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1 Overview

Summary and Quick Facts for Anxiety and Anxiety Disorders

- Anxiety disorders affect about 18% of the U.S. adult population. Nearly 29% of adults will experience an anxiety disorder in their lifetime.
- Anxiety is a multifaceted disorder and must be addressed as such to achieve symptomatic relief.
- Nutrients such as L-theanine, saffron extract, lemon balm, omega-3 polyunsaturated fatty acids, and magnesium, in conjunction with healthy eating habits and stress management techniques, can support the body's stress response mechanisms.

What are Anxiety Disorders?

Anxiety is a normal response to stress that can serve a useful purpose: helping us avoid situations that threaten our sense of security. Anxiety disorders, on the other hand, arise when the degree of anxiety experienced is disproportionate to the threat posed by given circumstances.

There are different types of anxiety disorders including generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, phobias, and social anxiety disorder.

Anxiety disorders arise from complex interactions between the brain, the body's stress response network, and

even the gut microbiome.

Some natural interventions such as L-theanine, certain probiotic species, saffron extract, and omega-3 fatty acids may help support a healthy stress response and mitigate a tendency to respond with anxiety disproportionate to stimuli.

What are the Risk Factors for Anxiety Disorders?

- Personal or family history of anxiety disorder or other mental illness
- Sex – women are nearly twice as likely as men to develop an anxiety disorder
- Chronic stress
- Age – most anxiety disorders develop by young adulthood, although the elderly may experience unique anxieties
- Experiencing traumatic or stressful events
- Lifestyle factors, including smoking and alcohol use

Note: People with anxiety disorders are at an increased risk of a wide range of mental and physical health problems, including depressive or bipolar disorder, cardiovascular disease, and diabetes.

What are the Signs and Symptoms of an Anxiety Disorder?

- Difficulty concentrating
- Irritability
- Tense muscles
- Sleep disturbances
- Difficulty overcoming worries
- Symptoms of different kinds of anxiety disorders can vary, and may include panic attacks, compulsive behavior, dread of social interactions, and re-experiencing traumatic events.

What are Conventional Medical Treatments for Anxiety Disorders?

- Cognitive-behavioral therapy
- Drug therapy:
    - First-line antidepressants, including selective serotonin reuptake inhibitors (SSRIs) (eg, fluoxetine [Prozac] and sertraline [Zoloft]) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine [Cymbalta] and venlafaxine [Effexor])
    - Second-line antidepressants, including tricyclic antidepressants (TCAs) (eg, amitriptyline [Elavil] and clomipramine [Anafranil]) and monoamine oxidase inhibitors (MAOIs) (eg, tranylcypromine [Parnate] and phenelzine [Nardil])
    - Other antidepressants, including mirtazapine (Remeron), trazadone (Desyrel), vilazodone (Viibryd), and vortioxetine (Trintellix)
    - Benzodiazepines such as diazepam (Valium), alprazolam (Xanax), and clonazepam (Klonopin)
    - Buspirone (BuSpar)
    - Hydroxyzine (Vistaril, Atarax)
    - Pregabalin (Lyrica), an anticonvulsant drug that is also effective in treating anxiety
    - Quetiapine (Seroquel), an antipsychotic drug that is also effective in reducing symptoms of anxiety

What are Some Emerging Treatments for Anxiety Disorders?

- Ketamine, a general anesthetic that is also effective for use in anxiety disorders
    - Esketamine (Ketanest), a derivative of ketamine delivered intranasally, has been approved for intractable depression
- Agomelatine, a synthetic version of melatonin
- Oxytocin
- Etifoxine (Stresam)
- Neurostimulation techniques

- Repetitive transcranial magnetic stimulation
- Vagus nerve stimulation
- Transcranial magnetic stimulation
- Deep-brain stimulation

What Dietary and Lifestyle Changes May Be Beneficial for Anxiety Disorders?

- Get enough sleep
- Exercise regularly
- Moderate caffeine intake
- Relaxation techniques, including meditation and mindfulness-based cognitive therapy
- Eat a healthy balanced diet – the Mediterranean diet has been shown to reduce mood disorders

What Natural Interventions May Be Beneficial for Anxiety Disorders?

- **B-vitamins**. B-vitamins are cofactors in the synthesis of neurotransmitters. Declining levels of B-vitamins can lead to increased homocysteine levels and anxiety—supplementation may help lower homocysteine levels and relieve anxiety.
- **L-theanine**. L-theanine, an amino acid found in green and black tea, has been shown to improve stress-induced anxiety, depression, sleep problems, and enhance cognitive performance.
- **Magnesium**. Magnesium deficiency has been linked with anxiety disorders. Supplementation may help reduce anxiety.
- **Omega-3 fatty acids**. Omega-3 fatty acids have a wide variety of health benefits; they have been shown to improve mood and symptoms of anxiety.
- **Lemon balm**. Lemon balm may suppress levels of stress hormones and promote neurogenesis. A combination of lemon balm and *valerian* was shown to improve symptoms of anxiety.
- **Saffron**. Saffron extracts have been shown in multiple trials to reduce symptoms of anxiety, depression, and improve mental health.
- **Probiotics**. Certain probiotic species have been shown to improve behaviors and symptoms related to anxiety, stress, and depression.
- Other natural interventions such as **melatonin**, **gamma aminobutyric acid** (**GABA**), and **N-acetylcysteine** may help improve symptoms of anxiety.

2 Introduction

Anxiety is a normal and necessary emotion that signals potential harm and helps us avoid situations that threaten our safety. Anxiety *disorders* differ from normal or illness-related anxiety in that the emotional response is not related to, or is disproportionate to, the threat.[1] Anxiety disorders are persistent; interfere with the ability to function normally; and can manifest in a wide range of cognitive, emotional, physical, and/or behavioral symptoms such as fear, memory impairment, rapid heart rate, hot flashes, restlessness, sleep disturbance, and more.[2,3]

North Americans have the highest prevalence of anxiety disorders in the world. Estimates suggest that 18% of the US population suffers from an anxiety disorder, and nearly 29% will have an anxiety disorder at some point in their lifetime.[4] Unfortunately, anxiety disorders are often overlooked by physicians or misdiagnosed as physical ailments.[5,6] It is estimated that about 40% of cases of anxiety and similar disorders go untreated.[7]

There are several types of anxiety disorders. These include generalized anxiety disorder, panic disorder, phobias, social anxiety disorder, separation anxiety disorder, and other less common conditions.[3] In some cases, anxiety is caused or aggravated by use or discontinuation of medications, alcohol, or other substances.[8]

Anxiety disorders are associated with complex interactions between environmental, genetic, and epigenetic factors. Certain patterns of neural signaling and specific brain structures have been identified as playing a role in anxiety response. Genetic variation has been estimated to account for anywhere from 30% to 67% of anxiety risk, while the remainder of risk is attributable to environmental factors such as traumatic life events.[1] Anxiety is closely related to **stress**, and early-life stress and stressful life events can predispose to the development of

anxiety disorders.[9,10] The likelihood of developing an anxiety disorder is roughly twice as high in women as in men.[4,11]

People with anxiety have an increased risk of developing **depression** and substance abuse.[1,11] In fact, anxiety and depression occur together so frequently that some experts consider mixed anxiety and depression to be a distinct disorder.[6,12] Anxiety disorders are also associated with a range of other chronic conditions, including **cardiovascular disease** as well as neurological, metabolic, endocrine, gastrointestinal, musculoskeletal, autoimmune, and respiratory disorders.[3,13,14] Because these conditions may cause symptoms that overlap with those of anxiety, accurate diagnosis and appropriate treatment can be challenging.[6]

Social support, healthy coping skills, and physical activity appear to be protective against anxiety disorders, while cigarette smoking, alcohol and cannabis use, negative perceptions of life events, and certain work-related factors are associated with increased risk.[15] In addition, healthy eating patterns and relaxation practices can help to reduce anxiety.[16-18]

Anxiety disorders are usually treated with either medication, psychotherapy, or a combination of the two. Of the psychotherapy modalities, cognitive behavioral therapy has the greatest evidence for efficacy.[1,6] Although medications have been found to be effective in many cases, they are unsuccessful for roughly one-third of patients. This can be due to intolerable side effects or lack of efficacy.[19] Perhaps even more troubling, debate continues among experts in the field as to whether commonly prescribed medications are even superior to placebo.[20] In generalized anxiety disorder and panic disorder, medications have been found to be less effective in milder cases.[21] Fortunately, a number of integrative interventions have been found to reduce anxiety and improve mood, including omega-3 fatty acids, B vitamins, probiotics, and L-theanine, as well as preparations from herbs like lavender, passionflower, kava, saffron, and lemon balm.[22,23]

In this protocol you will learn about the underlying causes of anxiety and how anxiety affects the body, as well as the connections between stress, depression, and anxiety. You will also learn how specific anxiety disorders are diagnosed, and about treatment approaches spanning conventional, investigational, and integrative therapies.

