Anxiety Disorders

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for health and mental health providers involved in the identification, treatment, and care of patients with anxiety disorder.

Accreditations & Approvals

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A complete Works Cited list begins on page 70.

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Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to appropriately identify and treat patients with anxiety disorders, addressing knowledge gaps, enhancing clinical skills, and improving patient outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Review basic concepts related to anxiety disorders, including safety behaviors/signals and primary features.
2. Outline the epidemiology of anxiety disorders in the United States.
3. Describe general risk factors for and comorbidities of anxiety disorders.
4. Describe risk factors for and the clinical course of specific anxiety disorders.
5. Discuss the pathogenesis of anxiety disorders in relation to contributing genetic, physiologic, and psychologic factors.
6. Review the pathophysiology of specific anxiety disorders, including social anxiety disorder, agoraphobia, and specific phobia.
7. Evaluate the clinical and diagnostic criteria for anxiety disorders presented in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5).
8. Analyze key components of screening for anxiety disorders.
9. List conditions to consider in the differential diagnosis of anxiety disorders.
10. Describe general treatment considerations for anxiety disorders, including predictors of response or nonresponse to therapy.
11. Discuss the role of various psychotherapy approaches in the treatment of anxiety disorders.
12. Outline pharmacotherapy options for the treatment of anxiety disorders.
13. Recognize clinical issues related to the treatment of anxiety disorders.
14. Compare and contrast the treatment recommendations for specific anxiety disorders.
15. Analyze the evidence base supporting the efficacy of novel, emerging, and alternative/complementary approaches to the treatment of anxiety disorders.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Anxiety disorders are characterized by states of chronic, excessive dread or fear of everyday situations. The fear and avoidance can be life-impairing and disabling. Anxiety disorders result from the interaction of biopsychosocial factors, whereby genetic vulnerability interacts with situations, stress, or trauma to produce clinically significant syndromes. The influence of hereditary factors and adverse psychosocial experiences on pathogenesis and pathophysiology is complex, but neuroscience advances have greatly improved the understanding of the underlying factors in the development and maintenance of anxiety disorders.

BACKGROUND

SAFETY BEHAVIORS AND SIGNALS

Safety behaviors are coping tactics by persons with anxiety disorders, especially panic disorder, agoraphobia, and social anxiety disorder, to temporarily diminish feelings of threat and reduce one's anxiety level. Safety behaviors can emerge in response to an external (e.g., situations, persons, activities) or internal (e.g., thoughts, emotions, memories) focus of perceived threat and are anticipatory (avoidant) or consequential (escape) [1].

Safety signals are the people or objects used by patients with anxiety disorders to diminish distress in situations that elicit anxiety. Safety signals maintain anxiety over time by preventing direct confrontation of feared stimuli in the absence of "safe" objects/people and by maintaining perceptions of risk/harm and coping inability. Patient use of safety signals can interfere with therapy progress, especially exposure therapy, and are considered antitherapeutic. However, safety behaviors may be helpful early in treatment by making exposure therapy more tolerable and less threatening [1].

PRIMARY FEATURES OF ANXIETY AND RELATED DISORDERS

The distinguishing features of specific anxiety disorders are summarized in the following section. Related conditions of post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are included because, although no longer classed as anxiety disorders by the 2013 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), they are often included in research that pre-dates 2013 and can co-occur with anxiety disorders [2]. Situations or objects that evoke intense anxiety in patients with agoraphobia, social anxiety disorder, or specific phobia are either avoided or endured with significant personal distress.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive and inappropriate worrying that is persistent (lasting more than a few months) and not restricted to particular circumstances [3]. Patients with GAD have physical anxiety symptoms and key psychologic symptoms (i.e., restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and disturbed sleep). GAD is often comorbid with major depression, panic disorder, phobic anxiety disorders, health anxiety, and OCD [3].

Panic Disorder

Panic disorder is characterized by recurrent unexpected surges of severe anxiety ("panic attacks"), with varying degrees of anticipatory anxiety between attacks [3]. Panic attacks are discrete periods of intense fear and discomfort accompanied by multiple physical and/or psychologic anxiety symptoms. These attacks typically peak within 10 minutes and last around 30 to 45 minutes. Most patients also develop a fear of having further panic attacks [3].

Agoraphobia

Around two-thirds of patients with panic disorder develop agoraphobia, defined as fear of having panic attacks in places or situations from which escape might be difficult or where help might not be available [3]. These places or situations can include crowds, outside of the home, or using public transport [2].

Social Anxiety Disorder

Social anxiety disorder (SAD) is characterized by a marked, persistent, and unreasonable fear of being negatively evaluated by others [3]. It is associated with physical and psychologic anxiety symptoms.

Specific Phobia

Specific, simple, or isolated phobia is the excessive or unreasonable fear of (and restricted to) animals, objects, or specific situations (e.g., dentists, spiders, elevators, flying, seeing blood) [3].

Separation Anxiety Disorder

Adult separation anxiety disorder (SEPAD) is characterized by fear or anxiety concerning separation from those to whom an individual is attached. Common features include excessive distress when experiencing or anticipating separation from home and persistent and excessive worries about potential harms to attachment figures or untoward events that might result in separation [3].

Post-Traumatic Stress Disorder

PTSD is characterized by exposure to actual or threatened death, serious injury, or threats to the physical integrity of self or others (the trauma) with development and persistence of intrusive symptoms (e.g., recollections, flashbacks, dreams), avoidance symptoms (e.g., efforts to avoid activities or thoughts associated with the trauma), negative alterations in cognitions and mood, and hyper-arousal symptoms (e.g., disturbed sleep, hypervigilance, exaggerated startle response) [2].

Obsessive-Compulsive Disorder

OCD is characterized by recurrent obsessive ruminations, images, or impulses and/or recurrent physical or mental rituals. These obsessions are distressing and time-consuming, causing interference with social and occupational function. Common obsessions relate to contamination, accidents, and religious or sexual matters; common rituals include washing, checking, cleaning, counting, and touching [3].

Illness Anxiety Disorder

Illness anxiety disorder is a somatic-symptom related disorder characterized by excessive or disproportionate preoccupations with having or acquiring a serious illness. This includes excessive health-related behaviors and high levels of alarm about personal health status [3].

OVERALL PREVALENCE, RISK FACTORS, AND CLINICAL COURSE

Each year in the United States, anxiety disorders (DSM-5 plus PTSD and OCD) impact approximately 42 million adults, or 19% of the population [4; 5]. The pattern of sex distribution is consistent among anxiety disorders, and the overall female-to-male ratio is approximately 2:1 across all age ranges [6].

PAST YEAR AND LIFETIME PREVALENCE

Data on anxiety disorders in the United States reported 12-month prevalence, lifetime prevalence, and lifetime morbid risk (***Table 1***). The two lifetime measures differ. Lifetime prevalence measures the proportion currently or previously diagnosed with the disorder, while lifetime morbid risk measures the proportion who will develop the disorder at some point, whether or not they have a lifetime history at the time of assessment. By including future cases, lifetime morbid risk is believed to be more accurate.

COMPARISON OF PREVALENCE, MORBID RISK, AND RATIO OF LIFETIME PREVALENCE TO MORBID RISK FOR ANXIETY DISORDERS				
Anxiety Disorder	**12-month**	**Lifetime**	**Lifetime Morbid Risk**	**Lifetime/Lifetime Morbid Risk**
Generalized anxiety disorder	2.0%	4.3%	9.0%	0.5
Panic disorder	2.4%	3.8%	6.8%	0.5
Agoraphobia	1.7%	2.5%	3.7%	0.7
Social anxiety disorder	7.4%	10.7%	13.0%	0.8
Specific phobia	12.1%	15.6%	18.4%	0.8
Separation anxiety disorder	1.2%	6.7%	8.7%	0.8
Source: [7]				*Table 1*

Lifetime prevalence and lifetime morbid risk are usually equivalent for disorders with early-life onset, but diverge for disorders with increasingly later onset. The ratio of lifetime prevalence to lifetime morbidity risk falls below 1.0 in disorders with increasingly later onset; the further the ratio values fall below 1.0, the later the median age of onset [7].

Anxiety disorders with earlier median age of onset are phobias and separation anxiety disorder (15 to 17 years of age), and those with latest age of onset are panic disorder and generalized anxiety disorder (23 to 30 years of age). Lifetime morbid risk is considerably higher than lifetime prevalence for most anxiety disorders, with magnitude of difference much higher for disorders with later than earlier age of onset. Also, the ratio of 12-month to lifetime prevalence roughly reflects persistence, but varies meaningfully in ways consistent with differential persistence of these disorders [7].

OVERALL RISK FACTORS

Demographic

The odds for a lifetime diagnosis of any anxiety disorder were calculated, and the same pattern was found for past 12 month diagnosis [8]. These odds are organized according to sex, socioeconomic status, education level, and age. Overall, the risk of developing an anxiety disorder is greater for women/girls than men/boys.

Persons with lower incomes also experience increased odds versus those with higher incomes (48% increased risk with $35,000 to $69,000; 52% with $20,000 to $34,000; 100% with $19,000 or less). Lower educational attainment is a risk factor. Compared with college graduates, the odds of developing an anxiety disorder are increased 44% with 13 to 15 years of education, 76% with 12 years of education, and 86% with 0 to 11 years of education. These disorders are also 40% more likely in persons 15 to 24 years of age compared with older adults (45 to 54 years of age) [8].

Temperament

Behavioral inhibition is defined as the tendency for timid and shy responses to novel situations, and it is highly associated with temperament factors of neuroticism and introversion. Anxiety disorders are associated with behavioral inhibition in childhood, and behavioral inhibition is an identifiable early childhood predictor of later anxiety disorders. Introversion and behavioral inhibition are also strongly linked to later development and severity of situational avoidance, which is a core feature and risk factor in agoraphobia and SAD [9].

CLINICAL COURSE

Anxiety disorders in aggregate show a U-shaped age of onset—higher in childhood and young adulthood and lower in adolescence. The greatest concentration occurs during transition to early adulthood. Unlike biologically driven pubertal transitions, adulthood transitions involve distinct psychosocial events (e.g., independent living, full-time employment), and this represents a key period for understanding the development of adult anxiety disorders such as panic disorder and agoraphobia [10].

Community studies of persons with sub-diagnostic anxiety symptoms over time often show episodic symptoms and prolonged periods of remission, with symptoms reappearing or worsening during adverse life events and psychosocial stressors. In contrast, studies of clinical anxiety disorder populations typically show a chronic course with fluctuating symptom severity between periods of remission and relapse, with long-term course varying by disorder [3].

Healthcare Utilization

Distressing anxiety symptoms can spur patients to initiate primary care contact. If anxiety is unrecognized, costly medical tests may be performed. Recognizing a pattern of subjective worry or anxiety with accompanying physical signs can help healthcare providers avoid costly diagnostic tests but still consider possible medical causes of anxiety. Effective treatment with pharmacotherapy or cognitive-behavioral therapy (CBT) should reduce symptoms and healthcare seeking [2; 3].

COMORBID DEPRESSION

Anxiety symptoms often co-occur with other psychologic symptoms. Depressive symptoms are highly prevalent with more severe anxiety symptoms, with anxiety and depressive symptom severity strongly correlated. Patients with anxiety disorder have high comorbidity rates of major depressive disorder (almost 50%), schizophrenia, substance use disorders, and physical illness [3; 11]. Overlapping symptoms of anxiety and depression, such as sleep disturbance, fatigue, and difficulty concentrating, make differentiation challenging. Depressive disorders are sometimes termed "anxious-misery" when high levels of sadness and anhedonia are present [2].

SPECIFIC DISORDERS

Generalized Anxiety Disorder

Epidemiology

Studies in the United States on GAD prevalence rates have found a 5.1% lifetime rate and a 2.0% to 3.1% past-year rate. The lifetime and past-year prevalences are 3.6% and 2.0% in men/boys and 6.6% and 4.3% in women/girls. The majority of persons with GAD diagnoses are female. Childhood or adolescent onset was found in more than 50% of those seeking help for anxiety, reflecting the chronicity of the disease [2].

Risk Factors

No single etiology has been identified for GAD, but it likely involves the interaction of multiple familial/genetic and environmental risk factors. A review of twin and family studies found significant associations between GAD, other anxiety disorders, and depression, suggesting a common underlying genetic basis. A significant number of patients and their first-degree relatives develop GAD (odds ratio 6:1) [12]. Civilian trauma (e.g., motor vehicle accidents, physical or sexual assault, sudden unexpected loss of a loved one, bullying or peer victimization in childhood or adolescence) is a risk factor for GAD [13]. The presence of another anxiety disorder (e.g., panic disorder, SAD, specific phobia) is another possible factor. Panic disorder is comorbid in 25% of patients with GAD [13].

Late-onset GAD (on or after 65 years of age) is very uncommon. The primary predictors include female sex, recent adverse life events, and chronic physical (e.g., respiratory and cardiac disorders, dyslipidemia, cognitive impairment) or mental health (e.g., depression, phobia, past GAD) disorders. Other risk factors include poverty, parental loss/separation or

low emotional support during childhood, and history of parental mental health problems. Late-onset GAD is described as a multifactorial, stress-related affective disorder resulting from proximal and distal risk factors of which some are potentially modifiable by healthcare intervention [14].

Clinical Course

The course of GAD tends to be chronic in primary care patients, and GAD may "switch" to other diagnoses, particularly depression and somatoform disorders [15; 16]. GAD is associated with impairments in psychosocial functioning, role functioning, work productivity, and health-related quality of life comparable to major depressive disorder or panic disorder. Patients with GAD and comorbid major depression show significantly greater impairment in health-related quality of life than in either disorder alone. Primary care patients with GAD showed significantly higher annual medical costs than patients without GAD (median $2,375 versus $1,448) and higher mean annual medical costs ($2,138) than patients with other anxiety disorders. GAD is frequently under-recognized in primary care, and only 20% to 32% of patients receive adequate treatment. Suboptimal treatment adds to the health-related quality of life burden of this disorder [17].

Panic Disorder

Epidemiology

In the United States, 4% to 28% of the population experience panic attacks at some time during their life. The 2.4% annual incidence of panic disorder in the United States is one of the highest prevalence rates worldwide [7; 18].

Panic disorder prevalence in primary care is approximately 7%, and substantially higher in patients presenting with cardiac or gastrointestinal symptoms. Relative to white patients, the odds of developing panic attacks and panic disorder are higher in Native Americans, and lower in Asian, Hispanic, and black patients [18; 19].

Panic attacks are most likely to develop in patients who are in their mid-20s and slightly earlier in men than women. Panic disorder age of onset is usually between late adolescence and 35 years of age, while the age of onset for panic disorder with agoraphobia spans the early 20s to early 30s. Panic disorder is more common among women, with a 2:1 ratio and increasing to 3:1 with panic disorder with agoraphobia. Panic symptoms during adolescence elevate risks for other anxiety and mood disorders in adulthood. Depressive disorders are highly comorbid (33% to 85%), especially among those with agoraphobia [2; 20]. Panic disorder is highly comorbid with other anxiety, mood, and substance use disorders, including nicotine dependence, and cigarette smoking may increase the risk for later-onset panic disorder [21].

Risk Factors

As with GAD, the etiology of panic disorder probably results from a combination of risk factors. There is a five-fold greater risk of developing panic disorder when the disorder is present in first-degree relatives. Shared genetic factors account for 30% to 40% of panic disorder heritability [12]. In addition, major adverse life events precede the onset of panic attacks in roughly 80% of patients. Trauma history is prevalent in patients with panic disorder, especially women [22].

Behavioral inhibition may contribute to panic risk in adulthood. Learned escape and avoidance behaviors can maintain the condition and worsen functional impairment over time. Anxiety sensitivity, or the tendency to catastrophically misinterpret physical symptoms as dangerous, is a risk factor for panic disorder. Personality pathology, particularly avoidant and dependent personality traits, are predictors of panic disorder or agoraphobia development [23; 24].

