by improving secondary messenger signaling.

Specifically, inositol is involved in 5HT2 serotonin signaling, one of the same serotonin receptors affected by antidepressants. Interestingly, some evidence has found that the clinical response to inositol typically takes around four weeks, similar to standard medication (Levine 1997).

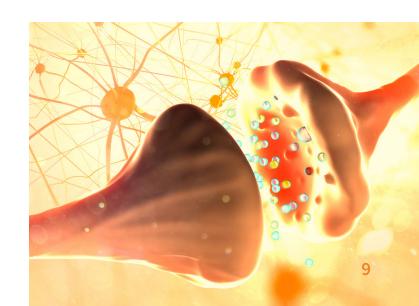
One of the first clinical trials of inositol explored its use for panic attacks. The small trial administered 12 grams of inositol or placebo per day and found that inositol reduced the number of panic attacks on average per week from almost ten to just under four. The severity of panic attacks were also significantly reduced by around 85% (Benjamin 1995).

A separate trial around the same time also explored inositol supplementation for obsessive compulsive disorder (Fux 1996). The study found modest, but significant improvements in symptoms, including both obsessive and compulsive components.

A comparison trial between inositol and fluvoxamine for panic disorder found the treatments to be similar in efficacy, albeit with lower side effects from inositol.

A comparison trial between inositol and fluvoxamine for panic disorder found the treatments to be similar in efficacy, albeit with lower side effects from inositol (Palatnik 2001).

When dosing inositol, it's often best to have a bulk powder. Typically, dosing starts around 500 mg (1/2 gram) twice per day and is increased slowly to minimize any potential nausea or gastrointestinal side effects. The maximum daily dose is usually 6 grams twice daily or 12 grams total per day.



# Magnesium

Treating deficiencies of magnesium is crucial when addressing anxiety. By far, the most common nutrient deficiency I encounter in my practice is magnesium. Some of the latest research suggests that half of individuals in the United States don't consume enough of the mineral to meet their minimum requirements (Blumberg 2017). It is also worth noting that a study on early humans suggests that we used to consume around four times more magnesium than we do now (Eaton 2000).

Magnesium is critical for normal function. The mineral is needed for over 300 different biochemical reactions throughout the body (Long 2015). In fact, it is the second most abundant electrolyte found within the body's cells. Most functions are influenced by magnesium and the mineral has key roles in muscle contraction and relaxation along with energy production.

Of interest, magnesium also has a role in balancing the stress response. Stress increases demands for the nutrient, as magnesium is lost in the urine during stressful events. Stress resilience is decreased if magnesium becomes deficient (Seelig 1994).

Stress resilience is decreased if magnesium becomes deficient.

Not surprisingly, magnesium is also crucial for normal brain function. Magnesium helps to block excitatory signaling, slowing overactive brain circuitry. It also helps protect brain cells from damage or death (Kirkland 2018). As such, magnesium plays a neuroprotective role, helping to maintain balance and function.

It should come as no surprise that magnesium deficiency has been associated with poor mental health. Anxiety, irritability, depression, agitation and even psychosis have all been linked to low levels of the mineral (Wacker 1968, Seelig 1975).

# By far, the most common nutrient deficiency I encounter in my practice is magnesium.

While the quality of the evidence is poor, a recent review on magnesium still concluded that the published research suggests benefits for anxiety in those more vulnerable to anxiety states (Boyle 2017).

Animal models also lend credence to the idea that magnesium has anti-anxiety effects. Magnesium deficiency has been shown to worsen anxiety and alter normal gut flora in mice (Pyndt 2015). Other research has confirmed an anxiety-induced state in mice due to magnesium deficiency that appears to be rooted in a disruption of the normal stress response (Sartori 2012).

Most individuals struggling with an anxiety disorder will likely benefit from supplemental magnesium. Considering the frequency of deficiency and the increased need for magnesium in stressed individuals, magnesium supplementation makes sense for most people.

Generally, reasonable doses of magnesium around 400-600 mg per day in patients without kidney disease are quite safe. The most common side effect is diarrhea, which often can be addressed by switching forms of the nutrient. Chelated forms, like magnesium citrate, malate, glycinate, and threonate usually work best.



# Herbal and Plant-Derived Treatment for Anxiety

Beyond basic nutrients, there is an expanding arsenal of plant-based medicines for treating anxiety that slowly, but steadily, are accruing evidence of efficacy in the mainstream medical literature. Two of these treatments, L-theanine and ashwagandha, are covered in the following pages.

## L-Theanine

L-theanine is a naturally occuring amino acid found in green tea. It appears to hold promise for a number of different health conditions, including for the treatment of stress and anxiety. A recent meta-analysis of clinical studies concluded that L-theanine "may assist in the reduction of stress and anxiety in people exposed to stressful conditions (Williams 2019)."