3 Types of Anxiety Disorders

The phenomenon of anxiety has been described since the beginning of modern psychiatry in the late 1700s.[24] Today, anxiety disorders are defined by the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, or DSM-5, published by the American Psychiatric Association. They include generalized anxiety disorder, panic disorder, agoraphobia and other phobias, and social anxiety disorder, as well as separation anxiety disorder and selective mutism, which mainly affect children. Although these are distinct disorders, they have overlapping symptoms and often occur together.[1]

Social Anxiety Disorder

Social anxiety disorder (also known as social phobia) is characterized by persistent and excessive fear or anxiety in social situations due to fear of scrutiny, embarrassment, or rejection.[1,25,26] In addition to excessive fear or worry, symptoms of social anxiety may include blushing, hand tremor, nausea, or urinary urgency.[1] The anxiety is out of proportion to the situation and causes significant distress and long-term functional impairment affecting realms of life such as relationships, work, and school.[25] Social anxiety disorder typically emerges during adolescence and can persist into adulthood without treatment. It is the most common type of anxiety disorder, affecting as many as 15% of people at some point in their lifetime.[25,26] It is estimated that up to 90% of individuals with social anxiety disorder develop other mental health problems such as major depression, alcohol use disorder, and other anxiety disorders. The presence of other psychiatric ailments in those with social anxiety disorder is associated with more severe symptoms, lower likelihood of treatment response, increased impairments in functioning, and higher risk of suicide, making it all the more important to identify and treat this condition.[25]

Phobia

Phobia is defined as intense fear or anxiety triggered by a specific object or situation.[1] It is estimated that 7.4% of people experience a phobia disorder in their lifetime.[27] People with phobia experience fear or anxiety that is disproportionate to the threat posed by the object of the phobia, leading to chronic distress and impaired functioning.[27,28] Examples of phobias include fear of[27]:

- *Animals* such as insects, spiders, or snakes
- *Natural situations* such as heights or thunderstorms
- *Blood*, *needles*, or *medical procedures*
- *Other situations*, such asairplanes, elevators, or closed spaces

Generalized Anxiety Disorder

An estimated 5.7% of US adults will have generalized anxiety disorder at some point in their lifetime, yet it often goes undiagnosed and untreated.[29,30] People with generalized anxiety disorder experience excessive apprehension or worry about everyday situations. While many people experience generalized anxiety from time to time, the diagnosis of generalized anxiety disorder is made when this anxiety occurs on more days than not for at least six months, is difficult to control, causes distress and difficulty functioning, and is associated with symptoms such as restlessness, fatigue, difficulty concentrating, muscle tension, and sleep disturbance.[5,31]

Panic Disorder

Panic disorder is characterized by recurrent unexpected panic attacks. Panic attacks are sudden episodes of intense fear or discomfort that come on rapidly with no clear trigger and last for several minutes or longer.[5,28] Physical symptoms, such as heart palpitations, sweating, trembling, shortness of breath, chest pain, nausea, dizziness, a sensation of choking, chills, and numbness or tingling, accompany feelings of fear during a panic attack.[32] Psychological symptoms, including feeling detached from oneself, fear of going crazy, and fear of dying, also occur.[1,5]

Separation Anxiety and Selective Mutism

Separation anxiety and selective mutism are anxiety disorders that mainly affect children, but may also occur in, or persist into, adulthood.[1,33,34] Individuals with separation anxiety have persistent intense anxiety about being apart from people to whom they are attached due to uncontrollable fear or worry that some adversity will befall these people while they are separated. Selective mutism is a rare anxiety disorder characterized by an inability to speak in certain circumstances, despite having normal language skills. Selective mutism typically comes on before age five and is frequently associated with other anxiety disorders.[28]

Other Anxiety Disorders

There are other specified and unspecified types of anxiety disorder that do not fit into the categories listed above. Among them are:

- **Agoraphobia**. Agoraphobia is a phobia marked by pronounced fear and avoidance of situations or places in which the individual feels they might become trapped, unable to escape or get help, or embarrassed. It usually occurs in people with another type of anxiety disorder, particularly panic disorder. People with agoraphobia may avoid using public transportation, being in open spaces, being in enclosed spaces or in crowds, standing in lines, or being away from home alone. In severe cases, agoraphobic patients become homebound.[3,28]
- **Illness anxiety disorder**. Illness anxiety disorder was first defined in 2013 to cover a portion of patients who would have previously been diagnosed with hypochondriasis. It is marked by excessive worry about having or developing a serious medical illness that is not relieved despite normal findings on physical exams and lab tests. The fear of illness is persistent and chronic, manifesting as over-attention to normal body sensations and either frequent health care seeking or health care avoidance, and causing extreme distress and impairing daily life.[35]

Anxiety in the Elderly

Anxiety disorders are common late in life, yet often go unrecognized and untreated. They frequently occur along with depression, sleep disorders, and substance use disorders, and may hasten cognitive decline and increase the risk of dementia, illness, and death in the elderly. The most common late-life anxiety disorder is generalized anxiety disorder, which affects about 7% of elderly people, while agoraphobia has been estimated to affect about 5% of elders. Panic disorder affects about 4% of elders.[36,37]

Fear of falling, a type of phobia particular to this age group, is reported to affect anywhere from 21% to 85% of

seniors. The risk of falling increases with age, and some degree of concern is to be expected; however, those with phobic fear of falling have an intense and consuming fear that is out of proportion with the risk and interferes with daily life. While having fallen in the past is thought to be a risk factor, fear of falling is also prevalent among those who have never fallen and may be a marker of declining cognitive function.[8,38] Results from a pilot trial showed that a treatment intervention utilizing psychotherapy, exercise therapies, and a home safety evaluation helped reduce fear and avoidance behaviors in elderly people affected by fear of falling.[39]

A variety of medical conditions common in older individuals can be mistaken for anxiety disorders. These include neurologic, cardiovascular, gastrointestinal, and endocrine or metabolic disorders, as well as vitamin B deficiency states. It is important that these be ruled out before an anxiety disorder diagnosis is made. The same is true for medications that may cause anxiety, and a thorough medication history must be taken. Although treatment decisions will vary based on many factors, a useful rule of thumb is that non-pharmacological approaches are preferred as a first approach. These can include lifestyle modification, behavioral and cognitive therapies, mindfulness practices, and other types of activity-based interventions. When medication is used, selective serotonin reuptake inhibitors (SSRIs) are usually first-line treatment, while benzodiazepines are either avoided or used on a short-term basis because they are prone to causing adverse effects in the senior population.[37,40]

4 Risk Factors and Associated Conditions

The risk of anxiety disorders is related to genetic and environmental factors.[41] A family history of anxiety is one important determinant, as children of anxious parents have been found to be significantly more likely to have anxiety disorders.[42] Women are nearly twice as likely as men to develop anxiety disorders.[4,7] In addition, shyness in childhood, adverse or stressful events in early life or adulthood, and a family history of anxiety disorders or other mental illnesses are associated with increased risk.[28] Certain personality traits have also been linked to anxiety disorder risk. Specifically, traits that predispose to poor responses to stress, interpreting ordinary situations as threatening, and experiencing minor frustrations as overwhelming have been linked to anxiety.[1,43]

Although the elderly experience unique types of anxiety (see sidebar titled “Anxiety in the Elderly”), most anxiety disorders begin during childhood, adolescence, and young adulthood.[2] Separation anxiety and phobia disorders usually appear during childhood, and social anxiety more often comes on during adolescence or young adulthood; for panic and generalized anxiety disorders, the age of onset is usually between 21 and 35 years.[44]

Certain lifestyle factors have been shown to influence risk of anxiety disorders. Smoking in particular has been closely linked to increased risk of anxiety disorders. Alcohol use has also been reported to be associated with vulnerability to anxiety disorders. On the other hand, strong social connections, positive coping skills, and physical activity appear to be protective against anxiety disorders.[15]

Stress

Early life stress, **chronic stress**, immune activation, and traumatic brain injury have been linked to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and a predisposition to stress-related disorders later in life.[45] Communication between the HPA axis and a brain region known as the amygdala plays a major role manifesting anxiety as a response to stress.[46] The amygdala is involved in emotional processing and interpreting stimuli relevant to emotions. Stress can alter the structure and function of the amygdala,[46-48] and over-active neuronal signaling in the amygdala is a consistent feature across the major anxiety disorders.[47]

Multiple neurotransmitters and hormones, including several “neurohormones,” which fulfill both roles, are involved in the interaction between stress, anxiety, and the amygdala. These include norepinephrine, corticotropin releasing factor, serotonin, dopamine, gamma aminobutyric acid (GABA), glucocorticoids, and others. The stress response rapidly activates the HPA axis, partly through the release of several of these neurohormones, which may then activate the amygdala and promote anxiety.[46,49-51]

The Role of Inflammation

Chronic low-level inflammation may be a driving factor in anxiety disorders. Excessive levels of inflammatory proteins, such as C-reactive protein and some cytokines, have been reported in some studies in people with

anxiety disorders, and inflammation may help sustain anxiety-related symptoms.[52-54]

Research has shown inflammatory cytokines influence signaling in fear- and anxiety-related brain structures such as the amygdala.[52,53,55] It has been suggested that the role of inflammation in the body's response to acute assaults such as infection and injury may also extended to psychological stressors, such that stress may promote an inflammatory response.[53] Stressful experiences and trauma, including events that provoke fear and anxiety, increase the reactivity of the HPA axis and promote the release of pro-inflammatory cytokines.[52] When these stressors become chronic, the HPA axis and the immune system can become dysregulated. This is one possible mechanism behind the association between inflammation, chronic diseases such as cardiovascular and metabolic conditions, and mood and anxiety disorders.[53]