Asthma severity is associated with an incremental risk for panic disorder, and respiratory variability may also increase risk for later onset panic disorder [25]. Baseline respiratory abnormalities are specific to panic disorder pathophysiology [6]. As noted,

cigarette smoking and nicotine dependence is disproportionately high among patients with panic disorder and may be temporally related to elevated risk for developing panic disorder [26]. Additionally, panic attacks may be related to poorer cessation outcome during smoking treatment among patients with cancer [27]. Caffeine use is also positively correlated with increased anxiety symptoms and risk of inducing panic attacks in patients with panic disorder [28].

Clinical Course

Prospective studies of panic disorder show high rates of symptom chronicity, relapse after remission, and "switching" to other diagnoses [29; 30]. Panic disorder symptoms remain persistent for 50% to 80% of cases even after treatment, increasing disability and impaired quality of life [31].

Agoraphobia

Epidemiology

Agoraphobia usually, but not always, occurs with panic disorder. In community populations, about 25% of those with panic disorder also have agoraphobia, but the proportion is substantially higher in clinical populations [20].

Agoraphobia was made an independent diagnostic entity in the DSM-5, and accordingly, epidemiologic and clinical data that consider agoraphobia in the absence of panic disorder are pending. In the DSM-IV-TR, panic disorder could be specified with or without agoraphobia. Lifetime and 12-month prevalence of panic disorder with agoraphobia were 1.0% and 0.5%, respectively [32].

Risk Factors

Much of the published agoraphobia research assumes panic disorder causation or comorbidity. As such, many of the known risk factors are the same. Comorbid panic disorder and agoraphobia aggregate in families, while agoraphobia without panic disorder is non-familial but may enhance familial transmission of panic disorder [33]. The risk of agoraphobia development in patients with panic disorder is elevated with female sex, more severe dizziness during panic attacks, cognitive factors, dependent personality traits, and SAD. Panic disorder with agoraphobia is associated with greater severity and worse prognosis [34].

Longitudinal studies show low remission rates (0% to 23%) over time in panic disorder or agoraphobia, and subjects with panic disorder with agoraphobia or agoraphobia with panic attacks at baseline were more likely to develop agoraphobia, panic attacks, and other anxiety disorders and experience greater severity (e.g., impairment, disability, treatment-seeking, comorbidity) than subjects with panic disorder without agoraphobia or agoraphobia without panic attacks at baseline [35].

A late-life subtype of agoraphobia (onset at or after 65 years of age) was identified through assessing elderly patients at baseline and four years later. Baseline agoraphobia prevalence was 10.4%, and 11.2% developed agoraphobia during the four-year follow-up. Agoraphobia in the elderly, unlike younger populations, was not more common in women and not associated with panic attacks. Risk factors for late-onset agoraphobia were severe depression, trait anxiety, and poor visuo-spatial memory [36]. Incident anxiety appears to be a response to subjective memory complaints independent of depressive symptoms [37].

Patients with panic disorder who experience their first panic attack driving or using public transportation had higher rates of comorbid agoraphobia. Those with first panic attack at home had higher fear-of-dying rates than with first panic attack outside of the home and felt more severe distress from their first panic attack whether or not agoraphobia developed. Treatment of patients with panic disorder whose first panic attack was at home should address fear and distress elicited by the attack [38].

Clinical Course

In persons with panic disorder with or without agoraphobia, the strongest predictors of incidence and relapse were past history of panic attacks, GAD/major depression, nicotine dependence, female sex, younger age, and major financial crises. Most predictor variables were similar between panic disorder

and panic disorder with agoraphobia. Clinicians should understand the relapsing-remitting nature of panic disorder/panic disorder with agoraphobia in order to avoid prematurely reducing or eliminating effective treatments. Close attention should be paid to concurrent factors linked to relapse that can be clinically addressed, such as comorbid major depression, GAD, and nicotine dependence [39].

One study followed 711 participants with anxiety disorder diagnoses over 15 years. At baseline, those with early-onset (≤20 years of age) panic disorder were more likely to have comorbid major depressive disorder, GAD, and SAD. Those with early-onset panic disorder with agoraphobia were less likely to be married and more likely to have comorbid GAD and SAD. During follow-up, persons with panic disorder with agoraphobia were significantly more likely to have illness recurrence after periods of recovery, while findings for the other disorders failed to reach significance. This was thought to reflect differences in typical age of onset among anxiety disorders. The onset of panic disorder with or without agoraphobia is usually early adulthood; earlier onsets are relatively uncommon and may signal a particularly pernicious form of illness. The results further support the particularly adverse effects of early-onset psychiatric illness [40].

Social Anxiety Disorder

Epidemiology

SAD can develop at any time during a lifespan, but the average age of onset is during late childhood and adolescence. The prevalence of SAD in pre-adolescence is 3.5%, with rates increasing to about 14% during adolescence [41]. The incidence is as high as 7% in primary care settings [19]. Gender distribution is generally equal during pre-adolescence and becomes increasingly more common in girls/women through adolescence and adulthood. An estimated 70% to 80% of individuals with SAD have comorbid anxiety, mood, or substance use disorders. There are cultural variants in Asian and Eastern cultures that involve fears of offending others or making others uncomfortable [2].

Risk Factors

A combination of biologic, familial, environmental, and cultural risk factors contributes to the development of SAD. Transitions, losses, poverty, and experiences of humiliation or embarrassment may contribute to SAD risk [42]. Compared with data from the general population, first-degree relatives are up to six times more likely to be at risk of SAD. Concordance rates are 24% in monozygotic twins and 15% in dizygotic twins [43].

Behavioral inhibition, shyness, introversion, and anxiety sensitivity are all common among patients with SAD. Emerging early in life, behavioral inhibition is a heritable trait, and 15% to 20% of young children with behavior inhibition exhibit extreme signs. Relative to children without behavioral inhibition, these patients are typically shy, fearful, and cautious and show elevated physiologic arousal signs at resting, such as higher stable heart rate, increased pupil dilation, and higher cortisol levels. Brain profiles of children with behavioral inhibition show distinct patterns, including electroencephalography asymmetry, functional differences in amygdala response to faces, and structural differences in the ventral prefrontal cortex. Roughly 40% of children with behavioral inhibition develop SAD, and childhood behavioral inhibition is a primary predictor of SAD. Other components of SAD probably appear later in development, including social-evaluative concerns and coping skills deficits that contribute to functional impairment [44; 45].

A bi-directional relationship exists between parenting style and childhood anxiety. Parenting styles of criticism, over-protection, over-control, and lack of warmth can create insecure attachment and risk for SAD. Likewise, temperamentally introverted and anxious children may shape and change parenting styles, with parents becoming over-protective or over-controlling [42]. Studies suggest that challenging parenting behavior (especially in fathers) may play a protective role in anxiety development in the most vulnerable children [46; 47].

Early childhood anxiety disorders, especially separation anxiety and other phobias, are associated with elevated SAD risk in adulthood. SAD is highly comorbid with other anxiety disorders, mood disorders, and substance use disorders; substance abuse is often used to regulate anxiety symptoms and social skills [48].

Multiple social cues can develop the capacity to elicit anxiety-related symptoms. Learned escape and avoidance behaviors maintain anxiety, interfere with skill development, and can lead to functional impairment and disability over time. Similarly, safety behaviors, such as only entering social situations with a trusted companion, averting eye contact, and staying on the periphery of social gatherings, may maintain anxiety-related impairments. Selective attention to social cues of negative evaluation and internal cues supporting danger perception may develop [49; 50].

Primary Prevention

Childhood presence of fearfulness and behavioral inhibition can lead to chronic, disabling SAD. Early recognition of childhood impairments and evidence-based treatment intervention may offset the SAD trajectory of persisting into and through adulthood. Educational-behavioral interventions involving older children/adolescents, parents, school staff, and healthcare providers have been found to reduce the development of social anxiety [51; 52; 53].

Clinical Course

SAD tends to run a chronic course in primary and secondary care settings [54; 55].

Specific Phobia

Epidemiology

Women are two to three times more likely to develop phobias than men, with the exception of blood-injection-injury phobia, which is evenly distributed by sex. Roughly 70% of specific phobics report more than one clinically relevant fear. Animals and heights are the most common stimuli, followed by flying, enclosed spaces, and blood-injection-injury. The average age of onset is 7 to 10 years, with declining probabilities of onset into later adulthood. The majority of animal phobias develop before 8 years of age [2; 41; 56]. The average age of treatment engagement is 31 years, although only 8% of persons with specific phobia are reported to seek treatment [56].

The odds of developing phobias are significantly less in Hispanic and Asian individuals and greater in white individuals. Animal fears are prevalent in Japan and Hong Kong [56; 57].

Risk Factors

For specific phobias, familial concordance rates among first-degree relatives are moderate. The greatest heritability indices are found in animal and blood-injection-injury phobias [58; 59; 60].

Intense anxiety or unexpected panic responses in the presence of specific objects or situations can mark phobia onset but are not the sole causal route. Disgust, either alone or combined with fear, may trigger the onset and maintenance of animal (particularly spiders, snakes, and worms) or blood-injection-injury phobias. Onset can occur indirectly by observing others reacting fearfully. Some stimuli are more likely to induce phobias than others (e.g., animals vs. electrical outlets) through evolutionary threat relevance.

Phobia onset can be precipitated by relationship problems, relocation, employment loss, or economic difficulties. In addition, anxiety, mood, or substance use disorders can co-occur with or predate phobia onset. Substance use disorder can maintain phobic symptoms. Phobia symptoms in adolescence predict adult symptoms but are not a risk factor for developing other anxiety, mood, or substance use disorders.

Adult Separation Anxiety Disorder

Epidemiology

The lifetime prevalence of adult SEPAD is 6.6% in the general population, 12% to 40% in psychiatric clinic settings, and more than 75% among those seeking treatment at anxiety disorder clinics [61]. In adults with lifetime SEPAD, 22.5% have childhood age of onset that persisted into adulthood, while 77.5% had adult onset. Girls/women show higher overall prevalence than boys/men and substantially higher rates of childhood-onset SEPAD persisting into adulthood [62]. SEPAD and panic disorder are highly comorbid in clinical settings. Among adult patients with panic disorder, 53.2% were diagnosed with SEPAD. Patients with panic disorder and SEPAD (versus no SEPAD) were more commonly female and younger and showed higher rates of childhood SEPAD and greater lifetime prevalence of mood disorder spectrum symptoms [63].

Risk Factors

Children of adults with anxiety disorders have higher rates of anxiety disorders. Early, traumatic separation from attachment figures and a positive family history of anxiety or depressive disorders may also elevate risk of SEPAD, school phobia, and depressive-spectrum disorders during adolescence or adulthood. Early, traumatic separation can include prolonged severance of contact with the primary caregiver during the neonatal period; later sudden hospitalization; early loss of attachments from death or divorce; or an interactive pattern with an overprotective, needy, or depressed parent [64].

Clinical Course

In one study, children with SEPAD were 3.5 times more likely to later develop panic disorder and more than twice as likely to develop any anxiety disorder but did not significantly differ in later development of depression or substance use disorder. These findings were considered supportive of a developmental psychopathology model of anxiety disorders [65].

ETIOLOGY AND PATHOPHYSIOLOGY

ANXIETY DISORDERS IN GENERAL

Anxiety disorders are characterized by diverse neuroendocrine, neurotransmitter, and neuroanatomical disruptions, the result of interactions between multiple genetic, environmental, and social factors. Although each disorder may have unique features, this group shares some underlying pathophysiology.

Pathologic Alterations in Brain Structure and Function

Fear and anxiety are thought to involve two major brain circuits: the limbic system and the prefrontal cortex. In the limbic system, which consists of the amygdala, hippocampus, central nucleus of the amygdala, insular cortex, and cingulate cortex, emotion-processing brain structures generate primitive innate responses to simple, overtly threatening stimuli. Functions of limbic structures include processing emotionally important external stimuli and initiating behavioral responses; mediating expressions of fear, aggression, and defensive behavior; and forming and retrieving emotional and fear-related memories [66; 67]. The prefrontal cortex, comprised of the orbitofrontal cortex and the prefrontal, ventromedial, and dorsomedial prefrontal cortex, dampens emotional responses to anxiety-inducing stimuli. The prefrontal cortex functions to regulate impulses, emotions, and behavior via inhibitory "top-down" control of emotional-processing structures; this works to control impulses and regulate mood [66; 67].

Altered limbic and prefrontal cortex functioning characterize anxiety disorders, with amygdala hyperresponsivity to threatening stimuli and impaired ventromedial prefrontal contex inhibitory control over limbic-generated, anxiety-inducing signals, associated with aberrant communication and functional connectivity between the amygdala and the prefrontal cortex [67].

Narrowing brain region contribution, amygdala and insula hyperactivation contribute to anxiety disorders triggered by specific stimuli (e.g., panic disorder, specific phobia). The insula integrates sensory, emotional, and cognitive information through extensive connections between the lateral prefrontal cortex, ventromedial prefrontal cortex, orbitofrontal cortex, cingulate, amygdala, bed nucleus of the stria terminalis, and ventral striatum. Changes in the level of insula activation influence anxiety level [66].

Amygdala-medial prefrontal cortex functional connectivity shows a developmental trajectory, and early temperamental risk for anxiety is associated with disruption of these circuits. Aberrant amygdala-prefrontal cortex connectivity is found in patients with adult-onset anxiety disorders who showed childhood temperament risk factors but did not develop early-onset anxiety. This suggests aberrant connectivity is a lingering biomarker of risk [68].

Familial and Environmental Contribution

Persons with anxiety and mood disorders show a shared genetic predisposition, with specific manifestation the product of genetic and environmental interactions. A developmental dynamic pattern of genetic influence on individual differences in anxiety and depression symptoms is apparent. Genetic influence on psychopathology changes over the lifespan, with different developmental stages associated with a unique pattern of risk factors [67].

Significant early-life stress (e.g., maternal deprivation) may degrade prefrontal cortex functional connectivity with subcortical panic-generating circuits, elevating risks of anxiety disorders and other psychopathology. Many significant early-life stress events (e.g., child abuse, neglect, parental loss from death or abandonment) are receiving heightened attention as contributing factors to anxiety disorders and trauma pathology, as in PTSD. Previous childhood or adult trauma is considered a predisposing/contributing factor to panic disorder and SEPAD as well as major depressive disorder and PTSD that may be primary or comorbid with other anxiety disorders [69]. Aversive experiences can lead to complex behavioral adaptations, including increased levels of anxiety and fear generalization.

Alterations in Brain Transmitter Chemicals

Neurotransmitters allow communication between brain regions. Alterations in neurotransmitter systems implicated in anxiety disorder pathogenesis include the monoamines serotonin (5-hydroxytryptamine or 5-HT), norepinephrine, and dopamine. Aberrant limbic signaling is associated with decreased inhibitory signaling by gamma-amino-butyric acid (GABA) or increased excitatory neurotransmission by glutamate. Many other neurotransmitter systems participate in the modulation of fear and anxiety, including the neuropeptide substances P, N, and Y; corticotropin-releasing factor (CRF); and endocannabinoids. Abnormalities in these systems are associated with structural and functional alterations in specific brain areas, such as the amygdala, prefrontal cortex, locus coeruleus, and hippocampus, and represent the therapeutic targets of drug therapy [70].

Gene products that regulate monoamine signaling may be critical in facilitating antidepressant effect. Monoaminergic regulators include transmitter receptors; vesicular monoamine transporter, which packages monoamines into vesicles; oxytocin and vasopressin; transmitter-specific reuptake transporters, such as the serotonin transporter, norepinephrine transporter, and dopamine transporter; monoamine oxidase, which degrades monoamines; and catecholamine-O-methyltransferase, which degrades norepinephrine and dopamine [67]. However, the cause of anxiety disorders is not simply a deficiency of one neurotransmitter or excess of another. The networks governed by these transmitters are extensively inter-related, with multiple feedback mechanisms and complex receptor structures. This complexity contributes to unpredictable and sometimes paradoxical medication responses [70].