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L-theanine provides these benefits through a number of mechanisms. Glutamate is the main excitatory neurotransmitter, whereas gamma aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. L-theanine appears to affect both. The compound is an analog of glutamate, acting as an inhibitor of glutamate activity.

Research in patients with schizophrenia even found reduced glutamate concentrations in the brain with L-theanine supplementation (Ota 2015).

While the research on GABA is in animals, it still suggests that L-theanine raises GABA levels, likely contributing to its stress-reducing properties (Nathan 2006).

Additionally, research shows increased dopamine and serotonin levels with L-theanine supplementation. Overall, L-theanine appears to be neuroprotective, also increasing antioxidant and anti-inflammatory activity in the brain (Takeshima 2016).

Some of the effects of L-theanine on brain function can be measured by electroencephalography (EEG). Alpha waves are a slower wave pattern seen in the EEG of more relaxed individuals. A small study found that L-theanine increased alpha brain waves with the effects being stronger in those with higher levels of anxiety (Kobayashi 1998).

Dosing of L-theanine is typically between 100 ang 400 mg total per day, usually divided twice daily. The compound has been shown to be quite safe without direct sedative properties unlike some of the standard anxiety medications.



# Ashwagandha

Another herb that continues to attract attention due to multiple potential benefits is ashwagandha. Ashwagandha is an ayurvedic herb from India with a long history of use as a tonic, often with a focus on the nervous system (Singh 2011).

More recently, research has been starting to verify the effects and benefits of ashwagandha. A randomized, double-blind, placebo-controlled trial exploring ashwagandha extract in highly stressed adults found anxiolytic benefits. Over two months, anxiety levels were reduced by 41% with ashwagandha supplementation as measured by the Hamilton Anxiety Rating Scale (HAM-A) (Lopresti 2019).

A randomized, double-blind, placebo-controlled trial exploring ashwagandha extract in highly stressed adults found anxiolytic benefits. Over two months, anxiety levels were reduced by 41% with ashwagandha supplementation.

A study in patients with schizophrenia found that ashwagandha supplementation helped reduce symptoms of both depression and anxiety (Gannon 2019). The effect size for anxiety was found to be medium, which is more than double the effect size seen with standard medications for treating depression (Hieronymus 2020).

Earlier studies on stress and anxiety have also found significant benefits (Pratte 2014). At least part of the mechanism of ashwagandha's effects on stress include lowering cortisol levels. One study on highly stressed individuals found an average 28% reduction of serum cortisol with ashwagandha supplementation (Chandrasekhar 2012). Ashwagandha even appears to help improve sleep (Langade 2019).

One study on highly stressed individuals found an average 28% reduction of serum cortisol with ashwagandha supplementation.

The most recent meta-analysis on anxiety and stress appears to confirm benefits of ashwagandha supplementation for both (Akhgarjand 2022).

Dosing of ashwagandha depends on the product, although standardized extracts are often dosed between 250 mg and 1000 mg per day depending on the severity of the condition and product recommendations. Generally, dosing is divided, twice daily.



# **Treatment Summary**

While the following is not meant to be a comprehensive summary of treatments for anxiety disorders, it does include some of the treatments that I've found to be most useful with patients.

Generally, for any mental health condition, best results are found by doing a comprehensive evaluation and laboratory testing to identify treatment needs and nutrient deficiencies. However, in some cases, a simpler treatment approach using one or two of the following supplements may still provide significant relief.

Anxiety Supplement	Dosing	Notes
5-HTP	50 mg to 200 mg per day	Start at 50 mg and increase slowly to minimize GI side effects. Caution is advised if combining with SSRIs or SNRIs due to serotonin syndrome risks.
Inositol	500 milligrams to 6 grams twice per day	Start low and increase slowly to minimize GI side effects.
Magnesium	200-300 mg twice daily	If diarrhea, reduce dose or try a different form of magnesium
L-theanine	50-200 mg twice daily	Non-sedating
Ashwagandha (standardized extract)	125-500 mg twice daily	Dosing can vary based on the extract

Anxiety conditions are common and symptoms aren't often fully controlled with standard treatment. Fortunately, a number of additional treatments based around the concepts and principles of Functional Psychiatry, like those listed above, can often provide relief.

While the treatments outlined will typically improve patients' symptoms, in some cases a more comprehensive approach is necessary. Evaluating for nutritional deficits, inflammation, toxicities, chronic infections, hormonal imbalances, gut flora problems, and genetics can yield a more comprehensive understanding of the factors contributing to a patient's anxiety symptoms. To learn this more comprehensive approach, consider additional training in Functional Psychiatry through courses or a fellowship with *Psychiatry Redefined*.

There is a path forward for people struggling with anxiety that haven't found adequate relief. Functional Psychiatry can often provide additional tools and answers to reduce symptoms and restore health.

In Good Health,

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