Anxiety and the Gut Microbiome

Gut microbes are increasingly being recognized as important players in the regulation of social behavior, mood, and pain sensitivity, possibly by impacting amygdala function.[56,57] Evidence from preclinical and clinical studies indicate bacteria in the gut produce neurotransmitters, hormones, and other inflammation-modulating compounds that influence brain function and contribute to stress reactivity and the risk of psychiatric and cognitive disorders.[58,59] Interactions between the gut **microbiome** and the brain may underlie connections between chronic gastrointestinal disorders and symptoms of anxiety and depression.[58,60] Because of its apparent importance in psychiatric health, using diet and probiotic and prebiotic supplements to support healthy microbial balance in the gut may benefit patients with anxiety disorders.[61,62]

Female Hormones and Anxiety

Anxiety disorders affect approximately twice as many women as men.[63] Women are more likely to develop anxiety disorders or experience worsening of symptoms during times of intense hormonal shifting such as puberty, premenstrually, pregnancy, and perimenopause. Also, women have a higher long-term risk of anxiety if they have undergone surgery to remove their ovaries.[64,65] Estrogen has neuroprotective effects such as lowering brain oxidative stress and inflammation, moderating neuronal hyperexcitability, and influencing nerve growth factor production.[66]

Hormone therapy has been found to lower anxiety and depression symptoms in perimenopausal women. One study found women with early menopause due to surgery to remove their ovaries had fewer depression symptoms after one month and fewer anxiety symptoms after three months of hormone therapy compared with perimenopausal women who did not receive hormone therapy.[67] Another trial found a synthetic estrogen-like medication and bioidentical estradiol were equally effective for improving anxiety and depression in women with natural menopause.[68] Other studies have reported the positive effect of hormone therapy on mood in perimenopausal women was enhanced by combining it with herbal therapy using kava extract.[69,70]

For more information, please see the **Female Hormone Restoration** *protocol.*

Other Conditions Associated with Anxiety

Anxiety is correlated with a wide range of mental and physical health problems. Not only does illness frequently lead to anxiety, anxiety sufferers have a higher risk of a range of mental and physical health problems.[14,71] These include:

- **Psychiatric illness**. Individuals with any anxiety disorder are at high risk of developing another anxiety disorder over time.[1] Patients with anxiety disorders also frequently have depressive disorders or bipolar disorder.[72] Suicide is much more common in individuals with anxiety disorders compared with the general population.[73]
- **Addiction**. Anxiety has been found to be more common in individuals with substance use disorders, pathological gambling, and internet addiction compared with individuals without these conditions.[4]
- **Cardiovascular disease**. Anxiety symptoms and disorders occur frequently in people with **heart disease** and have been found to be associated with a significant increase in cardiovascular illness, risk of stroke and heart attack, and cardiovascular disease-related death. Anxiety disorders occur in 18–25% of **stroke** survivors.[4,74-76]
- **Cancer**. The prevalence of anxiety in people with a history of cancer is between 15% and 23%, with even

higher rates in those with advanced cancers.[4]

- **Respiratory illness**. Anxiety is more common in people with **chronic obstructive pulmonary disease (COPD)** than those without COPD, and is associated with poor outcome.[77] Survivors of acute respiratory distress syndrome (ARDS) also have an increased prevalence of anxiety (see sidebar titled "Anxiety After Acute Respiratory Distress Syndrome").[4]
- **Diabetes**. People with **diabetes** have been found to be more frequently affected by an anxiety disorders than non-diabetics.[4,71]
- **Cognitive dysfunction and neurological diseases**. Anxiety frequently occurs in older individuals with **cognitive impairment**, as well as their caregivers,[4] and appears to increase the risk of dementia.[78] Anxiety disorders are also more common in people with **Parkinson disease**.[71]
- **Autoimmune diseases**. Anxiety disorders are more common in those with **rheumatoid arthritis**, **systemic lupus erythematosus (SLE)**, and **multiple sclerosis**.[71,79,80]
- **Digestive ailments**. The "anxious stomach"—digestive upset linked to stress or anxiety—is a well-known phenomenon. Likewise, anxiety disorders are frequently associated with chronic functional gastrointestinal disorders, such as **gastroesophageal reflux disease (GERD)**, indigestion, and **irritable bowel syndrome**.[81-83] Researchers have noted this relationship is likely bi-directional, with digestive and anxiety disorders each contributing to the other. This is probably a reflection of the close connection between the gut and the brain, mediated largely by the gut microbiome.[57,81,84] This close connection between the gut and the brain has been described as the "gut-brain axis," and the gut microbiome and gut-associated neurons have been referred to as the "second-brain."[85]

Anxiety After Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by severe lung injury and inflammation, and low blood oxygen levels. Survivors of ARDS can have lasting lung damage and reduced lung function, diminished overall health, and lower quality of life.[86] In addition, many experience long-term cognitive and emotional consequences, including anxiety, that further contribute to poorer quality of life.[87,88] Studies in ARDS survivors have reported 38–44% have anxiety and 26–33% have depression two years after discharge from the hospital, and many continue to be affected after five years. After one year of follow-up, the rate of anxiety and depression is as high as 66%.[87,89] Many ARDS survivors experience anxiety, depression, and post-traumatic stress disorder (a condition related to anxiety) simultaneously.[87,89,90]

Although the relationship between ARDS and psychiatric problems in survivors is not fully understood, a prolonged period of low oxygen, activation of the stress response, exposure to inflammatory cytokines, and use of sedatives and other drugs are factors that may contribute. A previous history of depression is believed to predispose to post-ARDS psychiatric illness.[87] Longer time in intensive care, on a mechanical ventilator, and under sedation have each been associated with increased risk of lasting psychological impacts.[91,92] Younger age, being female, and illness severity have also been linked to greater likelihood of developing mental health problems after ARDS.[89,93] Interestingly, longer treatment with corticosteroids may be associated with lower risk of persistent psychiatric symptoms.[93]

In 2003, a deadly viral respiratory illness known as sudden acute respiratory syndrome (SARS) spread to 29 countries, affecting more than 8,000 individuals in seven months. ARDS is one of the complications of SARS and a frequent reason for its lethality. Among SARS survivors, an alarming 64% continued to report substantial psychological distress after one year.[94]

5 Diagnosis

Diagnosing anxiety disorders involves screening through careful history-taking, ruling out other causes of anxious symptoms, and use of diagnostic surveys.

Screening

While many people report struggling with anxiety from time to time, those with anxiety disorders have chronic, excessive, uncontrollable symptoms, out of proportion to the provoking stimuli, and experience some degree of

disability from their anxiety.[3,4] The DSM-5 suggests physicians use the following screening questions to identify the possibility of an anxiety disorder[7]:

- During the past two weeks, how much have you been bothered by the following problems?
  - Feeling nervous, anxious, frightened, worried, or on edge
  - Feeling panic or being frightened
  - Avoiding situations that make you anxious

Other sets of questions (see Table 1) have been developed to help identify specific anxiety disorders. For patients who indicate mild or greater severity of anxious symptoms, the causes and impacts of their symptoms should be assessed and the use of diagnostic tools considered.

Table 1: Screening Questions for Specific Anxiety Disorders[7]

Panic disorder	Do you have sudden episodes/spells/attacks of intense fear that are unexpected or out of the blue? (If *yes*, continue) Have you had more than one of these attacks? Does the worst part of these attacks usually peak within several minutes? Have you ever had one of these attacks and spent the next month or more living in fear of having another attack or worrying about the consequences of the attack?
Social anxiety disorder	Does fear of embarrassment cause you to avoid doing things or speaking to people? Do you avoid activities in which you are the center of attention? Is being embarrassed or looking stupid among your worst fears?
Generalized anxiety disorder	During the past four weeks, have you been bothered by feeling worried, tense, or anxious most of the time? Are you frequently tense, irritable, and having trouble sleeping?