GENERALIZED ANXIETY DISORDER

Neuronal circuits implicated in GAD are distinct from panic disorder, likely involving much greater frontal and prefrontal lobe than amygdala involvement. GAD is characterized by abnormalities in frontal and limbic structures and in the connectivity between these regions. The most frequently implicated frontal regions are the prefrontal cortex and the anterior cingulate cortex; in the limbic region, the amygdala and possibly the hippocampus are involved. Structural abnormalities and decreased structural and functional connectivity between frontal and limbic regions have repeatedly been documented in GAD [71; 72]. Functional neuroimaging suggests that GAD is characterized by inefficient biologic mechanisms associated with emotion regulation. Worry induction increases prefrontal cortex activation and decreases amygdala activity in patients with GAD and non-anxious controls, but unlike non-anxious subjects, patients with GAD are unable to normalize this neural activity afterward. The results from studies using tasks that require conflict monitoring and emotion regulation support a model of GAD characterized by hypoactivation in the prefrontal cortex and anterior cingulate cortex indicative of deficient "top-down" emotional control [73].

PANIC DISORDER

Core Pathophysiology

Genetic, developmental, hormonal, and environmental factors interact to impair the ventromedial prefrontal cortex's ability to inhibit panic impulses generated by limbic regions. This underlies the pathogenesis of the initial onset of unexpected panic attacks. This pathology is further compounded by recurrent panic attacks with repeated activation of panic-generating subcortical sites, leading to recruitment and plasticity within extended amygdala fear-hippocampus-cortical circuits. This in turn facilitates the development of situational and anticipated panic attacks and agoraphobia. Imaging studies have demonstrated ventromedial prefrontal cortex structural abnormalities in patients with panic disorder, reflecting the loss of inhibitory control over panic-generating sites. CBT enhances medial prefrontal cortex activity in subjects with anxiety disorders, which may explain its efficacy in treating panic disorder [69].

Other Pathophysiologic Models

In addition to ventromedial prefrontal cortex inhibition, other alterations in brain function have been suggested in panic disorder. Involvement of the central nuclei of the amygdala and activation of other fear centers in the thalamus, hypothalamus, and hippocampus may dysregulate respiratory control in the brainstem [74; 75]. Additionally, it has been proposed that genetic risk variants partly drive fear network activity [76]. Exaggerated hypothalamic-pituitary-adrenal axis reactivity to environmental stimuli may be involved in panic disorder etiology [77; 78].

In patients with panic disorder, CBT significantly reduces left interior frontal gyrus region activation, and reduced activity is correlated with reduced agoraphobic symptoms [79]. This reduced activation appears to be a specific substrate of CBT effects in patients with panic disorder/agoraphobia without comorbid depressive disorders [80]. Functional magnetic resonance imaging (MRI) shows that pretreatment activation of the bilateral insula and left dorsolateral prefrontal cortex during threat processing is associated with rapid response to CBT [81].

AGORAPHOBIA

Patients with panic disorder and agoraphobia who are anticipating agoraphobia-specific stimuli have shown stronger region-specific activations in the bilateral ventral striatum and left insula versus controls. Patients processed these stimuli more intensively based on individual salience, and this activation is stronger than found in patients with panic disorder alone. Ventral striatum and insula hyperactivation when anticipating agoraphobia-specific situations may be a key neurofunction modulator in agoraphobia [82].

In patients with panic disorder/agoraphobia, fear conditioning has shown enhanced activation of the bilateral dorsal inferior frontal gyrus. Simple conditioning, safety signal processing, and anxiety sensitivity correlate with the extent of midbrain activation. These findings suggest alterations in "top-down" and "bottom-up" processes during fear conditioning, interpreted within a neural framework of defensive reactions that mediate threat through distal (forebrain) versus proximal (midbrain) brain structures. This network may play a key role in panic disorder pathogenesis [83].

Genetic polymorphism (variation) may influence panic disorder with agoraphobia treatment response. Serotonin transporter gene promoter polymorphism (5-HTTLPR) is conclusively linked to emotion regulation and related patterns of brain connectivity. During functional MRI imaging, the patient subgroup that showed inhibitory anterior cingulate cortex-amygdala coupling during fear conditioning predominantly possessed the L/L genotype of 5-HTTLPR polymorphism. This activation of inhibitory function, the normal function in non-anxious persons, suggests an intermediate connectivity phenotype that modulates response to exposure-based CBT [84].

Expanding on these results, patients with panic disorder/agoraphobia and the low-expression allele of 5-HTTLPR showed more favorable exposure therapy response than patients with other 5-HTTLPR genotypes. This genetic contribution to exposure therapy outcome implicates the serotonergic system as a response mediator to exposure treatments [85].

Balance System Abnormalities

Patients with panic disorder/agoraphobia have shown subclinical abnormalities in balance system function that seemed to influence agoraphobia severity and contribute to dizziness and disorientation symptoms in complex sensory environments (e.g., shopping malls, traffic, crowds). These patients also display greater balance control reliance on non-vestibular, proprioceptive, visually dependent cues and greater balance system reactivity to peripheral visual stimulation. These possibly link to a more active visual alarm system involving visual, vestibular, and limbic areas. Patients with panic disorder/agoraphobia also show high sensitivity to light or brightness stimuli with photophobic behavior and abnormal retinal and pupillary reflex responses possibly linked to serotonergic and/or dopaminergic dysfunction. This overall amplified sensitivity to environmental stimuli suggests that agoraphobia involves activation of complex systems beyond panic attack fear and behavioral avoidance, including emotional responses to destabilizing/distressing environmental stimuli and operant-learning avoidance of experiences that provoke this distress [86].

SOCIAL ANXIETY DISORDER

Patients with SAD have shown hyper(re)active limbic, frontal, and parietal brain regions involved in emotional and attentional processes. Compared to healthy subjects, patients with SAD display increased cortical thickness in frontal, parietal, and other brain areas. CBT treatment success and symptom improvement have been associated with changes in prefrontal regions involved in emotion regulation [87].

Persons with SAD and GAD share core features of persistent, debilitating focus on negative or potentially threatening experience. This negative affective bias is characterized by increased threat processing at the neural, psychologic, and behavioral levels, with engagement of the dorsal medial prefrontal cortex-amygdala circuit during aversive processing. Anxiety disorder subtypes frequently co-occur, and while abnormal activation of this neural circuitry that mediates bias toward threats is diagnosis-independent, it also represents a cardinal feature of SAD and GAD [88].

SAD pathophysiology includes heightened autonomic arousal to social cues and novelty. Fear processing appears mediated by the amygdala, in which neuroimaging studies show exaggerated activations with exposure to novel facial stimuli. Amygdala activation to novelty is also found in persons with a behavioral inhibition temperament.

Other pathophysiologic models suggest that exaggerated hypothalamic-pituitary-adrenal axis reactivity to environmental stimuli may be involved in SAD [89; 90; 91; 92].

SPECIFIC PHOBIA

Amygdala, anterior cingulate cortex, and insula hyperactivity is believed to be the underlying pathophysiology of specific phobia. Neuroimaging studies have shown increased amygdala activation with exposure to phobic-relevant cues, and heightened activity in thalamic, insula, and dorsal anterior cingulate cortex regions [93; 94; 95]. Meta-analyses suggest the left amygdala/globus pallidus, left insula, right thalamus, and cerebellum regions are all more active among patients with a phobia compared with controls when exposed to phobic-relevant stimuli. Acute, exaggerated parasympathetic nervous system activity with exposure to stimuli is thought to underlie the vasovagal syncope experienced by up to 80% of people with blood-injection-injury phobia [96]. Exposure-based therapy leads to deactivation in the right frontal cortex, limbic cortex, basal ganglia, and cerebellum, and increased activity in the thalamus [97].

ADULT SEPARATION ANXIETY DISORDER

SEPAD etiology is thought to arise during childhood by disrupted caregiving environments that promote greater hypothalamic/pituitary stress responsivity. Neuroimaging research has focused on brain circuitry that shows abnormal activity at single time points during anxiety from close attachments. The underlying neural circuitry that mediates separation-hypersensitive attachment includes subcortical areas (amygdala, hippocampus, striatum) and cortical limbic areas (insula, cingulate). Predisposing endophenotypes may interact with circuitry involved in attention, learning, and executive control (medial prefrontal cortex, superior temporal sulcus, and temporoparietal junction). With social interaction central to separation anxiety, neural circuitry involved in separation-sensitive social representations that predict danger when separation occurs may include the anterior temporal cortex [98]. SEPAD is associated with hypersensitivity to inhaled carbon dioxide, with a similar pattern to patients with panic disorder, suggesting SEPAD and panic disorder may share a common pathophysiologic basis [99; 100].

CLINICAL AND DIAGNOSTIC FEATURES

As with other psychiatric disorders, the treatment of anxiety disorders is guided by conceptualization of the disorder and theoretical basis for disorder/treatment relationships. The understanding of anxiety disorders has changed over time with input of new evidence. In the United States, the DSM, published by the American Psychiatric Association, is the authoritative reference in defining and diagnosing psychiatric disorders. In the modern era, revised DSM editions have been published in 1980, 1994, 2000, and most recently in 2013 with the DSM-5.

To better reflect current thinking on anxiety disorders, the DSM-5 made several important changes from the 1994 DSM-IV and its 2000 text revision [32; 101]. As noted, the chapter on anxiety disorders no longer includes OCD, PTSD, and acute stress disorder. New sections were added for these conditions: obsessive-compulsive and related disorders and trauma- and stressor-related disorders. Duration criteria for several anxiety disorders were extended to six months or longer to minimize overdiagnosis of transient symptoms, applied to all ages.

With agoraphobia, specific phobia, and SAD, the requirement that patients recognize their anxiety as excessive or unreasonable has been eliminated. This change was based on evidence that individuals with such disorders often overestimated the danger in "phobic" situations and that older individuals often misattributed "phobic" fears to aging. Instead, the anxiety must be out of proportion to the actual situational danger or threat, with consideration of cultural contextual factors [102].

The DSM-5 (and previous DSM editions) has been criticized for emphasis on reliability at the expense of diagnostic validity and for use of symptom-based diagnosis when symptoms alone may not best inform treatment selection. In response, the National Institute of Mental Health is developing the Research Domain Criteria, a new taxonomy for mental disorders that draws from genetics, neuroscience, and behavioral science [103]. Additionally, the DSM-5-TR, which was released in March 2022, includes the addition of prolonged grief disorder; the inclusion of symptom codes for suicidal behavior and nonsuicidal self-injury; refinement of criteria; and comprehensive literature-based updates to the text [104].

GENERALIZED ANXIETY DISORDER

GAD is characterized by excessive and inappropriate worrying that is persistent and not restricted to particular circumstances. Patients have physical anxiety symptoms and key psychologic symptoms. GAD is often comorbid with major depressive disorder, panic disorder, phobia, health anxiety, and OCD [3]. The DSM-5 diagnostic criteria for GAD remain unchanged from previous editions [2; 102]:

- Excessive anxiety and worry (apprehensive expectation) over a number of everyday concerns (e.g., school/work performance)
- Individual finds it difficult to control the worry
- Excessive anxiety and worry are associated with three or more of the following six symptoms, with at least some occurring more days than not for at least six months:
  - Restlessness, feeling "on edge"
  - Easily fatigued
  - Difficulty concentrating
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling or staying asleep, restless sleep)
- The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- Symptoms not better explained by another mental disorder
- The disturbance is not attributable to the physiologic effects of a substance or another medical condition

Patients with GAD in the absence of current or lifetime comorbidity are uncommon, and patients with GAD typically present to primary care with comorbid depression, anxiety disorders, or substance use disorders. The presence of comorbidity complicates diagnosis and treatment [2].

PANIC ATTACKS

Panic attacks are abrupt, unexpected periods of intense fear or discomfort with multiple physical or psychologic anxiety symptoms, often peaking by 10 minutes and lasting around 30 to 45 minutes. Panic disorder is characterized by recurrent unexpected surges of severe anxiety (panic attacks). As noted, most patients develop a fear of having further panic attacks. The extent of anticipatory anxiety between attacks varies, and patients may alter their behavior to reduce the recurrence risk [2; 3].

The essential features of panic attacks are unchanged in the DSM-5, but the complicated DSM-IV terminology for describing different types of panic attacks (i.e., situational-bound/cued, situational-predisposed, and unexpected/uncued) is replaced with unexpected and expected panic attacks. Panic attacks function as a marker and prognostic factor for severity of diagnosis, course, and comorbidity across an array of disorders, including but not limited to anxiety disorders. Hence, panic attack can be listed as a specifier, applicable to almost all DSM-5 disorders [102]. The DSM-5 criteria for panic attacks specify an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and includes four or more of the following symptoms [2]:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feelings of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, light-headed, or faint
- Chills or heat sensations
- Paresthesias (numbness or tingling sensations)
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or going crazy
- Fear of dying

Physical symptoms predominate.

Panic attack is not classified as a mental disorder and does not have a diagnostic code. Instead, an attack can occur with other mental disorders, such as depressive and anxiety disorders, and also be extant with physical disorders. While panic attack is a specifier for both mental and physical disorders, the elements of panic attack are contained within the criteria for panic disorder, making the specifier unnecessary for that diagnosis.

PANIC DISORDER

Panic disorder in the DSM-5 has an added criterion for unexpected panic attacks. This implies that expected panic attacks exist and that anticipated, situationally triggered panic attacks are somehow less pathologic than spontaneous panic attacks. This assumption is challenged on the basis that panic attacks are inherently pathologic, regardless of context or lack thereof, and individuals with panic disorder can have unexpected and expected panic attacks [18; 105]. Regardless, the DSM-5 diagnostic criteria for panic disorder require [2]:

- Recurrent unexpected panic attacks
- One or more of the attacks followed by at least one month of one or both of the following:
  - Persistent concern or worry about additional panic attacks or their consequences
  - Significant maladaptive change in behavior related to the attacks

The symptoms must not be attributable to substance-related effects, other medical conditions, or other psychiatric disorders. Up to 70% of patients report a history of at least one nocturnal panic attack [106]. Patients may present with symptoms suggestive of heightened sympathetic nervous system activity such as palpitations, increased systolic blood pressure, hyperventilation, sweating, or flushing. Other common symptoms include chest pain and discomfort, dizziness, and paraesthesias, while gastrointestinal symptoms such as nausea and vomiting are more common among men [2; 107].

The severity of distress during panic attacks by patients with panic disorder with or without agoraphobia is increasingly seen as traumatic. Panic attacks are frequently experienced as life threatening, and patients with panic disorder can experience PTSD symptoms in relation to their panic attacks. Patients with panic disorder/agoraphobia or PTSD were found to relive their trauma or panic attacks with equal frequency, report comparable bodily reactions and distress associated with trauma or panic attack memories, and avoid trauma or panic attack reminders (i.e., places and things associated with trauma or panic attacks). Trauma-like symptoms surrounding panic attacks are common, and panic attacks may be processed similarly to trauma in PTSD [108].

Intense, disorganized recollections, a core symptom of PTSD, are thought to result from inadequate processing of trauma information. A first panic attack resembles trauma; both are unexpected, frightening, and subjectively life-threatening events. Like PTSD, panic disorder with agoraphobia also involves fear conditioning after the first event. Therefore, panic attack and trauma processing may be similar, with panic attack and PTSD trauma memories sharing the characteristics of reliving and disorganization. A comparison of panic memories and PTSD trauma memories did not find differences between groups in reliving intensity and disorganization levels, suggesting that panic attacks may affect information processing similarly to a traumatic event [109; 110].

Patients with panic disorder exhibit considerably worse overall mental well-being than individuals with cancer, diabetes, heart disease, arthritis, hypertension, and other chronic physical conditions [111]. Current panic disorder is also related to worse quality of life and physical function and an elevated risk of attempting suicide [112]. These effects are similar to or greater than those associated with major depression. A study found that nearly 33% of these patients in primary care had seen three or more healthcare professionals and almost 20% had visited emergency departments [113]. Another study found that although the majority of individuals with panic disorder first present to the primary care setting, only 38% of those with panic disorder with agoraphobia and 24% of those with panic disorder without agoraphobia were receiving appropriate treatment, and the use of empirically supported interventions was rare [114].

AGORAPHOBIA

Agoraphobia is defined as the fear of panic attacks occurring in places or situations from which escape might be difficult or embarrassing or where help may not be available. These situations can include crowds, going outside the home, or using public transportation and are either avoided or endured with significant personal distress [3]. Agoraphobia can become severely disabling, and more than 33% of patients diagnosed with agoraphobia cannot endure leaving their home environment. Roughly 66% of patients with panic disorder develop agoraphobia [2].

In the DSM-5, agoraphobia was de-aggregated from panic disorder and is now classed as a separate diagnostic entity. The former DSM-IV diagnoses of panic disorder with agoraphobia, panic disorder without agoraphobia, and agoraphobia without history of panic disorder are now replaced by two diagnoses with separate criteria: panic disorder and agoraphobia. Co-occurring panic disorder and agoraphobia are also coded as two diagnoses. This change recognizes that a substantial number of individuals with agoraphobia do not experience panic symptoms, although clinical prevalence is much lower than community prevalence. The diagnostic criteria for agoraphobia are derived from the DSM-IV descriptors, with endorsement of fears from two or more agoraphobia situations now required to more effectively distinguish agoraphobia from specific phobias. The criteria for agoraphobia are also extended to concord with criteria sets for other anxiety disorders [102]. Diagnosis is based on marked fear or anxiety about two or more of the following [2]:

- Public transportation (e.g., traveling in planes, automobiles, buses, trains, ships)
- Open spaces (e.g., parking lots, market places, bridges)
- Being in shops, theatres, or stadiums
- Standing in line or being in a crowd
- Being outside of the home alone in other situations

The individual with agoraphobia fears or avoids these situations due to thoughts that escape might be difficult or help might not be available in the event of panic-like symptoms. These situations almost always provoke fear or anxiety and are actively avoided, require presence of a companion, or are endured with marked fear or anxiety. The fear or anxiety is out of proportion to the actual threat posed by an agoraphobic situation. The fear, anxiety, or avoidance is persistent, typically lasting at least six months, and causes clinically significant distress or impaired functioning. Avoidance symptoms in PTSD differ in that the situations avoided are trauma-associated, such as a park or street where an assault occurred or riding in a car after a motor vehicle accident [2].

Major personality dimensions, such as introversion and neuroticism, have been studied for contribution to the risk of developing agoraphobia and other anxiety disorders. Genetic factors that influence individual variation in extraversion and neuroticism have been found to account entirely for genetic liability in SAD and agoraphobia but not animal phobia, emphasizing the importance of both introversion (low extraversion) and neuroticism as risk factors [115]. Situational avoidance is the most disabling aspect of agoraphobia. Temperament is shown to influence agoraphobia severity, with introverted temperament significantly associated with the presence and severity of agoraphobic situational avoidance [9].

The longitudinal relationship between personality disorder traits and panic disorder (with or without agoraphobia) is important for understanding agoraphobia etiology. A large-scale study that assessed community-dwelling adults at baseline and again 12 to 15 years later found that after excluding participants with baseline panic attacks, baseline timidity with avoidant, dependent, and related traits predicted the onset of panic disorder or panic disorder with agoraphobia during the follow-up period. These results suggest that avoidant and dependent personality traits are predisposing factors, or markers of risk, for panic disorder or panic disorder with agoraphobia, and not simply epiphenomena [24]. Additionally, personality and temperament traits may be potentially related to poor treatment response [116].

SOCIAL ANXIETY DISORDER

SAD is often misconstrued as mere shyness but can be considerably disabling and produce much greater distress and more severe symptoms. SAD is characterized by a marked, persistent, and unreasonable fear of being observed or evaluated negatively by other people in social or performance situations, which is associated with physical and psychologic anxiety symptoms. Feared situations, such as speaking to unfamiliar people or eating in public, are either avoided or are endured with significant distress [3]. Social phobia has been renamed SAD to reflect a new, broader understanding of the condition in a variety of social situations.

Previously, social phobia was primarily diagnosed in patients reporting extreme discomfort or fear when performing in front of others. Research indicates this definition is too narrow, and SAD in the DSM-5 can be diagnosed based on patient response to a variety of social situations. For example, the patient may be so uncomfortable engaging in conversation he or she is unable to talk to others, especially strangers. A patient with anxiety regarding being observed may be unable to go out to dinner over fears of being watched while eating and drinking [102].

The essential features of SAD remain unchanged. However, a number of changes have been made, including deletion of the requirement that individuals older than 18 years of age must recognize that their fear or anxiety is excessive or unreasonable and addition of a duration criterion. A more significant change is that the "generalized" specifier has been deleted and replaced with a "performance only" specifier. The DSM-IV-TR generalized specifier was

problematic in that "fears include most social situations" was difficult to operationalize. Individuals who fear only performance situations (i.e., speaking or performing in front of an audience) appear to represent a distinct subset of SAD in terms of etiology, age at onset, physiologic response, and treatment response. The DSM-5 establishes the following diagnostic criteria for SAD [2]:

- Marked fear or anxiety about social situations in which the person may be exposed to scrutiny by others
- Fear that actions or showing anxiety symptoms will cause negative evaluation (e.g., embarrassment, humiliation) or offend others
- The social situation:
  - Almost always provokes fear or anxiety
  - Is actively avoided or endured with marked fear or anxiety
- The fear, anxiety, or avoidance:
  - Is disproportionate to actual threat posed by the social situation
  - Is persistent, typically at least six months
  - Causes significant distress or functional impairment
- If another medical condition is present (e.g., stuttering, obesity), the disturbance is unrelated or out of proportion to it

If the fear is restricted to speaking or performing in public, diagnosis should specify "performance only." Other diagnostic features of SAD include [2]:

- Post-event processing: Tendency to replay social encounters in a negative, self-critical manner
- Attentional bias: Heightened attention to negative evaluative threat cues and lack of attention to positive or benign cues
- Social skills deficits: Poor eye contact, closed stance, quiet tone of speech, and difficulties initiating conversations

Patients with SAD highly inflate perceived social costs from committing hypothetical blunders. Accounting for much of this social cost inflation are concerns about revealing self-flaws and, in particular, concerns over appearing socially incompetent [117].

SPECIFIC PHOBIA

Specific, simple, or isolated phobia describes excessive or unreasonable fear in the presence of phobic stimuli, typically involving specific animals, objects, or situations (e.g., dentists, spiders, elevators, flying, seeing blood). Phobic stimuli are either avoided or are endured with significant personal distress [3]. This fear or anxiety must be markedly stronger than the actual threat of the object or situation (e.g., likelihood of being stuck on a well-maintained elevator) [2]. The core features and different types of specific phobia remain unchanged from the DSM-IV, but the requirement was removed that individuals older than 18 years of age must recognize their fear and anxiety as excessive or unreasonable. The duration requirement of longer than six months now applies to all ages [102].

Specific phobias can develop after a traumatic event or from witnessing traumatic events. The fear or anxiety happens every time the person is exposed to the stimulus and may include panic attack symptoms.

The median age of onset with specific phobia is 13 years [2]. According to the DSM-5, specific phobia is diagnosed when the following criteria are met [2]:

- Marked fear or anxiety about a specific object or situation (e.g., flying, seeing blood)
- Phobic object or situation almost always provokes immediate fear or anxiety and is actively avoided or endured with marked fear or anxiety
- Fear or anxiety out of proportion to the actual danger posed by the specific object or situation
- The fear, anxiety, or avoidance is persistent, typically at least six months
- Marked distress or functional impairment

Specific phobia subtypes are organized by phobia categories:

- Animal: Dogs, snakes, insects
- Natural environment: Storms, heights, dark
- Blood-injection-injury: Injections, blood draws, medical procedures
- Situational: Driving, flying, enclosed spaces
- Other: Choking, vomiting, clowns

Specific Phobia Coding

Approximately 75% of individuals diagnosed with specific phobia fear more than one object. In the past, when this occurred, more than one ICD-10 code was given [2]. However, the ICD-11 eliminated this component. When individuals experience panic attacks in response to their phobia, clinicians should add "with panic attacks" to the diagnosis.

SEPARATION ANXIETY DISORDER

Separation anxiety is a basic human fear and readily observable in children. Being close to nurturing parental figures in infancy is necessary for survival, and forming close relationships throughout life provides support in times of stress. Separation anxiety does not vanish with development and maturation, but prominent separation anxiety in adults becomes less apparent as a problem on its own. Manifestations of pathologic separation anxiety include uncontrollable apprehension over losing important attachment figures, intense fears of leaving home or going out unaccompanied, and nightmares around themes of separation. Persons with SEPAD have substantial impairments in many aspects of community life, although not all individuals show problems in attachment [118; 119].

Pathologic early childhood attachments can have far-reaching consequences in adulthood. These patients often have a grossly impaired ability to experience and internalize positive relationships or to develop mental capacities for self-soothing, anxiety tolerance, affect modulation, and individuation. Adults with SEPAD feel unable to function in the absence of a mother surrogate. Separation anxiety has long been considered the distal antecedent to panic disorder. In adults, separation anxiety may reflect excessive activation of fear circuits in response to separation and over-activation of reward circuits with reunion, likely the result of abnormalities or deficits in underlying social representation and cognition systems [98].

SEPAD is characterized by fear or anxiety concerning separation from those to whom an individual is attached. Common features include excessive distress when experiencing or anticipating separation from home, and persistent and excessive worries about potential harms to attachment figures or untoward events that might result in separation [3].

The core features of SEPAD are mostly unchanged from DSM-IV, but the wording is modified to more adequately represent SEPAD expression in adulthood. For example, attachment figures may include the children of adults, and avoidance behaviors may occur in the workplace as well as at school. Diagnostic criteria no longer require childhood history of SEPAD or onset before 18 years of age, because a substantial number of adults report onset later in life. Adults with the condition include those with adult-onset and those with childhood onset and symptom persistence into adulthood. A duration criterion of six months or longer was added [64; 102]. For a diagnosis of SEPAD, the persistent and excessive anxiety related to separation or impending separation from a major attachment figure (e.g., spouse, close family member) must be evidenced by at least three of the following criteria [2]:

- Recurrent excessive distress when anticipating or experiencing separation
- Persistent and excessive worry about losing a major attachment figure or about possible harm to him or her
- Persistent and excessive worry about experiencing an untoward event (e.g., getting lost, kidnapped, into an accident) that causes separation from a major attachment figure

- Persistent reluctance or refusal to go out, away from home, to school, to work, or elsewhere because of fear of separation
- Persistent and excessive fear of or reluctance about being alone or without a major attachment figure
- Persistent reluctance or refusal to sleep away from home or to go to sleep without major attachment figure near
- Repeated nightmares involving the theme of separation
- Repeated complaints of physical symptoms (e.g., headaches, stomachaches, nausea, vomiting) when separation occurs or is anticipated

To meet the criteria for this disorder, the symptoms must cause clinically significant distress or impairment in social, academic, occupational, or other important areas of functioning. Symptoms must not be better explained by another mental disorder (e.g., delusions or hallucinations concerning separation in psychotic disorders); refusal to go outside without a trusted companion (as in agoraphobia); worries about ill health or other harm befalling significant others (as with generalized anxiety disorder); or concerns about having an illness (as in illness anxiety disorder) [2]. Panic attacks commonly occur with youth and adult SEPAD.

Differential Diagnosis

In the past, adult SEPAD was often diagnosed as panic disorder, and it shares features with other psychiatric conditions. Excessive attachment toward others is a feature of a dependent personality, and avoidance behavior is a predominant feature of agoraphobia. With SEPAD, the focus involves key attachment figures, unlike dependent personality disorder, which is more indiscriminate. Panic and phobic-like behavior in SEPAD is specific to fears of separation from, or harm to, attachment figures and not spontaneous or triggered by other factors. Social and occupational function is frequently impaired, but individuals with SEPAD do not show impaired function in family life compared to controls and often function well in family environments. Borderline personality disorder differs by pervasive mood and relationship instability uncharacteristic of SEPAD [61].

A study exploring whether SEPAD in patients with panic disorder/agoraphobia was a manifestation of anxious attachment, a form of agoraphobia, or a specific condition with clinically significant consequences found that patients with SEPAD had greater panic symptom severity and quality of life impairment than those without separation anxiety. A greater rate of symptoms suggestive of anxious attachment was found among patients with panic disorder and SEPAD versus those without SEPAD. However, the relationship between SEPAD and attachment style was weak, and SEPAD occurred in some patients who reported secure attachment style. There was also little evidence SEPAD was a form of agoraphobia. SEPAD was found to be a distinct condition associated with impairment in quality of life and should be better recognized and treated in patients with comorbid panic disorder [119].

SELECTIVE MUTISM

Separation anxiety disorder and selective mutism were included in the DSM-IV section Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence, but were classed as anxiety disorders and moved to the anxiety disorder section in the DSM-5 [102]. The majority of children with selective mutism are anxious, and while selective mutism is now considered an anxiety disorder, it remains a disorder primarily of childhood and is beyond the scope of this course [102].

ASSESSMENT

Effective anxiety disorder treatment relies on accurate diagnosis. Diagnosis is made when diagnostic criteria are met and the anxiety is not better explained by the effects of other medical conditions, medications, substances, or other mental disorders [2].

The management of patients presenting with anxiety symptoms should initially follow the flow of these five components [120]:

1. Screen for anxiety and related symptoms.
2. Consider differential diagnosis and severity, impairment, and comorbidity.
3. Identify specific or multiple anxiety disorder(s).
4. Initiate psychologic and/or pharmacologic treatment.
5. Perform follow-up.

Evidence suggests that in primary care, patient tendency to ascribe pathologic anxiety symptoms to physical causes contributes to high rates of missed diagnoses and the misdiagnosis of GAD and panic disorder. To offset this requires a broad differential and caution to identify confounding variables and comorbid conditions [121].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Psychiatric Association recommends that the initial psychiatric evaluation of a patient include assessment of anxiety and panic attacks.

(https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890426760. Last accessed April 11, 2022.)

Strength of Recommendation/Level of Evidence: 1C (Recommendation with low confidence that the evidence reflects the true effect)

SCREENING FOR ANXIETY DISORDERS IN THE PRIMARY CARE SETTING

In primary care settings, panic disorder prevalence is around 10%, with GAD co-occurring in 68% of patients with panic disorder and in 38.6% of those with major depression [34; 122]. The American Academy of Family Physicians states that rates of missed diagnoses and misdiagnosis of GAD and panic disorder are high in primary care, with symptoms often ascribed to physical causes [121]. One study of older patients with GAD found low rates of anxiety symptom recording (34%) and anxiety disorder diagnosis (9%) despite high levels of healthcare utilization [123]. In the current managed care environment, anxiety is usually treated in the primary care setting, and given the increasing time constraints imposed on primary care providers, it is not surprising that anxiety disorders are underrecognized and undertreated [70].

Many patients with anxiety and depressive symptoms do not seek help, and in those who do, anxiety symptoms are often not the presenting complaint. Patients and providers often have difficulty initiating discussion of emotional problems and distress. Primary care providers with greater sensitivity to nonverbal communications have been found more likely to detect and diagnose anxiety, while those tending to "blame" patients make fewer psychologic inquiries and are less accurate in detecting distress [3; 124].

PATIENT SCREENING

The American Academy of Family Physicians suggests using screening and monitoring tools, such as the Generalized Anxiety Disorder 7-Item Scale (GAD-7) and the Severity Measure for Panic Disorder, to help establish diagnosis and monitor therapy response [121]. In theory, patients and providers should benefit from screening tools to detect anxiety disorders. However, use of screening tools requires other changes in practice structure, and it is uncertain whether routine screening and disclosure to "screened positive" patients improves clinical outcomes. One primary care educational intervention using this design did not find patient outcomes improved [3; 125].

In the past, routine screening of anxiety symptoms was not recommended, but in 2022, the U.S. Preventive Services Task Force recommended screening all children older than 7 years of age for anxiety, and in 2023, they expanded their recommendation to include screening all adults, including pregnant and postpartum persons, for anxiety disorders [349; 350]. Primary care providers can improve anxiety detection skills by acknowledging that many patients are reluctant to discuss psychologic problems. This can be offset with greater sensitivity to nonverbal expression of psychologic distress and using repeated patient contact to ask about possible anxiety symptoms if suspected but not confirmed in earlier appointments [3].