Ruling Out Other Causes

Anxiety is a common symptom that can be caused by an array of medical conditions, such as heart, lung, neurological, and psychiatric disorders. **Hyperthyroidism** can also cause anxiety.[2,7,13] Patient history, physical examination, and basic laboratory tests can help rule out other medical disorders as a cause of the symptoms. In certain cases, when symptoms are unusual or to follow-up on abnormal results from the history, exam, and labs, more complex diagnostic tests may be called for, including additional lab work, brain imaging, and others.[3]

Anxiety can also be caused by taking or stopping certain medications and substances. These include:

- caffeine[97]
- alcohol[98]
- cocaine[99]
- amphetamines[99]
- over-the-counter decongestants[100]
- some antidepressants[101]
- some heart disease medications[102]
- steroids[103]
- bronchodilators (used to treat asthma)[104]
- Parkinson disease medications[105]
- levothyroxine (Synthroid, used to treat hypothyroidism)[106]
- benzodiazepines[107]

- benzodiazepines
- opioid pain relievers[108]

A thorough history of use and stoppage of anxiety-inducing medications and substances should be reviewed as part of an evaluation for anxiety disorders.[7]

Diagnostic Surveys

The Hamilton Anxiety Scale (HAM-A) is the questionnaire used most commonly by physicians when determining whether their patients' symptoms meet the criteria for diagnosis of an anxiety disorder. The Beck Anxiety Inventory (BAI) is widely used for self-assessing anxiety symptoms. Other anxiety rating scales have been developed and validated for their ability to detect anxiety disorders.[109] Tools specific to children, adolescents, and the elderly are also available.[8,110]

6 Conventional Treatment

Anxiety disorders are generally treated with psychotherapy, medications, or a combination of both.[28] The efficacy of these approaches has been demonstrated in multiple trials and confirmed by meta-analyses.[111-114] In addition, psychotherapeutic and pharmacologic approaches have each been shown to have benefits that persist long after treatment ends. A meta-analysis of 93 randomized controlled trials found patients with anxiety disorders treated with psychotherapy experienced improvements that endured for up to two years after therapy was stopped. Patients treated with medications exhibited benefits with similar durability over two years post-treatment. Although mood improvement tended to increase after finishing cognitive behavioral therapy, yet tended to decline after discontinuing medication, the difference was not statistically significant.[115] Drug therapies, however, pose risks of adverse side effects, which in some cases can include severe withdrawal symptoms.[116,117] The choice of treatment depends on the type and severity of anxiety disorder, as well as patient characteristics such as age, associated conditions, and treatment preferences.[28]

Cognitive Behavioral Therapy

Cognitive behavioral therapy is a type of psychotherapy in which patients develop cognitive and behavioral strategies for changing dysfunctional patterns of thinking and behavior. Numerous clinical trials and meta-analyses have shown cognitive behavioral therapy can improve symptoms in individuals with generalized anxiety disorder, panic disorder, social anxiety disorder, as well as post-traumatic stress disorder and **obsessive-compulsive disorder**, all which of fall under the broad umbrella of anxiety-related disorders.[114] Cognitive behavioral therapy is widely used to treat anxiety in children and adolescents and has been found effective in numerous rigorous clinical trials.[118-121]

One meta-analysis found cognitive behavioral therapy led to remission in 51% of people with anxiety and related disorders.[122] Modifying cognitive behavioral therapy with techniques such as mindfulness (focused awareness, without judgement, on the present moment) may lead to greater therapeutic success for some individuals.[123-125] Recent studies have found digital delivery of cognitive behavioral therapy strategies may be useful as a complement to in-person therapy.[124] A 2017 meta-analysis found that the addition of pharmacotherapy to cognitive behavioral therapy had little additive benefit. There is some evidence that medication is more likely to be helpful in those who fail to respond to cognitive behavioral therapy.[126] Overall, psychotherapy and pharmacotherapy are considered roughly equally effective for anxiety disorders, and cognitive behavioral therapy can be effective in both group and individual settings.[7]

Antidepressants

Antidepressants are widely used as first-line medications for treating most anxiety disorders, and are generally considered to be as effective as psychotherapy.[1,2,7] However, some authors suggest that the evidence for antidepressant treatment of anxiety disorders remains equivocal. In generalized anxiety disorder and panic disorder, for instance, those with mild symptoms derive little benefit from antidepressant treatment, and potential harm may outweigh benefits.[21] An exhaustive review of randomized controlled trials of antidepressant treatment of panic disorder concluded that antidepressants may be more effective than placebo, but the evidence was not strong enough to firmly recommend their use in clinical practice.[111] And some authors have found little to no advantage of pharmacologic antidepressant treatment over placebo, psychotherapy, or exercise—all of which have

much lower risk of adverse effects.[127,128]

First-line antidepressants. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), two classes of antidepressants, are the first-line drugs for treating anxiety disorders in adults.[129,130] They are believed to work in part by increasing the availability of serotonin and norepinephrine (also known as noradrenaline) in specific areas of the brain.[111] Duloxetine (Cymbalta), venlafaxine (Effexor), escitalopram (Cipralex, Lexapro), sertraline (Zoloft), and paroxetine (Paxil) are examples of drugs in these classes that are recommended for patients with generalized anxiety, panic, and social anxiety disorders.[1,7] However, these medications often take 4–6 weeks to reach peak efficacy, and can cause adverse side effects that some individuals find intolerable, such as weight gain and sexual dysfunction, as well as headache, digestive upset, insomnia, or sedation.

A painstaking process of trial and error is not uncommon in seeking the right medication "fit" between patient, drug, and dosage.[131] In addition, stopping medications in these classes often causes withdrawal syndromes that can be protracted and severe.[116] Recent reports of severe and persistent withdrawal syndromes associated with stopping SSRIs and SNRIs have raised questions about the assumed superiority of these drugs over benzodiazepines (see below) in the treatment of anxiety.[117]

Second-line antidepressants. Tricyclic antidepressants (TCAs), such as amitriptyline (Elavil), clomipramine (Anafranil), and doxepin (Silenor), are members of an older class of drugs that increase levels of norepinephrine and serotonin in synapses (ie, the gaps between communicating neurons through which neurotransmitters pass). TCAs can cause a range of unpleasant side effects such as dry mouth, constipation, blurry vision, sedation, and weight gain. They can also cause heart rhythm disturbances, making SSRIs and SNRIs the preferred first-line medications for anxiety and depression.[130,131] Nevertheless, TCAs may have a role in treating patients with anxiety disorders that are unresponsive to other medications.[130]

The use of monoamine oxidase inhibitors (MAOIs) increases brain synapse levels of dopamine, serotonin, and norepinephrine. MAOIs are also an older class of drugs that has largely been replaced in practice by medications with a better safety profile. However, MAOIs are still sometimes recommended in intractable cases that are not responsive to other medications.[130,131] MAOIs, examples of which are tranylcypromine (Parnate) and phenalzine (Nardil), can cause dangerous interactions with other medications and some foods, and can cause side effects such as fatigue, low blood pressure, dry mouth, headache, insomnia, digestive symptoms, weight gain, and sexual dysfunction.[131,132]

Second-Line Anti-Anxiety Medications

Benzodiazepines. Benzodiazepines are sedative-hypnotics that work by increasing activation of receptors for the neurotransmitter GABA. This class of drugs includes diazepam (Valium), lorazepam (Ativan), alprazolam (Xanax), and clonazepam (Klonopin).[130] Benzodiazepines have a rapid onset of action and are generally prescribed for short-term usage. The popularity of benzodiazepines for treating anxiety has declined over the last several years because of their potential for abuse and addiction.[129,130,133] However, whether benzodiazepines or antidepressants should generally be declared the preferred drugs for generalized anxiety remains controversial,[134] and determining the best drug regimen for each patient requires an individualized approach. Benzodiazepines may be useful for controlling anxiety during the first few weeks after antidepressants are started, since antidepressants take several weeks to reach full effect. The benzodiazepines can then be tapered off as the antidepressants begin to take effect.[134] Common side effects of benzodiazepines include sleepiness, fatigue, dizziness, sweating, dry mouth, constipation, and agitation.[130,135]

Buspirone. Buspirone (Buspar) is an anti-anxiety medication used primarily to treat generalized anxiety disorder. It appears to work by increasing serotonin receptor activation, but also reduces dopamine activity.[130,136] Individuals using buspirone may experience adverse side effects such as dizziness, nausea, diarrhea, headache, nervousness, insomnia, blurred vision, confusion, weakness, tremor, muscle pain, numbness, chest pain, and rash. In addition, buspirone has been linked to movement disorders that may persist after stopping the drug.[136]

Hydroxyzine. Hydroxyzine (Vistaril, Atarax) is an antihistamine that has been studied for decades for the treatment of anxiety-related conditions. Although thought to be more effective than placebo for generalized anxiety disorder, the low quality of available studies does not permit hydroxyzine's consideration as a first-line

therapy.[130,137,138] Hydroxyzine can cause sleepiness, dry mouth, dizziness, and headache.[138]

Other Medications

Mirtazapine (Remeron), **trazadone** (Desyrel), **vilazodone** (Viibryd), and **vortioxetine** (Trintellix) are antidepressants with complex mechanisms of action. These antidepressants have less evidence supporting their efficacy and are not approved by the Food and Drug Administration (FDA) for treating anxiety disorders, and thus are not first-line therapies. In general, their side effect profiles are similar to SSRIs and SNRIs. Mirtazapine and trazadone are considered to have sedative properties. Vilazodone and vortioxetine have been approved to treat major depressive disorder, but do not have a large body of evidence supporting their use in anxiety disorders.[130,131]

Pregabalin (Lyrica) is used to treat anxiety disorders, primarily generalized anxiety disorder, and is structurally related to GABA.[139] In patients with generalized anxiety disorder, pregabalin has been found to reduce symptoms more quickly than the SNRI venlafaxine, and as effectively as benzodiazepines.[130,140] Nevertheless, it is not FDA-approved for this use.[138] Adverse side effects of pregabalin include weight gain, dizziness, sleepiness, headache, dry mouth, and vision distortion. Importantly, pregabalin can cause dependence and has been associated with fatal overdose, especially when used with other medications.[130]

Quetiapine (Seroquel), a drug in the atypical antipsychotic class, is mainly used at high doses to treat psychiatric illnesses such as bipolar disorder and schizophrenia. Lower doses of quetiapine have shown efficacy in reducing anxiety symptoms in subjects with generalized anxiety disorder. Quetiapine has been associated with weight gain and metabolic disease, although these issues are of greater concern at higher doses. Quetiapine is not FDA-approved for anxiety, even though this off-label drug is considered one of the most efficacious for this purpose.[130,140] Olanzapine (Zyprexa) and risperidone (Risperdal) are other atypical antipsychotics sometimes used as off-label treatments for anxiety disorders.[140]

7 Novel and Emerging Therapies

Many medications used to treat anxiety have questionable efficacy, an unfavorable side effect profile, or both. Therefore, research is ongoing with the hope of discovering safer and more effective medications to treat anxiety disorders. Most novel treatments under investigation are pharmacologic. Neurostimulation, which has been known for decades to have positive psychological effects, is a promising non-pharmacological approach under investigation.

Pharmacological Therapies

Ketamine. Ketamine (Ketalar) is a drug with wide ranging effects on the central nervous system due to its inhibition of glutamate receptors, known as N-methyl-D-aspartate (NMDA) receptors, in the brain. Although approved for use as a general anesthetic, ketamine has recently attracted interest for its effects in psychiatric disturbances, including substance use, depression, and anxiety disorders. Ketamine is administered intravenously, but a derivative intranasal drug (esketamine [Ketanest]) has been approved for treating intractable depression.[141]

Ketamine has been reported to relieve symptoms in patients with social anxiety and generalized anxiety disorders.[142,143] Some evidence suggests ketamine may induce increases in neuron connectedness and excitability.[143] The safety of repeated and long-term ketamine use is still being explored. Unfortunately, abuse and dependence are concerns due to ketamine's psychedelic properties.[141-143]

Agomelatine. Agomelatine (Valdoxan), a synthetic version of the neurohormone melatonin, is approved in Europe as a treatment for depression and has demonstrated anti-anxiety effects.[143] Agomelatine activates melatonin pathways, which play an important role in regulating circadian cycles and serotonin signaling, affecting sleep and mood, and also potentially enhancing neurogenesis and neuroplasticity (the ability to form new neuronal connections).[138,143] Three randomized controlled trials have found agomelatine to be effective in subjects with generalized anxiety disorder. These trials also found that agomelatine had a favorable side effect profile, better clinical response, and faster onset of action than SSRIs and SNRIs.[144,145] Agomelatine has been associated with mostly mild-to-moderate adverse effects including headache, dizziness, sleepiness, fatigue, and digestive upset. Its long-term safety has yet to be explored, but rare cases of liver toxicity have been reported; nevertheless, agomelatine appears to be safer than many current medical treatments for anxiety.[145,146]

Oxytocin. Oxytocin is a hormone released in areas of the brain involved in stress, fear, and anxiety, including the amygdala, where it counteracts these states by reducing neuronal activity. Oxytocin is involved in social behavior, mood, reproductive behavior, and stress responsiveness; low oxytocin is associated with increased anxiety.[143,147] Oxytocin is administered to pregnant women to induce uterine contractions. Intranasal administration of oxytocin has been found to have rapid anti-anxiety effects in preliminary trials in patients with generalized anxiety and social anxiety disorders. Evidence for the therapeutic use of oxytocin in anxiety disorders is preliminary, but it is considered a promising drug development target.[143,147]

Etifoxine. Etifoxine (Stresam) is an anti-anxiety and anti-seizure drug that, like benzodiazepines, quiets the nervous system by increasing GABA receptor responsiveness. Preclinical research suggests etifoxine may also reduce brain inflammation and increase production of factors that promote neuroplasticity. Preliminary trials suggest etifoxine may reduce anxiety symptoms without affecting memory or alertness, and without causing dependence, withdrawal symptoms, or rebound anxiety when stopped.[148,149] Etifoxine, which was developed in the 1960s, is marketed in a number of countries for treating anxiety disorders, but remains under investigation for this use in the United States. Etifoxine can cause adverse side effects including rash, colitis, liver toxicity, and abnormal uterine bleeding.[143]

Psychedelic Therapy

Psychedelics have a long history of use throughout the world in rituals, for recreation, and as medicine. Research into their possible therapeutic applications dates back to the 1940s and 1950s, when lysergic acid diethylamide (LSD) and the chemical psilocybin—the active constituent in “magic” mushrooms—were discovered by renowned pharmaceutical chemist Albert Hoffer.[150,151] These compounds were marketed and made available to researchers. Investigation into their neurological and psychiatric effects developed along two trajectories[151]:

- Low-dose treatment to enhance psychotherapy at multiple sessions. This approach was used to treat anxiety disorders and some other psychiatric conditions.
- High-dose treatment to induce one or a few transformative experiences. This approach was studied mainly in patients with substance abuse disorder.

Research into psychedelics in the United States was halted by the passage of the Controlled Substances Act of 1970, in response to illicit manufacture, recreational use, black market distribution, and cases of tragic outcomes. However, interest in psychedelics has been growing, and a number of well-designed controlled trials are underway or have been published, including from a prominent group at Johns Hopkins University in Baltimore, Maryland.[150-153] The results suggest psychedelics, used under controlled circumstances supervised by a qualified healthcare provider, may be a valuable therapeutic modality for people with anxiety and depression, particularly in those with cancer or other life-threatening illness, or when associated with end-of-life palliative care.[150,154]

Psilocybin is an alkaloid compound most closely associated with mushrooms in the *Psilocybe* group, but present in other types of fungi as well.[155] It works by interacting with serotonin receptors in ways that alter perceptions, thoughts, consciousness, and mood.[151] Two randomized controlled trials in patients with advanced-stage cancer found that psilocybin, as either a single dose or dual dose (a high-dose first session followed five weeks later by a low-dose session), in conjunction with psychotherapy resulted in substantial and lasting reductions in anxiety and depression. In the single-dose trial, psilocybin plus psychotherapy was compared with placebo plus psychotherapy. Participants in both trials reported on average less hopelessness, improved spiritual well-being, and enhanced quality of life, and these changes persisted for more than six months after treatment.[156,157] In a trial in patients with life-threatening illness, LSD-assisted psychotherapy led to reduced anxiety and increased quality of life, and produced lasting benefits affecting emotional health, habits, and world view 12 months after treatment.[158]

Another psychedelic substance, methylenedioxymethamphetamine (MDMA, also known as ecstasy), is the subject of active investigation as an adjunct to psychotherapy for the treatment of post-traumatic stress disorder.[159] Importantly, limited serious adverse effects have been reported in clinical trials using these or other

psychedelic substances, given careful screening, preparation, and supervision.[160]

The treatment of anxiety with psychedelics is currently limited to the research setting and should under no circumstances be attempted without oversight by a qualified healthcare provider. If research continues to demonstrate that these therapies are safe and effective, psychedelic-based treatment programs may become more common.

Cannabis and Anxiety

Cannabis (or marijuana) is one of the most widely used psychoactive substances in the world.[161] As the push for decriminalization and legalization intensifies, it is important to understand how cannabis and its major active constituents, tetrahydrocannabinol (THC) and cannabidiol (CBD), affect mental health.[162]

Cannabis constituents, known as cannabinoids, interact with endocannabinoid receptors in the human nervous system.[161] Endocannabinoids are endogenous signaling molecules with many important effects on brain function, including modulating appetite, sleep, memory, learning, motivation, and pain perception.[163,164] There are cannabinoid receptors throughout various parts of the body, suggesting global effects beyond the brain as well.[165] Interestingly, a decrease in endocannabinoid signaling, which can occur as a result of chronic stress, is associated with increased stress responsiveness along the HPA axis and increased anxiety behavior.[166] By interacting with the endocannabinoid system, cannabinoids hold much therapeutic potential for treating an array of neurological and psychiatric ailments.[161,163,167]

A single dose of THC has been shown to induce numerous acute psychiatric effects, such as delusions and hallucinations, flattened affect, loss of motivation, and mood changes, that do not appear to be buffered by CBD.[162] The therapeutic potential of THC, CBD, and their combination has been the subject of many preclinical and clinical trials. A large meta-analysis of clinical trials found THC, with or without CBD, promoted small improvements in anxiety symptoms in patients with other medical conditions,[168] and CBD alone has demonstrated some benefits in the treatment of generalized anxiety, social anxiety, and substance use disorders.[169,170] CBD has also been found to have anti-panic effects in healthy volunteers.[171]

Despite its possible usefulness in treating anxiety, chronic excessive use of cannabis may pose substantial mental health dangers, increasing risk of anxiety, depression, and sleep disorders, as well as psychosis and suicidality. However, it should be noted that some degree of reverse causality may account for this: people with existing mood and psychological disorders may turn to cannabis in the hope of finding relief. And one study found that in individuals who habitually overuse cannabis, a reduction in use resulted in improvements in anxiety, depression, and sleep.[172-174]

CBD alone has been reported to cause mild side effects, such as tiredness, diarrhea, and changes in appetite and weight, but overall has a favorable adverse effect profile; however, further research is needed to understand the effects of long-term CBD use.[175]