Healthcare providers can create a more comfortable environment for a patient of another culture by acknowledging the impact of culture and cultural differences on physical and mental health. Symptom presentation is influenced by cultural factors, and in some cultures, anxiety may be expressed through somatic symptoms, such as musculoskeletal pain and fatigue. Providers may consider starting the conversation with the patient by focusing on physical symptoms. The concept of anxiety also varies across cultures, and patients may not seek medical treatment unless symptoms manifest as psychosis, conversion disorders, or significant physical ailments.

IDENTIFYING PATIENTS WHO REQUIRE TREATMENT

The potential chronicity and disability of anxiety disorders indicates that most patients meeting anxiety disorder diagnostic criteria should receive psychologic and/or pharmacologic treatment. Treatment selection is guided by severity, duration, patient distress and impairment, the presence of depression and other comorbid disorders, previous treatment response or contraindication, evidence base, patient preference, provider experience, and treatment availability [3; 126]. However, many patients with anxiety disorders who could benefit do not receive treatment. Fewer than one in five patients with an anxiety disorder receive appropriate medication; this improves to one in three for patients with comorbid depression [127].

Treatment quality is improved with accurate diagnosis and regular monitoring. Inadequate dosage and treatment duration were found common in the primary care treatment of patients with panic disorder, but improved outcomes were more likely with enhanced patient education and follow-up contact than with physician education [3; 128]. Worth noting is the contrast between concerning media reports of medicalization and inappropriate psychotropic prescribing for "normal" anxiety, shyness, or situational stress, and the repeated findings in primary care studies of inadequate or no prescribing and a high level of unmet patient need [3].

SCREENING QUESTIONS

General Screening

Ask patients if they have recently felt excessively nervous, anxious, or on edge, or if they worry uncontrollably. The DSM-5 suggests the following questions for identifying anxiety-related symptoms [2]:

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

A positive history of anxiety symptoms should be explored with screening questions for specific anxiety disorders.

Screening for Specific Anxiety Disorders

In addition to the general questions suggested for all patients with complaints of anxiety, it is important to inquire regarding disorder-specific symptoms. This will allow for more specialized assessment and diagnosis.

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 or irritable, or do you have trouble sleeping?

Panic Disorder

- Do you have sudden, unexpected episodes/spells/attacks of intense fear or discomfort? If yes, then 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?

Agoraphobia

- Do you avoid certain situations or places where panic attacks have occurred or may occur?

Social Anxiety Disorder

- Does fear of embarrassment cause you to avoid doing things or speaking to people?
- Do you avoid activities where you are, or may be, the center of attention?
- Is being embarrassed or looking stupid among your worst fears?

Specific Phobia

- Do you feel intense anxiety or fear when confronted by certain animals, objects, or situations?
- Are you avoiding these animals, objects, or situations because of your fear?
- In what ways has this anxiety or fear interfered with your life?
- How would you react if you were exposed to the animal, object, or situation right now?
- Have you ever fainted or almost fainted around blood, injuries, or needles?

Separation Anxiety Disorder

- Do you feel anxious, fearful, or upset thinking about separation, or being away from, your (spouse, partner, primary support person)?

Positive responses to screening questions is followed by a formal assessment.

EVIDENCE-BASED PRACTICE RECOMMENDATION

If an adult with possible social anxiety disorder finds it difficult or distressing to attend an initial appointment in person, the National Collaborating Centre for Mental Health recommends making the first contact by phone or Internet, but aiming to see the person face to face for subsequent assessments and treatment.

(https://www.nice.org.uk/guidance/cg159/resources/social-anxiety-disorder-recognition-assessment-and-treatment-pdf-35109639699397. Last accessed April 11, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

PATIENT HISTORY

A patient history is performed to assess patient and family history for clinically relevant information. Patients should be assessed for onset of anxiety symptoms, duration (remission or persistent), association with life events or trauma, level of distress, and effect on current functioning (academic, occupational, relationships, leisure activities, role functioning). Also inquire about a personal history of physical or emotional trauma, anxiety or mood disorders, medications or therapies, and patient response. Family history should be assessed for anxiety, mood, and substance use disorders [2]. Screening for depression is very important, given its high comorbidity rate and associated risk of suicidal behavior [129].

A thorough list of prescribed, over-the-counter, and herbal medications should be obtained [2]. Furthermore, substance use should be assessed, including:

- Current and past tobacco use
- Current and past alcohol use
- Current and past use of illicit drugs (e.g., cannabis, cocaine, heroin, methamphetamine)
- Current and past use of pharmaceutical drugs (e.g., opioids, stimulants, benzodiazepines)
- Current and past use of "legal high" or novel drugs (e.g., club drugs, "bath salts," "synthetic cannabis")
- Having been told their substance use is a problem
- Having received counseling or treatment for a substance use problem

PHYSICAL EXAMINATION

There are usually no objective findings in persons presenting with anxiety disorders, although patients may become noticeably anxious or nervous when discussing their anxiety. Signs reflective of heightened sympathetic nervous system activity may be present (e.g., tachycardia, hyperventilation, sweating, flushing). Vasovagal fainting may also be present, especially when individuals with blood-injection-injury phobia are exposed to medical situations or procedures. These patients should be assessed for other medical conditions associated with fainting risk (including blood glucose levels and orthostatic hypotension) [2].

Diagnosis is made through self-report, clinical interview, and behavioral observation of impairments in personal, social, or occupational domains; no laboratory testing is necessary. Several empirically validated self-report questionnaires are available to assess baseline functioning and track treatment response. Assessment of anxiety symptoms and associated impairments optimally includes key informant interviews with family members or close friends [2].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is performed to eliminate potential underlying causes that, if present, would better account for patient anxiety complaints. As noted, screening for other anxiety, mood, and substance-related disorders should be routinely conducted due to high comorbidity rates.

Other Mental Disorders

To confirm or rule out the presence of comorbid anxiety or related disorders, determine the nature and focus of patient apprehension/anxiety. It may be [2]:

- Diffuse, non-specific (GAD)
- Discrete, intense anxiety episodes (panic disorder)
- Fear of one's panic attacks and avoidance of places or situations where they may occur (agoraphobia)
- Embarrassment in public (SAD)
- Fear of specific objects or situations (specific phobia)
- Attachment figure separation (separation anxiety)
- Contamination (OCD)
- Weight gain (anorexia nervosa)
- Multiple physical complaints (somatization disorder)
- Serious illness (hypochondriasis)
- Strictly trauma-related (PTSD)

A diagnosis of SAD should rule out avoidant personality disorder. Some symptoms of avoidant personality disorder resemble SAD, such as a pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation. However, avoidant personality disorder is distinguished by non-social avoidance that extends to novel situations and positive affect. Roughly 36% of patients with SAD are comorbid for avoidant personality disorder, and some believe avoidant personality disorder is a more severe variant of SAD [130; 131].

EVIDENCE-BASED PRACTICE RECOMMENDATION

When assessing an adult with possible social anxiety disorder, the National Collaborating Centre for Mental Health recommends that clinicians be aware of comorbid disorders, including avoidant personality disorder, alcohol and substance misuse, mood disorders, other anxiety disorders, psychosis, and autism.

(https://www.nice.org.uk/guidance/cg159/resources/social-anxiety-disorder-recognition-assessment-and-treatment-pdf-35109639699397. Last accessed April 11, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Medication or Substance Use

It is important to rule out medication side effects as the underlying cause of anxiety by obtaining a complete list of currently used prescribed, over-the-counter, and herbal medications. Examples of common medications with anxiety side effects are asthma medications (e.g., albuterol, theophylline), herbal medicines (St. John's wort, ginseng, *ma huang*), corticosteroids, and antidepressants [2].

Patients should also be assessed for current use of alcohol, nicotine, stimulants, benzodiazepines, and opioids, because the direct, adverse, or withdrawal effects can mimic anxiety or panic symptoms [132]. Illicit or illicitly used drugs with acute effects most commonly associated with anxiety include cocaine, methamphetamine, prescription amphetamines (e.g., lisdexamfetamine), methylphenidate, and MDMA ("Ecstasy") [2]. Caffeine may also provoke anxiety in sensitive patients, including those with anxiety disorders [28]. Alcohol use disorder is highly prevalent among persons with anxiety disorders. Acute anxiety relief may powerfully reinforce alcohol use, but frequent or heavy drinking commonly exacerbates the anxiety disorder symptoms. When these two disorder co-occur, treatment can be complicated.

Medical Conditions

Careful history taking and physical examination are warranted for all patients to rule out medical causes of anxiety symptoms. Conditions that can mimic or cause anxiety complaints include hyperthyroidism and hypothyroidism, asthma, cardiac arrhythmias, pheochromocytoma, and temporal lobe epilepsy. As noted, screening for depression is very important, given its high comorbidity rate and associated risk of suicidal behavior [129].

Laboratory Tests and Imaging

Although usually negative in the absence of other suggestive evidence, laboratory testing or imaging studies may be indicated to help rule out medical cause. For example, a routine blood panel with thyroid-stimulating hormone and blood glucose levels may help to identify or rule out conditions such as hyperthyroidism or hypoglycemia that may be responsible for intense, persistent anxiety and panic. Toxicology screening may also be indicated to determine whether illicit substances are contributing to the clinical presentation. An electrocardiogram is required in all patients presenting with chest pain (to exclude cardiac causes), and pulmonary function tests are used to rule out pulmonary disease in patients with shortness of breath. It is important to note that cardiopulmonary disorders can co-occur with anxiety disorders [2].

Screening Tools

The Primary Care Evaluation of Mental Disorders (PRIME-MD) was developed as a screening instrument, but its administration time has limited its clinical usefulness. The instrument contains modules on 12 different mental health disorders [133]. The panic screen contains four yes or no questions to assess the presence of panic attacks within the last four weeks. Responding "yes" to all four questions indicates likely presence of panic disorder. The panic screen also includes 11 somatic and cognitive symptoms, with endorsement of at least 4 of these symptoms indicative of likely panic disorder [133].

Developers of the PRIME-MD subsequently created the Patient Health Questionnaire (PHQ), which is a self-administered version of the PRIME-MD. The PHQ contains mood, anxiety, alcohol, eating, and somatoform modules as covered in the original PRIME-MD [134]. The GAD-7 was subsequently developed as a brief self-report measure for assessing anxiety severity in primary care. In total, seven items are scored on a 0 to 3 scale, with a cut score of ≥10 indicative of a likely anxiety disorder. Designed to measure generalized anxiety, the GAD-7 is also sensitive in detecting panic-related symptoms [135].

GENERAL TREATMENT CONSIDERATIONS

Information in this section is derived from published research, meta-analyses, and clinical practice guidelines. The most recent anxiety disorder guideline (on panic disorder) by the American Psychiatric Association was published in 2009. The 2014 Anxiety Disorders Association of Canada (ADAC) guidelines are the most recent and comprehensive North American publication and are emphasized accordingly [120]. Successful treatment requires tailoring options to individuals and may often include a combination of modalities [121].

CBT, which includes an exposure therapy component, is used to address and work through maladaptive beliefs and avoidance behaviors that reinforce pathology surrounding fear-eliciting stimuli. CBT with some variant of exposure is the first-line psychotherapy approach for most pathologically anxious patients. Pharmacotherapy, also a first-line treatment for anxiety disorders, uses various agents to induce rapid anxiolytic effects (e.g., benzodiazepines, some anti-epilepsy drugs) or agents that require prolonged, long-term treatment (e.g., antidepressants) to attenuate symptoms of pathologic fear and anxiety [136].

Advances in anxiety disorder neuroscience have increasingly pointed to the necessary role of fear extinction learning (through exposure therapy) in addressing underlying pathophysiology. While efficacy is shown with CBT and exposure, patients can have difficulty with the demanding and exhausting therapy process, and many who do manage to complete therapy respond partially and relapse with time. Efforts to improve CBT/exposure outcomes have led to the investigation of augmenting agents. In contrast to standard anti-anxiety drugs, these agents are not anxiolytic but are used to promote and accelerate long-term adaptive changes in brain function initiated by successful exposures [137].

Any review of treatment efficacy for anxiety disorders, and pharmacotherapy in particular, requires a disclaimer. Most treatment outcomes were based on studies using methodologies that excluded those with additional anxiety disorders and comorbid psychiatric or medical disorders. Patients seeking care for anxiety problems in primary care and other real-world settings often differ from carefully screened study participants. The extent that efficacy, response, and remission rates reported in the published research generalize to typically more complex clinic patients has been questioned [138].

Treatment refusal and attrition are significant problems. Patients with anxiety disorders show treatment refusal rates of 25% to 30% and treatment dropout rates of 10% to 82% [139]. Treatment dropout is very high in exposure therapy, as patients repeatedly confront (with graded intensity) the situations or objects that trigger their greatest fear or panic response. The intensity of distress during exposure can overwhelm patients, and with avoidance the hallmark feature of most anxiety disorders, attrition is significant [2; 139]. Attrition can interfere with evaluating treatment efficacy (or the lack thereof), and unless explicit in study reporting, can be misleading. Attrition is also a clear concern in the clinical care of patients with anxiety.

PREDICTORS OF WORSE TREATMENT RESPONSE AND OUTCOMES

SEPAD

Pathologic SEPAD is associated with a pervasive negative influence on treatment response. Comorbid SEPAD is highly correlated with poor treatment response and patient outcomes across a range of anxiety and mood disorders. SEPAD negatively impacts response to major depression treatment and is linked to worse symptom chronicity and quality of life. SEPAD decreases CBT response and predicts worse outcomes in patients treated for panic disorder, GAD, or SAD. SEPAD also predicts nonresponse to selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) in patients with panic disorder with agoraphobia [98; 140].

Chronic Pain

Uncontrolled pain is also increasingly recognized to negatively impact anxiety disorder treatment outcomes. In primary care patients with a GAD or panic disorder diagnosis treated for severe anxiety and followed for one year, patients with moderate or greater pain levels were found to show significantly lower rates of clinical improvement [141]. A cohort of 1,122 individuals with remitted anxiety or depressive disorders were followed up to four years, and pain (but not chronic disease) was associated with recurrence during follow-up [142].

Social Drinking

Problematic, excessive drinking clearly disrupts treatment response, but social drinking can also aggravate panic disorder and probably other anxiety syndromes. The short-acting effects of alcohol wear off rapidly, followed by rebound to a state of hyper-excitability that may be more problematic for patients with anxiety. This can occur with one to two drinks in some patients, who often do not even consider this a contributing factor to their anxiety complaint. Explaining the simple physiology of rebound excitation after profound neuronal inhibition will often convince patients that alcohol may be sensitizing the neural circuits subserving their anxiety and that a trial period of abstinence is indicated [28].

Other Anxiety Disorders

Highly symptomatic panic inhibits benefit from interpersonal psychotherapy, either alone or combined with SSRIs. The presence of any anxiety disorder impairs response to treatment of comorbid major depression [98]. Patients with major depressive disorder and a comorbid anxiety disorder demonstrate longer time to recovery and greater risk of early treatment termination. Patients with comorbid anxiety and depressive disorders generally have worse outcomes than patients with either disorder alone. Patients with comorbid GAD and major depression are significantly more likely to remain symptomatic than those with depression or GAD alone [143]. When anxiety symptoms are present within a dominant depressive disorder, antidepressant drugs are often effective in reducing anxiety [144]. However, depression that follows or is comorbid with an anxiety disorder usually indicates greater severity and worse prognosis [145].

Among treatment-seeking patients with panic disorder, SAD, or GAD followed over two years, symptom changes in GAD were most specifically related to changes in impairment, suggesting that treatment of patients with multiple anxiety disorders should initially focus on GAD symptoms or employ transdiagnostic modalities [146].

Patients with panic disorder/agoraphobia who display the low-expression allele of the serotonin transporter gene promoter show more favorable exposure therapy response than patients with other 5-HTTLPR genotypes. This genetic contribution to exposure therapy outcome implicates the serotonergic system as a response mediator to exposure treatments [85].