Neurostimulation

Neurostimulation techniques have shown promise as alternative methods to treat anxiety disorders as stand-alone therapy or in conjunction with other treatments.[176] Some of these treatments are believed to work by helping normalize the activity and function of neuronal networks, but fundamental questions about their mechanisms of action are as yet unanswered.[177]

Repetitive transcranial magnetic stimulation is the most studied type of neurostimulation for anxiety, and has demonstrated positive effects in generalized anxiety disorder.[176] It involves a magnetic coil placed on the scalp that generates a magnetic pulse to stimulate nerve cells in the brain.[178] **Transcranial direct current stimulation** is another type of neurostimulation and involves the delivery of very small magnitudes (1–2 mA) of electrical current through specific brain regions via two electrodes placed on the scalp. This method has been shown to be effective for anxiety, but its mechanism of action is not fully understood, and evidence suggests it works best when used in combination with medication and cognitive behavioral therapy.[179]

Another type of neurostimulation under investigation for its anti-anxiety potential is **vagus nerve stimulation**. The vagus nerve has connections in the amygdala and other brain regions involved in processing emotional and physical aspects of anxiety, and electrical stimulation of the vagus nerve has been reported to reduce anxiety symptoms in patients with panic disorder and other conditions with an anxiety component.[180,181] This type of neurostimulation involves the surgical implantation of an electrode that is wrapped around the left vagus nerve, and a pulse generator implanted below the collarbone. Due to possible surgical complications, as well as risk of sleep apnea, early or late onset abnormal heart rhythms, which in rare cases can be severe, and other potential adverse effects, the use of vagus nerve stimulation has historically been limited to severe and intractable cases. However, new techniques involving transcutaneous electrical stimulation of the vagus nerve are currently being explored as safer, less invasive, and less expensive options.[180]

Deep brain stimulation involves the use of electrodes implanted in the brain to deliver electrical impulses directly to specific brain regions, and is under investigation as a treatment option for individuals with obsessive-compulsive disorder and post-traumatic stress disorder. Deep brain stimulation is approved as a treatment for several conditions, including advanced Parkinson disease.[181,182] Although findings from clinical trials in Parkinson disease patients are somewhat inconsistent, deep brain stimulation appears to induce some improvement in depression and anxiety symptoms in some patients, with a greater effect in the short- and medium-term.[183-185] Some preliminary clinical evidence shows deep brain stimulation is able to relieve anxiety symptoms in various mood disorders.[186,187]

8 Diet and Lifestyle Interventions

Diet

The structure and function of the brain is determined in part by the availability of nutrients from our diet.[188] Dietary composition can affect a number of factors that influence brain function, including neurotransmitter synthesis and signaling, release of hormones by the gut, the composition of the gut microbiota, and gene expression patterns. Dietary factors also modulate adult nerve cell formation, neural plasticity, and brain immune function. All these factors are related to mental health and thus anxiety.[188-190]

A healthy diet, rich in plant-derived polyphenols and polyunsaturated fatty acids, along with vitamin supplements, may support healthy cognition, stress response, neuroinflammation, and mood.[188,191] Increased consumption of high-calorie and processed foods may increase the likelihood of anxiety disorders in childhood, adolescence, and adulthood, and animal studies have found repeated exposure to sugar-rich foods can provoke anxiety-related behavior.[192,193] On the other hand, phytochemicals like polyphenols promote a healthy microbiome, which in turn can modulate neuroinflammation in depression and anxiety.[194] In numerous studies, people with diets high in fruits and vegetables, as well as specific subgroups of plant-based foods such as berries, citrus, and leafy greens, have been noted to have higher levels of optimism and self-efficacy (confidence in one's ability to achieve goals) and lower levels of emotional distress, including depressive symptoms, compared to people with low fruit and vegetable intake.[195] However, the direction of causality is difficult to interpret in these studies.

Healthy eating patterns have been associated with better mental health in adults.[196] In older adults, one study found a dietary pattern characterized by high consumption of saturated fats and sugars was associated with higher anxiety levels.[16] Adherence to a Mediterranean-type diet, which emphasizes fruits, vegetables, whole grains, olive oil, nuts and seeds, and legumes, was associated in one study with lower risk of anxiety disorders and better mood overall. An analysis of the results of this study showed that fruits and vegetables were the dietary component most closely associated with reduced odds of depression, anxiety, and psychological distress.[197] An open trial in older subjects living independently in elder-care communities showed closer adherence to a six-month program of Mediterranean diet combined with exercise regimen reduced anxiety and depression and improved some aspects of cognitive function.[198]

Coffee drinking is associated with positive mood, healthy cognitive function, and overall well-being in most people.[199] However, too much caffeine may increase anxiety and sleep disruption, especially in sensitive individuals.[200] The benefits and risks of caffeine consumption therefore need to be considered on an individual basis in people with anxiety disorders.

Some, but not all, research suggests individuals with celiac disease may experience higher rates of anxiety disorders; while adopting a gluten-free diet may reduce anxiety symptoms for some with celiac disease, others may suffer from an increased sense of isolation and frustration brought on by the complexities of the diet.[201,202] Current evidence does not support the usefulness of a gluten-free diet for reducing anxiety in those without known celiac disease. More information is available in our **Celiac Disease and Non-Celiac Gluten Sensitivity** protocol.

Exercise

The protective and therapeutic effects of **exercise and physical activity** on anxiety disorders have been consistently demonstrated in numerous studies.[203,204] In addition, exercise improves physical health and may help reduce the risk of cardiovascular problems associated with anxiety disorders, including high blood pressure and early mortality.[205] One review noted high-intensity aerobic exercise programs have been found to be more effective than low-intensity programs at reducing anxiety, although the authors caution that exercise regimens should be carefully tailored to each individual's needs to reduce the risk of dropping out.[206]

Sleep

Sleep disturbance and insomnia is a common feature of anxiety disorders across the lifespan, and the relationship between sleep and anxiety may be bi-directional.[207-209] In fact, sleep disruption is one of the diagnostic criteria for multiple mood disorders including generalized anxiety disorder, and preclinical studies show disruption of circadian rhythms (day-night wake-sleep cycles) cause anxiety-like responses.[210] Poor sleep can promote or reinforce dysfunctional thought patterns and dysregulation of emotions.[211,212] This underscores the importance of identifying and treating underlying causes of sleep disturbance, such as restless leg syndrome.[213]

Good sleep hygiene has been shown to result in less anxiety and better overall physical and mental health, while poor sleep hygiene worsens insomnia and can reduce sleep quality. Sleep hygiene includes maintaining a consistent sleep-wake schedule; limiting eating, drinking, screen time, and stimulating activity before bed; limiting non-sleeping time in bed; and refraining from napping. Incorporating relaxation practices and cognitive therapies may also help promote sleep.[17,214] Individualized approaches to sleep support are likely to lead to the best outcomes.[215]

Relaxation

Meditation and relaxation have unique effects on mood, and may be a useful complement to other strategies for reducing symptoms in patients with anxiety disorders. A meta-analysis of 16 randomized controlled trials using relaxation therapies to treat anxiety disorders found these therapies can reduce depression, fear, and worry in individuals with anxiety disorders.[18] Meditation, stress reduction, and mindfulness-based cognitive therapy have been found in multiple studies to be beneficial in improving mood and reducing anxiety symptoms in subjects with anxiety disorders. These therapies emphasize calming the mind and directing one's attention to the experience of the present moment.[216-218] Yoga may also be a beneficial part of a holistic approach to treating anxiety disorders.[216]

Outdoor Activity and Exposure to Nature

Anxiety is more common in people living in urban centers, and a growing body of evidence suggests this may not be a coincidence.[219,220] Brain imaging studies suggest city living impacts the brain's processing of social information and stress, and is associated with activation of the brain's amygdala.[220] Nighttime lighting and activities that characterize city life may also disturb normal circadian cycles and cause dysfunctional stress signaling.[221] Other environmental factors, such as industrial activity and traffic, have been correlated with increased emotional distress.[222]

Access to natural environments, especially those with substantial tree canopy or bodies of water, has been linked to lower rates of anxiety and depression.[222,223] In one study, European urbanites reported mood improvement after just 10 minutes of exposure to natural outdoor environments.[224] Gardening, even in the context of a city environment, has been linked in multiple studies to positive effects on overall health, increasing mental, physical, and social wellbeing.[225]

L-theanine

L-theanine is an amino acid found in green and black tea that, when ingested, readily crosses the blood-brain barrier.[226] L-theanine has well-documented relaxing effects, and has been found to reduce symptoms of stress and anxiety and improve some aspects of cognition.[226,227] It appears to have complex effects on brain chemistry, with some studies suggesting it increases levels of GABA, modulates dopamine and serotonin levels, affects the function of NMDA glutamate receptors involved in nerve excitement, and increases levels of brain-derived neurotrophic factor, a protein that stimulates nerve growth and inter-neuron connections.[226,228-230]

A controlled trial in 30 healthy volunteers found 200 mg L-theanine daily for four weeks improved stress-induced anxiety, depression, and sleep problems, and enhanced cognitive performance.[231] Students consuming low caffeine green tea containing about 15 mg L-theanine per day for one week before and 10 days during a challenge experienced less perceived stress and activation of the stress response compared with placebo.[232] In a placebo-controlled trial in 46 patients with generalized anxiety disorder, the addition of L-theanine, at doses of 450–900 mg per day, to antidepressant therapy for eight weeks improved sleep satisfaction and reduced severity of insomnia in those with mild sleep-related symptoms.[233] L-theanine has also been found to reduce symptoms of anxiety in patients with major depressive disorder and schizophrenia.[234,235] A systematic review of findings from nine controlled trials concluded L-theanine, at doses of 200–400 mg per day, can help reduce stress and anxiety in people experiencing stressful conditions.[236]

Lemon Balm

Lemon balm (*Melissa officinalis*) is a member of the mint plant family used historically to treat anxiety, depression, and cognitive problems.[237] In an open clinical trial, 20 subjects with high perceived stress levels and mild-to-moderate anxiety and sleep disturbance were treated with two 300 mg doses of lemon balm extract per day for 15 days; at the end of the study, 70% of participants experienced alleviation of anxiety symptoms, 85% experienced remission of sleep symptoms, and 70% experienced recovery from both anxiety and sleep problems.[238] Placebo-controlled trials have shown lemon balm can effectively reduce anxiety in patients with heart palpitations and angina.[239,240] Another trial that included 100 adolescent girls with premenstrual syndrome found 600 mg lemon balm daily for three months reduced anxiety and sleep difficulty and improved social functioning more effectively than placebo.[241]

Saffron

Saffron (*Crocus sativus*) is a flowering plant best known for its culinary use and distinctive color. Saffron extracts have been reported in multiple clinical trials and reviews to reduce anxiety and depression symptoms and improve mental health, and have demonstrated efficacy comparable to that of currently used antidepressants.[242-246] In one placebo-controlled trial that included 60 participants with anxiety and depression, 50 mg saffron daily for 12 weeks reduced scores on tests assessing anxiety and depression symptoms.[247] In another trial, patients with type 2 diabetes who also had mild-to-moderate symptoms of anxiety and depression received either 30 mg saffron extract or placebo daily for eight weeks. At the end of the trial, those receiving saffron had greater reduction in symptoms and improvement in sleep.[248] Promising effects have also been reported from trials using combinations of saffron with other herbal extracts, including rhodiola and turmeric extracts.[249,250]

Probiotics

It has by now been well established that the gut microbiome has a profound effect on brain function and an essential role in regulating mood.[251] A growing body of evidence supports the use of probiotics in treating mood disorders, leading some to use the term “psychobiotics” to describe these beneficial microbes.[252-254] Several controlled trials have shown probiotic supplements containing *Lactobacillus* and *Bifidobacterium* strains improve anxiety, including stress-induced anxiety.[255] In a placebo-controlled trial in 66 healthy participants, the probiotic combination *L. helveticus* R0052 and *B. longum* R0175, at a dose of 3 billion colony forming units (CFUs) daily for 30 days, reduced measures of anxiety and depression.[256] A second analysis of the data from that study revealed this probiotic formula lowered perceived stress and symptoms of anxiety and depression even in those with the lowest stress level (as determined by urinary cortisol), suggesting it may have mental health-protective properties in healthy people.[257] In a placebo-controlled trial, 12 weeks of supplementing with a mixed-species

probiotic, providing a total of 135 billion CFUs per day, led to reductions in scores on anxiety tests in those with a genetic pattern believed to potentially be associated with increased risk for mood disorders.[258] Healthy adults with moderate stress levels who were given 1 billion CFUs of *L. plantarum* DR7 per day for 12 weeks experienced reductions in stress and anxiety, and had decreased inflammatory cytokine and stress hormone levels compared with those receiving placebo.[259] In a randomized controlled trial in healthy college students, probiotics reduced symptoms of anxiety and were more effective in students with higher baseline distress scores.[260] Another trial found taking a heat-inactivated *L. gasseri* supplement providing 10 billion bacterial cells per day for 24 weeks reduced anxiety symptoms and improved sleep better than placebo in medical students preparing for exams.[261]

Omega-3 Fatty Acids

The omega-3 fatty acids found in fish, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are components of most cell membranes. DHA, which can be consumed directly or be synthesized in the body from EPA, is the predominant polyunsaturated fatty acid in nerve cells, and is vital to normal nervous system function. Omega-3 fatty acids have anti-inflammatory properties that, in the brain, may restrain activation of the stress response, and help blunt anxious and depressive symptoms.[146,262] A review and meta-analysis of controlled trials noted the evidence supports a role for omega-3 fatty acids, at a dose of 2,000 mg per day or more, in reducing anxiety in patients with various clinical disorders.[263]

Individuals with social anxiety disorder were found to have lower omega-3 fatty acid levels in their red blood cell membranes compared with healthy people,[264] and in a study in depressed patients, those with anxiety had lower blood plasma levels of EPA and DHA than those without anxiety.[265] A number of studies have found omega-3 fatty acid supplements can reduce anxiety symptoms. In one placebo-controlled trial that included 68 medical students, taking 2,085 mg EPA plus 348 mg DHA daily for 12 weeks resulted in a 20% reduction in anxiety symptoms, as well as decreased levels of an inflammatory marker.[266] In a placebo-controlled trial in subjects with major depressive disorder, those taking omega-3 fatty acids in addition to an SSRI had lower anxiety sensitivity and improved sleep and emotional regulation after 12 weeks compared with those taking an SSRI plus placebo.[267] Other randomized controlled trials have found supplementing with EPA plus DHA reduced anxiety symptoms in heart attack patients,[268] women with premenstrual syndrome,[269] and individuals with substance abuse histories.[270-272]

Multivitamins and B-Complex Vitamins

B vitamins are critical cofactors in many biochemical pathways throughout the body, including the synthesis of neurotransmitters. Low levels of B vitamins are known to cause neurological and psychological disorders.[273,274] In a study in older adults, poor vitamin B6 status was associated with increased anxiety symptoms.[275] Another study found that people seen in an emergency department for panic attack were more likely to have low vitamin B6 levels than healthy volunteers.[276]

A meta-analysis of controlled trials concluded that vitamin and mineral supplementation, and particularly B vitamin supplements, can lower perceived stress levels, reduce mild anxiety, and improve overall mood.[277] In healthy adults, weekly at-home assessments over 16 weeks showed those taking a multivitamin had reduced stress and anxiety compared with those receiving placebo.[278] A placebo-controlled trial that included 60 participants with depression found taking a methylated vitamin B complex supplement for 60 days reduced depression and anxiety, and improved quality of life measures.[279]

Magnesium

Magnesium has several functions that may contribute to its ability to ease feelings of stress and anxiety, including regulating HPA axis activity and reducing excitability of neurons.[280] Low magnesium status may be associated with an increased risk of anxiety, especially in women. One study in Iranian subjects found women with the highest magnesium intake had a 39% reduced risk of anxiety compared to women with the lowest intake.[281] A controlled trial in 126 patients with mild-to-moderate depression found supplementing with magnesium chloride, providing 248 mg elemental magnesium per day, for six weeks led to decreased scores on scales measuring both depressive and anxious symptoms.[282] A systematic review of clinical trials found evidence suggesting magnesium, alone or in combination with vitamin B6 or herbal extracts, may reduce anxiety symptoms in individuals with mild-to-moderate anxiety, premenstrual syndrome, or high blood pressure.[283] Magnesium L-

threonate, an amino acid-bound form of magnesium, has been found to be particularly effective for raising brain magnesium levels, promoting neuroplasticity, and quelling fear responsiveness in animal models of anxiety.[284,285]

In an unpublished clinical study including 19 women with symptoms related to premenstrual syndrome and who consumed inadequate dietary magnesium, supplementation with magnesium acetyl taurate (770 mg/day, providing approximately 45 mg elemental magnesium) decreased some mood-related symptoms including anxiety, nervous tension, irritability, headache, fatigue, and depression.[355]

L-tryptophan and 5-Hydroxytryptophan (5-HTP)

L-tryptophan is an essential amino acid and precursor for serotonin production in the intestines and brain.[286] It is thought to play an important role in the communication between the gut and brain.[287] In healthy adults under acute stress, L-tryptophan conversion into serotonin has been shown to become less efficient.[288]

L-tryptophan has been used for decades to raise serotonin levels in order to improve mood and sleep.[289] A systematic review of findings from 11 controlled trials found L-tryptophan, in doses up to 3 grams daily, can decrease anxiety and increase positive mood in healthy individuals.[290]

5-hydroxytryptophan (5-HTP) is the immediate precursor of serotonin. It has been studied mainly for its antidepressant effects,[291] but some research suggests 5-HTP may also be helpful in anxiety disorders. In a placebo-controlled trial, patients with panic disorder had less reaction to a panic-inducing stimulus after taking 200 mg 5-HTP.[292] Beneficial effects of 5-HTP in subjects with panic and other anxiety disorders have also been reported.[293,294] In addition, 5-HTP, at doses of 200–400 mg per day, has been found to reduce anxiety symptoms in patients with fibromyalgia syndrome.[295,296] Most studies of 5-HTP in the context of psychiatric disorders are of questionable quality, making further rigorous research necessary.[297]

Melatonin

Melatonin is a hormone produced in the brain that participates in regulation of circadian rhythms and has influence on mood, pain, and sleep.[298] Preclinical studies have shown melatonin receptors are involved in mechanisms that underlie anxiety, depression, and sleep disorders.[299]

Abundant and conclusive evidence shows melatonin is helpful in promoting sleep, and holds great promise for a range of mental, neurological, and physical conditions.[300-302] Melatonin has been found in multiple placebo-controlled trials to reduce pre- and postoperative anxiety.[300,303] Based on evidence that melatonin and melatonin receptors play an important role in anxiety, a melatonin-like drug, agomelatine, has been proposed as an emerging therapy for anxiety disorders (see section on Novel and Emerging Therapies).