OVERLAPPING PSYCHOLOGIC AND DRUG THERAPY MECHANISMS

Emerging evidence is challenging conventional wisdom by showing that antidepressant therapeutic action may begin with the first dose and that psychologic and drug therapy approaches share common mechanisms. In one study, a single-dose of the norepinephrine reuptake inhibitor reboxetine reduced negative affective bias in depression by increasing the recognition of positive facial expressions and enhancing memory for positive vs. negative information [147]. These early changes in emotional processing reflect changes in frontolimbic circuitry involved in the detection and response to biologically salient information. These findings were replicated following seven days of escitalopram treatment [148]. Changes in neurocognitive processing that precede clinical improvement predict later antidepressant response [149]. A 2013 study found that single-session CBT for panic disorder/agoraphobia led to reduced threat processing the following day, with magnitude of early effect predicting therapeutic response after four weeks [150]. These findings challenge assumptions that psychologic therapies address conscious thought processes before automatic information processing and suggest a greater similarity between early effects of pharmacologic and psychologic treatments for anxiety than previously thought [149].

PSYCHOTHERAPIES: OVERVIEW

Psychologic treatments play an integral role in the management of anxiety disorders, and efficacy is established for several modalities. Most broadly effective are exposure-based and other CBT approaches. When choosing psychologic treatments for individual patients, the forms of therapy developed for the specific anxiety disorder should be used first.

Cognitive and Behavioral Approaches

Psychotherapy can be as effective as medication for GAD and panic disorder, and CBT has the best level of evidence [121]. CBT is the most extensively evaluated psychologic therapy in anxiety disorders and contains elements of cognitive and behavioral therapy approaches.

Behavior therapy is characterized by the use of exposure to modify dysfunctional behaviors that may contribute to the development and persistence of psychologic symptoms [151]. Cognitive therapy involves cognitive restructuring, a psychotherapeutic process of learning to identify and modify irrational or maladaptive thoughts using strategies such as Socratic questioning, thought recording, and guided imagery [34].

CBT is not a single treatment approach but a process that addresses factors that caused and maintain patient anxiety symptoms. The classic CBT approach involves disorder-specific treatment protocols that target the symptoms and the cognitive, behavioral, and emotional vulnerabilities that underlie development and maintenance of each disorder. This approach reflects the assumption that each form of psychopathology has a distinct cognitive profile, to which CBT is tailored accordingly. Disorder-specific CBT is the standard of care for anxiety and depressive disorders [152]. However, there are common components of CBT used in anxiety disorders (***Table 2***) [120].

There is some debate regarding whether the efficacy of CBT that targets common underlying factors would be comparable to standard diagnosis-tailored CBT. Support for CBT that addresses common underlying factors includes frequent comorbidities in anxious patients, such as major depressive disorder, which some studies found present in close to 50% of patients with anxiety [153]. The frequent co-presence of mood and anxiety disorders, substantial overlap in dimensional symptom ratings, and extensive evidence of shared vulnerability factors led to identification of common underlying factors that represent targets for CBT. These include [152]:

COMMON COMPONENTS OF CBT USED IN THE TREATMENT OF ANXIETY DISORDERS
Cognitive Strategies
Cognitive restructuring, behavioral experiments, and related strategies target exaggerated perception of danger (e.g., fear of negative evaluation in SAD). Therapy provides corrective information regarding the level of threat and can also target self-efficacy beliefs.
Arousal Management
Relaxation and breathing control skills help control increased anxiety levels.
Exposure
Encourage patients to face fears. Patients learn corrective information through experience. Extinction of fear occurs through repeated exposure. Successful coping enhances self-efficacy.
Safety Response Inhibition and Surrender of Safety Signals
Patients wean from and relinquish use of their usual anxiety-reducing safety signals and behaviors (e.g., presence of a companion, need for reassurance, knowing the location of nearest exit or toilet), which decreases negative reinforcement. Coping with anxiety without using anxiety-reducing behavior enhances self-efficacy, allowing patients to learn adaptive self-efficacy beliefs.
Source: [120] *Table 2*

- Motivational enhancement
- Psychoeducation and understanding emotions
- Emotional awareness training
- Cognitive reappraisal
- Attenuation of emotional and behavioral avoidance
- Awareness and tolerance of physical sensations
- Interoceptive and situational exposure
- Relapse prevention

Psychotherapy and drug therapy show similar efficacy in most anxiety disorders. Psychotherapy plus drug (combination) therapy outcomes vary and are conflicting, and current evidence does not support routine combination therapy as initial treatment. However, patients lacking response to CBT or drug therapy may benefit from adding the other modality [120].

Delivery of effective CBT is versatile. Individual or group delivery is effective in most anxiety disorders. A variety of self-directed or minimal intervention formats (e.g., bibliotherapy/self-help books, Internet/computer-based CBT with or without minimal therapist contact) have shown significant improvements in anxiety symptoms, and exposure therapy can be effective using a virtual reality format. These strategies can be very useful when real-life exposure is made difficult by inconvenience or patient reluctance [120].

Third-Wave Therapies

Mindfulness-based cognitive therapy, acceptance and commitment therapy, compassionate mind training, extended behavioral activation, metacognitive therapy, and schema therapy are diverse approaches originating from CBT. These modalities place greater importance on the form rather than content of patient cognitions. These third-wave therapies help patients develop more adaptive emotional responses to situations by focusing on the function of cognition. Mindfulness and acceptance are used in anxiety disorders to help patients observe symptomatic processes without overly identifying with or reacting to them in ways that perpetuate distress [154].

Mindfulness

Mindfulness involves attending to relevant aspects of experience in a non-judgmental manner. The goal of mindfulness is to maintain moment-by-moment awareness; disengage oneself from strong attachment to beliefs, thoughts, or emotions; and develop a greater sense of emotional balance and well-being. An aim of mindfulness practice is to take greater responsibility for one's life choices. Some evidence supports the efficacy of this approach in GAD and panic disorder [155; 156; 157].

Mindfulness versus active control was compared in ability to reduce negative thought intrusions activated by a worry-induction procedure. Negative thought intrusions significantly increased with progressive muscle relaxation and focused attention but not with brief mindfulness meditation, suggesting mindfulness might target anxiety by reducing negative elaborative processes that maintain worry [158].

Acceptance and Commitment Therapy

Acceptance and commitment therapy views psychologic events as a set of ongoing interactions between whole organisms and contexts defined historically and situationally. Acceptance and commitment therapy states that analyzing problematic behaviors but excluding the contexts that participate in the event misses the nature of the problem and pathways for its solution. This approach promotes a conscious posture of openness and acceptance of all psychologic events, including those deemed "negative" or "irrational." In acceptance and commitment therapy, when patients feel frustrated, afraid, angry, or anxious, this represents an opportunity to examine how powerful events in the present can become barriers to growth [159]. Some evidence suggests acceptance and commitment therapy may be as effective as CBT in anxiety disorder treatment, including panic disorder [151; 160; 161].

Acceptance-based skill training differs from traditional coping skills training by de-emphasizing control (over physiology or thoughts) to focus on acceptance of panic-related sensations and cognitions as they occur from moment to moment. Patients learn to pay nonjudgmental attention to thoughts, feelings, images, and bodily sensations. Thoughts are viewed as an ongoing process distinct from self, rather than events with literal meaning (cognitive defusion). Efficacy of acceptance approaches has been shown in patients with panic disorder/agoraphobia [162].

Education and Support

Psychoeducation states that providing information to patients with anxiety about their anxiety symptoms and theories of psychologic therapy may reduce these symptoms. By increasing the patient's sense of control, psychoeducation may reduce catastrophic thoughts and emotions. This is especially relevant in patients with panic disorder, in which cognitive coping mechanisms are disrupted and anticipatory anxiety may cause additional attacks [151].

Supportive psychotherapy is non-specific in nature and uses encouragement, rationalizing/reframing, and anticipatory guidance to reduce symptoms and maintain, restore, or improve self-esteem, ego function, and adaptive skills. This approach views the therapeutic alliance as the most important element. The archetype of supportive psychotherapy is the Rogerian client-centered approach; a warm, empathic, and non-directive therapeutic relationship helps clients become aware of their true feelings and achieve full self-acceptance. This approach may benefit patients with agoraphobia, but efficacy in panic disorder is unclear [151].

Physiologic Therapy

Physiologic therapies involve physical training (e.g., breathing retraining, relaxation techniques, biofeedback) to help patients control physiologic anxiety symptoms. Hyperventilation and hypocapnia are identified factors in panic disorder development and maintenance; panic attacks can be caused by acute hypocapnia states in a positive feedback loop between hyperventilation and anxiety. Breathing training is used to ameliorate panic symptoms, but it shows mixed efficacy in panic disorder [162]. Progressive muscle relaxation teaches patients with panic to reduce general tension and achieve a body state that lowers the risk for panic-inducing stressors. Applied relaxation teaches patients to observe the first signs of a panic attack and apply a rapid and effective relaxation technique to cope with and abort panic symptoms before escalation into a panic attack. Applied relaxation is comparable to progressive muscle relaxation in reducing panic attacks [151].

Psychodynamic Approaches

Psychodynamic therapies are psychologic approaches differing in length and depth, based on Freudian psychoanalysis and later refinements. Psychodynamic psychotherapy views psychologic symptoms as the manifestation of intra-psychic or unconscious conflicts; treatment involves uncovering, interpreting, and resolving such conflicts through the analysis of unconscious contents, dreams, past experiences, parental relationships, transference, and/or resistances [151]. A brief panic-focused psychodynamic psychotherapy, derived from psychodynamic theories, utilizes emotion-focused therapy, whereby the therapist is viewed as an "emotion coach" who works to enhance emotion-focused coping by helping patients become aware of, accept, and make sense of their emotional experience [163].

One psychodynamic psychotherapy approach proposes that fearful parental dependency in childhood may lead to anger toward the parent. A vicious cycle is created; anger threatens the needed tie to the parent and increases fearful dependency, which promotes further frustration and rage at the parent. This cycle may recur in adulthood when threats to attachment trigger intense feelings of abandonment, anger, and anxiety, promoting the development of pathologic anxiety. The goal is to address such underlying psychologic factors to decrease panic symptoms. Some evidence suggests this approach is a valid therapeutic option, especially when SEPAD is present [98; 151].

Exposure Therapies

Exposure therapy is defined as any treatment that encourages patients to systematically confront feared stimuli, which can be external (e.g., feared objects, activities, situations) or internal (e.g., feared thoughts, physical sensations) [136]. Exposure therapy is an effective, empirically supported treatment modality for anxiety disorders and a core component of CBT. Variants of exposure therapy include:

- In vivo exposure: Exposure that involves real-world confrontation of feared stimuli
- Imaginal exposure: Vividly imagining and describing the feared stimulus, including details about external (sights, sounds) and internal (thoughts, emotions) cues
- Virtual reality exposure: Patient immersion into a software-generated virtual world that allows them to confront their fears

The success of exposure therapy occurs by targeting maladaptive learning and fear conditioning, core mechanisms implicated in anxiety disorder etiology and maintenance. Standard exposure therapy involves exposure to feared objects or situations and gradual elimination of safety behaviors—the subtle avoidance behaviors that temporarily diminish distress in feared situations but interfere with long-term anxiety reduction. Patients are encouraged to continue confronting the feared situations through exposure until substantive reductions in fear occur. Exposure therapies facilitate extinction learning by diminishing the association between the avoided situation and fear and promoting new learning of the true nonthreatening nature of the situation [164; 165].

Exposures are graded in intensity, with the same process used for weaning safety signals. For instance, a patient with panic disorder and agoraphobia can initially practice walking through a congested shopping mall with a family member; on the next exposure, he or she may practice walking separately through the shopping mall, and eventually walk through the congested mall alone. Patients are taught that treatment setbacks are common and to distinguish between expected treatment lapses and relapses. Symptom flare-ups do not mean treatment failure, but instead are opportunities to revisit psychoeducation, cognitive restructuring, or exposure, and work toward regaining progress [166].

A substantial number of patients fail to achieve substantive symptom relief from exposure-based therapies or experience fear relapse following exposure therapy. This results from deficits in the mechanisms considered central to extinction learning (e.g., poor medial prefrontal cortex inhibition of amygdala-generated fear impulses) that contributed to the development of pathologic anxiety and avoidance in the first place. Because of this, effort is underway to optimize exposure therapies to improve significant and durable patient response [167]. This effort includes the therapeutic alliance as a potential prognostic indicator [168].

PHARMACOTHERAPY: OVERVIEW

The first-generation antidepressants monoamine oxidase inhibitors (MAOIs) and TCAs were introduced in the late 1950s and early 1960s, and the first report of antidepressant use in anxiety treatment was published in 1962. In this account, patients with agoraphobia who were given the TCA imipramine showed reductions in panic attacks and improved exposure to feared situations [169]. The benzodiazepine chlordiazepoxide (Librium) was introduced to the U.S. market in 1960. This was followed by diazepam (Valium) in 1963, which became the most prescribed drug in the United States from 1969 to 1982; in 1978, more than 2.3 billion diazepam doses were sold in the United States [170]. Panic disorder was first formalized as a psychiatric disorder in the 1980 DSM-III, and alprazolam (Xanax) became the first U.S. Food and Drug Administration (FDA)-approved drug for panic disorder treatment in 1981, remaining the most-prescribed benzodiazepine to date [171].

In the past two decades, antidepressant drugs have displaced benzodiazepines as the most widely prescribed and recommended anxiety disorder pharmacotherapy. Efforts to improve safety, efficacy, and tolerability led to introduction of the second-generation antidepressants, with trazodone (Oleptro) in 1982, bupropion (Wellbutrin) in 1985, and fluoxetine (Prozac)—the first domestically marketed SSRI—in 1987.

Antidepressants are generally recommended as first-line therapy for panic disorder because, unlike benzodiazepines, antidepressants treat comorbid depression and lack abuse risk and potential side effects of excessive sedation, cognitive impairment, and ataxia. All major antidepressant classes are comparably effective, but SSRIs and, increasingly, serotonin-norepinephrine reuptake inhibitors (SNRIs) are recommended over TCAs and MAOIs due to better safety and tolerability [172].

Tricyclic Antidepressants

Norepinephrine, serotonin (5-HT), and dopamine are termed monoamines. Monoamine reuptake transporters retrieve monoamines released into the synaptic cleft to terminate their activation of post-synaptic monoamine receptors. TCAs act by inhibiting norepinephrine and 5-HT reuptake transporters. This increases synaptic levels of norepinephrine and 5-HT by preventing their clearance, which increases post-synaptic receptor activation and signaling. TCAs generally have greater norepinephrine than 5-HT reuptake transporter potency. TCAs also act as histamine H1/H2, muscarinic acetylcholine, and alpha-adrenergic receptor antagonists, resulting in a range of undesirable side effects associated with patient intolerance and discontinuation, including [173]:

- Anticholinergic: Dry mouth, blurred vision, constipation, urinary hesitancy and retention, confusion, precipitation of glaucoma, delayed ejaculation, sweating
- Alpha-1-adrenoceptor antagonism: Postural hypotension, increased heart rate, dizziness
- Antihistaminergic: Sedation, psychomotor slowness, weight gain
- Cardiac sodium channel blockade: QTc prolongation, decreased cardiac conduction, fatal cardiac arrest in overdose

TCAs have comparable efficacy to SSRIs in panic disorder and GAD [174; 175]. TCAs are lethal in overdose and, compared to SSRIs, have a markedly broader, more problematic, and less tolerable side effect profile [172]. Nonetheless, TCAs may work when first-line agents do not [136]. Also, some patients with panic disorder are sensitive to both beneficial and adverse effects of TCAs, so they cannot tolerate imipramine doses >10 mg/day but may still experience panic blockade [172].

Monoamine Oxidase Inhibitors

MAOIs inhibit MAO, an enzyme that degrades and inactivates 5-HT, norepinephrine, and dopamine, thereby increasing monoamine levels and activity. The earlier MAOIs—phenelzine (Nardil) and tranylcypromine (Parnate)—are characterized by irreversibility and nonselectivity. Irreversibility refers to tenacious drug binding to the MAO enzyme for the 14- to 28-day lifespan of the drug molecule. Nonselectivity refers to phenelzine and tranylcypromine binding to both A and B isoenzymes of MAO. While tyramine and dopamine are metabolized by both MAO-A and MAO-B, MAO-A inhibition is established as the precursor to hypertensive crises [176].