N-Acetyl Cysteine

N-acetyl cysteine (NAC) is a precursor to the amino acid cysteine, an amino acid component of one of the body's major antioxidants, glutathione. It also has inherent free radical quenching capacity and anti-inflammatory properties.[146]

A placebo-controlled trial in veterans with post-traumatic stress disorder and substance use disorder, both of which involve anxiety, found taking 2,400 mg NAC per day along with cognitive behavioral therapy for eight weeks reduced psychological symptoms and cravings; many of these effects were still evident one month after treatment ended.[304] Several trials have also noted NAC use is associated with reduced obsessive and compulsive behaviors in patients with obsessive-compulsive disorder and related conditions, which have a substantial anxiety component.[305,306] In addition, controlled trials have shown NAC reduced depressive symptoms in individuals with a range of mood disorders.[307]

Lavender

Lavender (*Lavandula angustifolia*) is a plant in the mint family known for its characteristic fragrance. Lavender is approved in Europe for use as a botanical remedy for anxiety and stress, and its essential oil is used in aromatherapy for the same conditions. It appears to work by activating the parasympathetic nervous system to promote relaxation, affecting serotonin signaling, and decreasing nerve excitability.[308,309] Aromatherapy applications of lavender are likely to be more effective for immediate symptom relief, but oral lavender preparations appear to have better efficacy in long-term therapy.[310]

A meta-analysis of randomized controlled trials found that lavender aromatherapy reduces anxiety, decreases systolic blood pressure, lowers heart rate, and reduces salivary cortisol levels (a measure of an activated stress response).[311] Its positive effects on anxiety symptoms have been demonstrated in diverse settings including during cancer care, in intensive care, and around the time of dental or other surgeries, as well as in healthy volunteers. Despite these findings, better quality trials of lavender for anxiety are still needed.[312-314] Both aromatherapy and supplementation with lavender preparations were found in a review of four clinical trials to improve sleep difficulties and other menopausal symptoms in menopausal and older women.[315] In a controlled trial with 60 elderly participants, drinking lavender tea twice daily for two weeks reduced symptoms of anxiety and depression.[316] Using tea may incorporate both aromatherapy and internal medicinal actions of lavender.

Silexan is a standardized lavender flower essential oil product currently approved in Germany for the treatment of anxiety-related restlessness. Numerous clinical trials have investigated the effects of silexan in individuals with anxiety disorders, subclinical anxiety, and anxiety-related symptoms such as difficulty sleeping.[317] Findings from one clinical trial suggest its ability to promote sleep is related to its anti-anxiety effects rather than sedative effects.[318] A meta-analysis of five randomized controlled trials in which 645 patients with anxiety disorders were treated with silexan for 9–12 weeks found 80 mg silexan per day was as effective, and 160 mg per day was more effective, than a standard SSRI (paroxetine) at reducing symptoms.[317] Another meta-analysis included three randomized controlled trials in which 697 patients with anxiety below the diagnostic threshold for anxiety disorder were treated with 80 mg silexan per day for 10 weeks; treatment was found to be more effective at reducing anxiety and improving sleep than placebo.[319]

Passionflower

Passionflower (*Passiflora incarnata*), an important herb in western European herbal medicine, has been used traditionally to treat anxiety, sleep disturbance, and restlessness.[320,321] It has a mild sedative action related to its ability to enhance GABA signaling.[322]

In a randomized controlled trial that compared passionflower to a benzodiazepine (oxazepam [Serax]) in 36 patients with generalized anxiety disorder, both treatments were found to reduce anxiety symptoms; however, while oxazepam had a faster onset of action, it also had a greater negative impact on job performance.[323] Passionflower has also been found to be as effective as the benzodiazepine drug midazolam (Versed) at relieving anxiety prior to dental surgery.[324] Other controlled trials have found passionflower can reduce anxiety prior to other types of surgery.[325-327] Passionflower tea at bedtime was found in one controlled trial to be more effective than placebo for improving sleep in subjects with mild sleep disturbance.[328]

Valerian

Valerian (*Valeriana officinalis*) is a medicinal plant that has long been used as a mild sedative for restlessness and anxiety. Active compounds from valerian appear to exert relaxing effects by interacting with GABA receptors.[329]

In a placebo-controlled trial in 31 patients with obsessive-compulsive disorder, 765 mg valerian extract per day for eight weeks effectively improved symptoms.[330] A single 1,500 mg dose of valerian extract was also found to reduce anxiety in women about to undergo an invasive gynecologic diagnostic procedure.[331] Several additional studies have concluded that valerian provides modest anxiolytic and relaxing effects in varying settings.[332-335]

Gamma Aminobutyric Acid

In the nervous system, GABA is a neurotransmitter that functions as the primary inhibitor of nerve signal transmission. Benzodiazepines, which are sometimes used to treat anxiety and stress-related disorders, target certain GABA receptors.[336]

In a clinical study, oral GABA supplementation was found to increase alpha wave activity and reduce beta wave activity in the brains of healthy volunteers within one hour, indicating that GABA induces relaxation and decreases anxiety.[337] A placebo-controlled trial in 63 adults found 100 mg GABA taken 30 minutes before a mental task reduced stress-related changes in brain activity.[338] In a randomized controlled trial in 10 healthy subjects with mild sleep problems, 100 mg GABA taken 30 minutes before bed for one week shortened time needed to fall asleep and improved sleep quality compared with placebo.[339] Since sleep problems, stress, and anxiety frequently occur

together, GABA may be beneficial in treating this group of conditions.

L-lysine and L-arginine

In animal models, the essential amino acid L-lysine has been shown to interact with serotonin and GABA receptors and, alone or in combination with L-arginine, ameliorate anxiety.[340,341] Another potential mechanism of action for lysine's anxiolytic properties is a reduction in cortisol and nervous tone. In a randomized controlled study, fortifying wheat with L-lysine resulted in decreased chronic anxiety in men and a reduced cortisol response to a stressful event in women.[342] In another randomized controlled trial, 29 healthy individuals with anxious personalities were treated with 3 grams each of L-lysine and L-arginine for 10 days, and then exposed to a social stressor. Stress hormone levels improved, as did the participants' ability to manage the stress.[343] In a placebo-controlled trial that enrolled 107 healthy volunteers, taking 2.64 grams per day each of L-lysine and L-arginine for one week led to decreased stress-induced anxiety and reduced anxiety overall in both men and women. The amino acid combination also lowered markers of physiologic stress.[341]

Kava

Kava (*Piper methysticum*) is a plant in the black pepper family that is native to the South Pacific where it has been used for centuries as a relaxant. Kava appears to target the amygdala and other brain regions involved in fear and worry, and may promote relaxation by altering neurotransmitter signaling.[344] Several meta-analyses of controlled trials found kava effectively and safely reduced symptoms of anxiety when used for up to 24 weeks.[344-347] One review of clinical trials found, in patients with generalized anxiety disorder, kava extract providing 120–280 mg per day of kavalactones (bioactive compounds from kava) for four to eight weeks is safe and may decrease symptoms.[348]

Note: Kava use has, in rare cases, been associated with serious adverse side effects including skin reactions, cognitive problems, and liver damage, and its use should be carefully monitored.[349,350]

Other Herbal Therapies

A number of medicinal herbs are valued for their relaxing effects on the nervous system. In a placebo-controlled trial, one herbal medicine containing extracts from hawthorn (*Crataegus oxyacantha*) and California poppy (*Eschscholzia californica*) along with magnesium was found to benefit individuals with generalized anxiety of mild-to-moderate severity.[351] Galphimia (*Galphimia glauca*) is a Mexican herb used traditionally to treat anxiety and depression as well as a range of other conditions. Three animal trials have confirmed the anxiolytic effect of the constituent galphimines and related compounds. Three randomized controlled clinical trials compared galphimia extracts to anxiety medications, an SSRI or a benzodiazepine. All three trials reported that galphimia's effects were equal or superior to the prescription medications.[352,353] Extracts from herbs such as chamomile (*Matricaria recutita*), linden flower (eg, *Tilia cordata*), hops (*Humulus lupulus*), peppermint (*Mentha piperita*), black cohosh (*Cimicifuga racemosa*), lemon verbena (*Aloysia citriodora*), and chasteberry (*Vitex agnus-castus*) may be helpful in treating anxiety and related symptoms.[22,23,354]

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