During phenelzine or tranylcypromine therapy, dangerous and potentially fatal hypertensive reactions can result from co-ingestion of drugs with monoamine activity or foods high in tyramine content (e.g., cheese, beer, wine). Concurrent use of serotonergic agents or supplements such as St. John's wort can cause potentially lethal serotonin syndrome. Common side effects include orthostatic hypotension, weight gain, sexual dysfunction, sedation, headache, and insomnia. To avoid drug interactions, washout periods are required before an MAOI is started (≥5 days) or stopped before switch to another medication (≥14 days) [136].

Moclobemide is a reversible inhibitor of monoamine oxidase type A (RIMA). With reversibility, MAO enzyme detachment and/or displacement readily occur, greatly improving safety. Compared to tranylcypromine, it takes eight times the tyramine level (8 mg vs. 63 mg) with moclobemide to induce a 30 mm Hg rise in diastolic blood pressure; dietary and co-medication concerns are greatly reduced. No washout period is required for switching antidepressants. Moclobemide is safe in overdose, and 20,000 mg has been ingested without fatality. Common side effects include nausea, insomnia, tremor, and lightheadedness. Orthostatic hypotension is uncommon, even in the elderly [176]. Moclobemide lacks the cholinergic and histaminergic side effects of TCAs and the sexual side effects of SSRI/SNRIs. Depressive patients more commonly reported improved libido, erection/ejaculation, and orgasm with moclobemide. Weight gain or lowered seizure threshold are not side effects [177]. Moclobemide was slated for introduction in the United States in 1992. It was withdrawn from the application process because SSRI popularity cast doubts on its profit potential. This drug is available in Canada and throughout Europe and Asia [176; 178].

MAOIs and RIMAs are effective for panic disorder and SAD and are thought by some to be superior options for severe, treatment-resistant anxiety disorders. As noted, MAOIs have a substantial side effect profile and impose the greatest safety burden of all antidepressants. Therefore, they are usually reserved as the last treatment option after other drug therapies have failed to achieve remission [179]. Clinicians do not routinely prescribe MAOIs for anxiety disorders, although they are probably not considered often enough in treatment-resistant patients [136].

SSRIs

SSRIs are considered first-line therapy for GAD and panic disorder [121; 172]. SSRI mechanism is thought to involve serotonin transporter (SERT) inhibition at the presynaptic axon terminal of 5-HT neurons. SERT inhibition also occurs at the somatodendritic end of the neuron, where the increase in 5-HT causes 5-HT1A autoreceptors to downregulate, desensitize, and over time lose the ability to inhibit 5-HT release. The resultant increase in synaptic 5-HT level mediates the therapeutic action. SSRIs were termed "selective" because, unlike TCAs, they were believed to have little-to-no interaction with non-serotonin receptors and transporters [136; 180].

It is now recognized that SSRIs differ in pharmacologic effect, including activity beyond SERT inhibition [179; 180]:

- Fluoxetine: Antagonist at 5-HT2C receptors, which enhances norepinephrine and dopamine release. Therapeutic effects may emerge more slowly than other SSRIs.
- Sertraline (Zoloft): A weak dopamine transporter inhibitor, sigma-1 receptor activity. Along with fluoxetine, increases cortex monoamine levels to possibly explain patient reports of improved energy, motivation, and concentration.
- Paroxetine (Paxil): A weak norepinephrine transporter inhibitor, which contributes to antidepressant effects. Muscarinic cholinergic receptor activity may underlie some sedative and anxiolytic effects.
- Fluvoxamine (Luvox): Along with sertraline, has sigma-1 receptor activity that possibly contributes to the anxiolytic effects of both agents.
- Citalopram (Celexa): Mild antihistamine properties not observed with escitalopram.
- Escitalopram (Lexapro): Is considered the only SSRI without pharmacologic activity beyond SERT inhibition.

The atypical SSRIs vilazodone (Viibryd) and vortioxetine (Trintellix) display expanded serotonergic and other monoaminergic activity beyond those of standard SSRIs. Vilazodone and vortioxetine are likely to be treatment options for patients who do not respond to or cannot tolerate typical SSRIs/SNRIs.

Common SSRI side effects include gastrointestinal upset (nausea, vomiting, diarrhea), activation/insomnia (restlessness, agitation, anxiety, akathisia, sleep disturbances), sexual dysfunction (loss of erectile or ejaculatory function in men, loss of libido and anorgasmia in both sexes), headache, fatigue, and weight gain. Many side effects dissipate over time. Sertraline is particularly associated with diarrhea, and paroxetine with weight gain. Discontinuation syndrome from paroxetine is more severe and protracted than other SSRIs [181]. To avoid relapse, medication should be continued for at least 12 months after symptom improvement before tapering [121].

Vilazodone

Approved by the FDA in 2011, vilazodone primarily acts as a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, with modest action as a dopamine and norepinephrine reuptake inhibitor, with 5-HT4 receptor activity [173]. This profile resembles the combination of SSRI and buspirone, and GAD efficacy of both agents suggests a potential role for vilazodone in anxiety disorder treatment. Two eight-week randomized controlled trials of vilazodone treatment of GAD have been published. One using a flexible-dose design found nominal clinical improvement with vilazodone compared with placebo, while the other study using a fixed-dose design found statistically significant reduction in anxiety scores (vs. placebo) with vilazodone 40 mg but not 20 mg [182; 183]. Vilazodone does not appear to improve efficacy over drugs already in use, but it does have advantages of earlier onset of clinical response (beginning by two weeks) and little evidence of sexual dysfunction or weight gain. Vilazodone should be taken with food, which increases its absorption and bioavailability by 72% [184].

Vortioxetine

Approved by the FDA in 2013, vortioxetine is a multimodal antidepressant and potential anxiolytic with activity as an antagonist in 5-HT1D/3A/7 receptors, a 5-HT1A receptor agonist, 5-HT1B partial agonist, serotonin transporter inhibitor, and weak norepinephrine transporter inhibitor. This multiple receptor activity modulates serotonergic, noradrenergic, dopaminergic, and histaminic systems to produce clinical effect [185]. Results from four randomized controlled trials suggest vortioxetine may have potential efficacy in the treatment of severe GAD, but effects in patients with more moderate GAD were minimally improved compared with placebo. Nausea, the most common side effect, was dose dependent [186]. Sexual dysfunction rates were similar to placebo across the 5 –20 mg/day dose range, and vortioxetine can be taken without regard for meals [187].

SNRIs

Venlafaxine, the first SNRI approved in the United States, was introduced as immediate release (IR) in 1993 and extended release (XR) in 1997. This was followed by the introduction of duloxetine in 2004, desvenlafaxine in 2008, milnacipran in 2009, and levomilnacipran in 2013. SNRIs increase synaptic concentrations of 5-HT and norepinephrine by blocking reuptake of these neurotransmitters by their respective transporters. SNRIs lack significant affinity for adrenergic, cholinergic, histaminergic, opioid, glutamate, or GABA receptors and transporters [136; 188].

SNRIs differ in proportion of 5-HT/norepinephrine reuptake inhibition. Venlafaxine is the most serotonergic SNRI, followed by duloxetine and desvenlafaxine. Milnacipran shows relatively equal influence on 5-HT and norepinephrine reuptake inhibition, and levomilnacipran is a greater norepinephrine than 5-HT reuptake inhibitor. Such differences suggest that SNRIs are dissimilar from one another. Venlafaxine and duloxetine exhibit dose-related sequential effects on reuptake inhibition, while desvenlafaxine, milnacipran, and levomilnacipran act simultaneously on 5-HT and norepinephrine reuptake inhibition with proportionality intact with dose escalation [189].

Side effects from SNRIs overlap with SSRIs but can also include adrenergic effects of increased pulse rate and blood pressure, dilated pupils, dry mouth, and excessive sweating. Venlafaxine has a greater incidence of nausea and vomiting than SSRIs and may be associated with an increased risk for cardiovascular events [181]. Sexual side effects associated with SNRIs include decreased response to sexual stimuli, loss of interest in sex, anorgasmia, and much less frequently, genital anesthesia. Discontinuation syndrome from venlafaxine is markedly worse than other SNRIs and SSRIs [188].

Relative to SSRIs and TCAs, the SNRIs have relatively short half-lives, and few or no active metabolites for simpler overall pharmacology. In contrast to venlafaxine and duloxetine, desvenlafaxine, milnacipran, and levomilnacipran largely bypass the hepatic cytochrome P450 isoenzyme system, making drug interactions less likely. Of the five available SNRIs, only venlafaxine has an active metabolite (desvenlafaxine). Dosing with venlafaxine IR and milnacipran is twice daily; the remaining SNRIs are dosed once daily [184].

The impairing effects from synaptic plasticity induced by conditioned psychologic stress were found reversed by SNRI treatment. Long-term venlafaxine and milnacipran use suppressed long-term potentiation in hippocampal CA1 via 5-HT1A receptor and a1-adrenoceptor activity, contributing to reversal in synaptic plasticity-related impairment induced by conditioned fear stress. Increased responsiveness of a1-adrenergic and dopaminergic D3 systems, decreased responsiveness of 5-HT2 systems, and development of adaptive changes occurred despite lack of SNRI affinity for these neurotransmitter receptors [188; 190; 191].

Venlafaxine

Venlafaxine IR was introduced in 1993 but from the outset was plagued with side effects, leading to the 1997 introduction of venlafaxine XR. The XR formulation has become a widely prescribed agent with established efficacy in several anxiety disorders. In addition to the dose-related reuptake inhibition of 5-HT and norepinephrine mentioned, weak dopamine reuptake inhibition may appear at dosages greater than 300 mg/day. This sequential activity is mirrored by the initial predominant serotonergic side effects (headache, nausea, fatigue, sexual dysfunction), with noradrenergic effects at higher doses (activation effects, dry mouth, night sweats) [184].

Desvenlafaxine

Desvenlafaxine (Pristiq) shows a 10-fold higher selectivity for serotonin over norepinephrine reuptake inhibition at 50 mg/day, with selectivity unchanged by dose increase to 100 mg/day [184]. A primary advantage of desvenlafaxine over venlafaxine involves metabolic pathways and drug interactions. Venlafaxine is extensively metabolized by the hepatic CYP2D6 isoenzyme to desvenlafaxine, while desvenlafaxine is metabolized primarily via glucuronidation and minimally through CYP3A4 [178]. Venlafaxine, but not desvenlafaxine, clearance in patients with polymorphic 2D6 can be accelerated or delayed, resulting in non-efficacy or greater side effects/toxicity. This makes desvenlafaxine preferable to venlafaxine for these patients. The desvenlafaxine metabolic pathway also eliminates adverse drug interactions with 2D6 substrates that require consideration with venlafaxine prescribing [188; 192]. However, few trials have evaluated desvenlafaxine in anxiety disorder treatment [184]. A comparison of the efficacy and safety of desvenlafaxine and escitalopram for treatment of depression with anxiety found that both drugs reported similar efficacy, but escitalopram was better tolerated with fewer adverse effects [193].

Duloxetine

Duloxetine (Cymbalta) has greater potency in 5-HT reuptake inhibition than fluoxetine. It has an elimination half-life of roughly 12.5 hours, steady-state is usually achieved after three days, and metabolism occurs mainly through hepatic CYP 2D6 and 1A2 [178; 194]. Common adverse effects of duloxetine include nausea, headache, and weight loss. Certain adverse effects, including xerostomia, drowsiness, and fatigue, are dose related [178].

Milnacipran

Milnacipran (Savella) has been marketed in France since 1997 for the treatment of major depression, but it is indicated for use by the FDA solely for fibromyalgia [178]. Milnacipran is not available in a generic formulation, and the expiration of the patent is not imminent. Anxiolytic effects of milnacipran are at least partially mediated by 5-HT2A receptor agonism [188; 195]. Results of a systematic review were inconclusive regarding the comparative efficacy, acceptability, and tolerability of milnacipran versus other antidepressive agents; however, milnacipran reportedly was more favorable than TCAs in terms of acceptability and tolerability [196].

Levomilnacipran

Levomilnacipran (Fetzima) differs from other SNRIs in that it is a more potent and selective inhibitor of norepinephrine than serotonin, especially at low doses. Alcohol may disrupt the extended-release mechanism to release large amounts of drug over a brief period, and co-ingestion should be avoided. With reports of milnacipran increasing hepatic transaminases to cause fulminant hepatitis, levomilnacipran should be avoided in patients with a history of alcoholism or chronic liver disease. Levomilnacipran is not associated with weight gain [173; 178]. Levomilnacipran ER 40–120 mg daily was found to be effective in preventing relapse in patients with major depressive disorder [197].

Other Antidepressants

Bupropion

Bupropion (Wellbutrin) lacks effect on serotonin neurotransmission either presynaptically (through serotonin release or reuptake inhibition) or postsynaptically (acting on serotonin receptors). Instead, bupropion inhibits the reuptake of norepinephrine and dopamine without affecting release or transport of other neurotransmitters and without binding to other neurotransmitter receptors. This unique pharmacologic profile makes bupropion the only approved antidepressant that increases dopamine neurotransmission in the nucleus accumbens and prefrontal cortex. The side effect profile, distinct from other antidepressants, lacks sexual dysfunction, weight gain, and sedation. The activating effects of bupropion can increase insomnia and anxiety, leading to its infrequent use in anxiety disorders [179; 198].

Trazodone and Nefazodone

The anxiolytic effects of trazodone are mediated by activity as a highly potent 5-HT2A receptor antagonist and moderately potent 5-HT1A partial agonist, with additional activity in SERT and 5-HT2C receptor inhibition. The combined actions of 5HT2A/5HT2C antagonism and SERT inhibition only occur at moderate-to-high doses, with doses lower than effective for antidepressant action frequently used for the effective treatment of insomnia [178; 179; 199]. Nefazodone (Serzone) is highly similar in pharmacologic activity to trazodone, but it is rarely prescribed due to liver toxicity concerns [179].

Mirtazapine

Mirtazapine (Remeron) is a tetracyclic compound with a unique mechanism of action, leading to description as a noradrenergic antagonist-specific serotonin antagonist antidepressant. Pharmacologically, mirtazapine is a 5-HT1 receptor agonist, and antagonism of 5-HT2A/C receptors increases cortical serotonin, dopamine, and norepinephrine modulation. Inhibition of norepinephrine alpha-2 autoreceptors allows greater norepinephrine release from neuron terminals. Also antagonized are receptors of 5-HT3, 5-HT5, and H1 histamine. This unique profile helps account for earlier onset of action than SSRI/SNRIs. Mirtazapine tends to promote sleep or drowsiness, and the most frequent side effect of daytime sedation can be a beneficial effect in highly anxious patients [178; 179; 188].

Mirtazapine is found beneficial in patients with GAD, SAD, OCD, panic disorder, and PTSD [200]. It is relatively safe in overdose. Mirtazapine is particularly useful in patients with sexual dysfunction from other antidepressants and is a good choice in patients with significant insomnia. Weight gain is a side effect, and if the risks for elevated lipid levels and rare agranulocytosis are a concern, mirtazapine may be reserved as a third-line choice [200; 201].

Agomelatine

Agomelatine is approved for clinical use in Europe, Australia, and a total of 40 countries overall, but not by the FDA. It is discussed in light of its novel mechanism and particular benefit in GAD [202].

Agomelatine is a synthetic melatonin analog with activity as a melatonin MT1/MT2 receptor agonist and 5-HT2C receptor antagonist. Unique to agomelatine, and one of its most important properties, is a sleep-promoting and pro-chronobiologic effect. Its 5-HT2C antagonism promotes dopaminergic firing in the ventral tegmental area, frontal cortex, hypothalamus, hippocampus, medulla, pons, and retina by enhancing norepinephrinergic activity in the locus coeruleus [185; 203].

With a unique non-monoaminergic mechanism of action, clinical trials have shown a low risk of sexual dysfunction, lack of weight gain or withdrawal symptoms, and overall side effect profile similar to placebo. However, reports of liver injury require patients to receive liver enzyme monitoring [204].

Anti-Epileptic Drugs

Gabapentinoids

Pregabalin (Lyrica) and gabapentin (Neurontin) are structurally analogous GABA analogs, with pregabalin more extensively evaluated in anxiety disorders. The anxiolytic, antinociceptive, and antiseizure properties of pregabalin are mediated through binding to presynaptic α2δ subunits of central nervous system (CNS) voltage-gated calcium channels, which decreases calcium influx at presynaptic channels and inhibits neurotransmission of excitatory glutamate, norepinephrine, and substance P [185; 205].

The relative efficacy and early onset of effect of pregabalin versus benzodiazepines may represent a new therapeutic intervention for GAD as mono- and augmentation therapy. Pregabalin has a low risk of drug interactions, lacks withdrawal or physical dependence risk, is associated with minimal adverse effects (e.g., dizziness, weight gain, insomnia), and is safe and well tolerated. A potential role for pregabalin in patients with GAD tapering off long-term benzodiazepine therapy has been suggested [185].

Benzodiazepines have been the only anxiolytic agents that rapidly reduce anxiety, but trials conducted in the last decade have also found this effect with pregabalin. In 89 patients with moderate-to-severe dental anxiety (without anxiety disorder diagnosis) given single-dose pregabalin 150 mg, alprazolam 0.5 mg, or placebo four hours before a dental procedure, the onset of anxiolytic effects began within three to four hours after pregabalin and within two hours after alprazolam. The magnitude of anxiety reduction and tolerability were equivalent between pregabalin and alprazolam [206].

Common GAD comorbidities of insomnia, gastrointestinal symptoms, and depression do not impair efficacy and are specifically improved by pregabalin. Pregabalin is generally well tolerated; the adverse event profile includes dizziness, somnolence, incoordination, dry mouth, headache, and weight gain. Risk of withdrawal symptoms is low when tapered over one week [205].

Levetiracetam (Keppra) is an analog of the nootropic drug piracetam and structurally unrelated to other anti-epileptic drugs. It has a novel mechanism of action that involves binding to synaptic vesicle protein SV2A, a protein that modulates neurotransmitter release including GABA. Metabolism has no effect on the cytochrome P450 enzyme system. The most common side effects include somnolence, dizziness, and weakness [207]. In one study, adjunctive levetiracetam (mean: 1,969 mg/day for 9.3 weeks) in highly symptomatic patients with treatment-refractory anxiety disorders led to clinically and statistically significant improvement in illness severity [208]. Further research involving patients with panic disorder with or without agoraphobia given levetiracetam for 12 weeks showed significant improvement in panic attack frequency, anxiety, and global severity ratings. Clinical benefits were apparent by one to two weeks for most patients, and side effects were minimal [209]. Patients with SAD initially administered levetiracetam 250 mg/day and flexibly titrated up to 3,000 mg/day over eight weeks showed significant improvements on measures of social anxiety, overall anxiety, and illness severity [210]. In contrast to the anti-epileptic agents zonisamide and topiramate, levetiracetam has not shown decrements in neuropsychologic performance on tests of cognitive impairment in patients with seizure disorder [211].

Atypical Antipsychotics

Olanzapine, risperidone, aripiprazole, and quetiapine are dopamine D2 receptor antagonists, as with all antipsychotic drugs, but differ from typical (first-generation) antipsychotics by also acting as 5-HT2A receptor antagonists (minimizing development of extrapyramidal effects), 5-HT1A receptor partial agonists (producing anxiolytic effects), and histamine receptor antagonists (further augmenting sedative and anxiolytic effects) [185].

Quetiapine

Quetiapine (Seroquel) is the most-studied atypical in anxiety disorder treatment and has greatest efficacy in GAD. A review of quetiapine in GAD found efficacy and tolerability in all acute and long-term monotherapy trials and statistically significant changes in anxiety and symptom severity in three of five adjunct therapy studies. Quetiapine is a treatment option for patients unresponsive to first-line therapy, and potential benefits may outweigh risks with appropriate monitoring and side effect management [212]. While the unique efficacy of quetiapine monotherapy in GAD is supported by a Cochrane review, quetiapine was denied FDA approval for GAD, likely due to its tendency for inducing lipid abnormalities, weight gain, and glucose intolerance, and concerns over widespread use in primary care without careful consideration of alternatives or monitoring adverse metabolic effects during follow-up [136; 213].

Buspirone

Introduced in 1986, buspirone (BuSpar) was the first anxiety-specific medication unrelated to benzodiazepines or barbiturates in pharmacology, effect, and abuse potential. The 5-HT1A receptor partial agonism mediates the anxiolytic effects. Buspirone acts as a weak presynaptic dopamine D2, D3, and D4 receptor antagonist and alpha-1 agonist [214]. Buspirone is primarily used in the treatment of GAD and to augment antidepressants for improved response.

Hydroxyzine

Hydroxyzine (Vistaril) acts mechanistically as a potent H1 receptor inverse agonist, and as a 5-HT2A, D2, and alpha-1-adrenergic receptor antagonist. The serotonergic activity of hydroxyzine is more potent than its dopaminergic and adrenergic activity and likely accounts for its anxiolytic efficacy, as other antihistamines lacking this property have not been effective in the treatment of anxiety [215; 216]. Hydroxyzine efficacy in anxiety disorders is limited to GAD, for which anxiety-reducing efficacy is demonstrated [217; 218; 219].

Benzodiazepines

Since their introduction in the early 1960s, benzodiazepines have been the most prescribed drugs for anxiety over the majority of the past half-century. Although SSRI/SNRI agents have replaced benzodiazepines as the top-prescribed anxiolytics, benzodiazepine prescribing remains common. In 2018, alprazolam and lorazepam were among the top 25 most frequently prescribed psychotropic medications in the United States; alprazolam ranked second, and lorazepam ranked 10th [220; 221].

Pharmacology and Short-Term Effects

Numerous benzodiazepines are available and have similar pharmacodynamic properties and clinical actions; they mainly differ in pharmacokinetic properties (absorption, distribution, metabolism, elimination). Benzodiazepines bind to a specific receptor site in the GABA-A receptor complex. GABA is the primary inhibitory neurotransmitter in the CNS, and benzodiazepines cause non-selective GABA-A inhibitory effects throughout the brain that include drowsiness, cognitive impairment, dampening of fear and anxiety, memory impairment, anticonvulsant actions, and impairment of balance, motor control, muscle tone, and coordination. Adverse reactions to alprazolam also include amnesia, aggression, mood changes, and hostility. The newer Z drugs (e.g., zolpidem, zopiclone) have similar actions to benzodiazepines but are marketed for insomnia due to their pharmacokinetic profile, with high doses required for anxiolytic effects. There is evidence the Z drugs share similar risks to benzodiazepines [222; 223].

Meta-analyses suggest alprazolam, lorazepam, and diazepam are effective but comparable in GAD efficacy, while clonazepam shows much greater efficacy in the treatment of panic disorder than alprazolam, lorazepam, and diazepam, which all have modest efficacy [224].

Appropriate Prescribing

Benzodiazepine treatment of anxiety disorders is controversial. While effective in rapid anxiety reduction, the potential drawbacks with long-term use are substantial. These agents are indicated when potent, short-term anxiolytic effects are necessary to permit infrequent exposure to feared stimuli and potentially severe anxiety, such as airplane travel [121; 129; 136]. Clonazepam, lorazepam, and alprazolam are effective for short-term use in panic disorder, GAD, and SAD, but ineffective for, and potentially worsening, comorbid depression [28]. The rapid anxiolytic effects make benzodiazepines highly appealing to patients with anxiety, but aside from this specific context, benzodiazepine prescribing for as-needed use is discouraged [136; 225; 226]. Benzodiazepines can reinforce pill taking, serve as a safety signal that undermines self-efficacy, and become incorporated into conditioned fear responses; these concerns are heightened with as-needed use. On-demand dosing links pill taking to rapid anxiety reduction, powerfully reinforcing avoidance in anxiety-provoking situations and encouraging longer-term reliance on the drug. This iatrogenic effect also contributes to poor CBT response.

The current recommended prescribing is for time-dependent use, instead of panic response-dependent use, to minimize the risks [121]. This would also seem to maximize risk of withdrawal syndrome from uninterrupted versus intermittent drug exposure.

Benzodiazepines are also useful in the initial weeks of SSRI/SNRI initiation, to rapidly reduce anxiety and possible early anxiogenic medication side effects before the onset of SSRI/SNRI anxiolytic effects [121; 129; 136]. However, patients may discontinue the antidepressant when co-prescribed a rapidly effective benzodiazepine, believing the benzodiazepine's symptom relief makes the SSRI/SNRI unneeded. Supportive therapy with regular visits or phone contacts may also help patients remain adherent until the delayed onset of antidepressant benefits appears or early antidepressant side effects lessen [227].

Another indication for benzodiazepine use is for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress. Perhaps the greatest prescribing challenge with benzodiazepines is preventing short-term use from insidiously developing into long-term use. Patients with the most severe anxiety may obtain the greatest relief and become most hesitant to discontinue use [228]. In many cases, clinicians ignore the recommended two- to four-week prescribing limit, mainly because alternative options with superior anxiolytic effects are not available [229]. Clinicians intending to prescribe alprazolam should carefully consider the likelihood that its use will remain restricted to the very short term—a few days to a couple weeks—to see the patient through a crisis [228].

Benzodiazepines may be prescribed to augment SSRI/SNRI therapy for improved response in select patients with significant residual anxiety or non-response. In one study, patients with SAD and sertraline nonresponse after 10 weeks were given sertraline plus clonazepam (≤3 mg/day), venlafaxine (≤225 mg/day), or sertraline plus placebo for 12 weeks. Those with sertraline augmented by clonazepam showed greatest reduction in SAD symptoms and a better overall response rate than comparator groups, although remission rates did not differ significantly [230]. These agents are third- or fourth-line treatment in patients unresponsive or intolerant to other anxiolytic drugs who remain highly symptomatic [121; 129; 136]. Generally, patients with a history of substance abuse, personality disorder, or chronic pain should not be treated with benzodiazepines because of the high risk for overuse of these medications [129]. While benzodiazepines should usually be reserved for patients lacking response to at least two treatments (i.e., non-response to an SSRI/SNRI and a psychologic treatment), concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing, and impairing anxiety symptoms [231].

It seems the most appropriate guidance for benzodiazepine prescribing involves occasional, context-specific use or cautious use during SSRI/SNRI initiation [3; 231]. Otherwise, benzodiazepines should be reserved for patients lacking response to three or more treatments, such as an SSRI, an SNRI, and a psychologic intervention, who remain highly symptomatic.

Risks/Drawbacks

While alprazolam remains the most-prescribed benzodiazepine for anxiety disorders, evidence suggests that relative to other benzodiazepines, alprazolam is no more effective and may have specific drawbacks [171]. Alprazolam may have greater potential for dependence than other benzodiazepines due to its rapid onset of anxiolysis and short half-life. With the short half-life, persons prescribed fixed-interval alprazolam (e.g., every six to eight hours) can experience morning withdrawal symptoms following the last nighttime dose. This is frequently mistaken as relapse in anxiety for which the drug was originally prescribed, confirming the continuing need for the drug [228]. The alprazolam product monograph states that such emergence of interdose symptoms reflect insufficient plasma levels, best managed by adding the same dose for four times daily administration (but breakthrough anxiety and alprazolam withdrawal are not differentiated). The document also states that alprazolam treatment of panic disorder differs from sub-syndromal anxiety, in that recommended dosing is as close to around-the-clock as possible, or three or four times per day [232].

Long-term benzodiazepine use can result in added symptoms during stable-dose maintenance, including increasing anxiety and withdrawal-associated symptoms such as perceptual disturbances and paresthesia. This emerging withdrawal syndrome despite ongoing benzodiazepine use is much more likely with highly potent and rapidly eliminated alprazolam or lorazepam and is temporarily alleviated by dose escalation. As craving, dysphoria, and other withdrawal symptoms develop over time between doses, the motivation to continue benzodiazepine use for anxiolysis gradually merges with the need to avoid withdrawal symptoms [233].

Benzodiazepine prescriptions are associated with nonmedical use and the development of benzodiazepine use disorder unrelated to co-occurring drug use or anxiety disorder diagnosis/severity [221]. Acute cognitive-impairing side effects are drowsiness, increased reaction time, ataxia, motor incoordination, and anterograde amnesia. In one study, long-term use of an average 17 mg/day diazepam equivalent led to substantial cognitive decline that did not resolve three months after cessation [234]. Motor vehicle accident risks during benzodiazepine therapy are comparable to driving with a blood alcohol concentration of 0.050% to 0.079% [235]. Hip fracture risk is increased by ≥ 50% in older persons who take benzodiazepines; with zolpidem, the risk is increased 200% in persons older than 65 years of age [236]. The risk of overdose is particularly great when benzodiazepines are combined with sedative drugs such as opioids or alcohol.

Personality traits associated with long-term use, emotional dependence, and more severe/protracted benzodiazepine withdrawal have been described. Long-term benzodiazepine users often have poor stress coping abilities. Benzodiazepines compensate for these deficits, but their use interferes with learning stress coping strategies, including behavioral therapy for agoraphobia. Passive-dependent personality traits and lack of internal and external stress coping resources increases vulnerability to withdrawal symptoms and motivation for continued use. In these patients, benzodiazepine deprivation renders them unprotected from stress and re-exposes their coping deficits. Chronically anxious people have been found innately hypersensitive to punishing stimuli and punishment; benzodiazepines can be described as "depunishing" drugs [233].

Withdrawal

Withdrawal symptoms following benzodiazepine cessation are appropriately concerning and a liability of this drug class that all prescribers should understand. In patients with panic disorder discontinuing alprazolam following 1.5 to 22 months of treatment, 33% to 100% were unable to completely taper [181]. These data did not include the 50% of long-term benzodiazepine users who do not consent to withdrawal studies or who later quit the study. The experience of benzodiazepine withdrawal is known to deter patients from future attempts [237]. An estimated 25% to 76% of patients prescribed benzodiazepines are long-term users. Defining high-dose benzodiazepine varies, but users of high-dose benzodiazepines commonly have comorbid disorders and are unlikely to benefit from current discontinuation and withdrawal strategies that expose them to greater risk of impairment and injury [237].

Despite comparable dosing, patients with panic disorder often show greater difficulty tapering than patients with GAD. Problems during alprazolam tapering are most severe during the last half of the taper. Patients with panic disorder receiving diazepam or alprazolam had fewer problems during taper of the top 50% of daily dose. However, with abrupt discontinuation of the remaining dose, alprazolam caused significantly more anxiety, relapse, and rebound. This may reflect greater problems withdrawing from short half-life, high-potency benzodiazepines like alprazolam [181].

The patient experience of benzodiazepine withdrawal was studied in 41 high-dose benzodiazepine-using inpatients deciding to withdraw (median dosage: 70 mg/day diazepam equivalent; median duration: six years) [237]. Driving this decision were health concerns of cognitive and physical impairments; feeling addicted; belief benzodiazepine use was a moral burden that limited autonomy; and pressure or coercion by relatives or institutional or governmental bodies to change benzodiazepine consumption patterns. The patients had long histories of repeated unsuccessful attempts to stop taking benzodiazepines and disappointment and frustration by the outcomes. However, many wanted to withdraw completely, with abstinence the goal. Most subjects described benzodiazepine withdrawal symptoms as severe, unpredictable, diverse in manifestation, and of duration difficult to anticipate. Common symptoms included chills, weakness, headache, muscle pains, abdominal pain, nausea, vomiting, diarrhea, tachycardia, dizziness, vision disorders, irritability, nervousness, restlessness, difficulties sleeping, depression, anxiety, tickling sensations, dissociation, complete loss of appetite, and epileptic seizures. Most experienced prolonged post-withdrawal symptoms. Many initially tried withdrawing by abruptly stopping benzodiazepine usage at home; most stated this resulted in perceived epileptic seizures. All favored gradual, long-term tapering over abrupt withdrawal [237].

Normally used to reverse benzodiazepine overdose and post-surgery sedation, flumazenil has shown effects that diminish benzodiazepine withdrawal severity and duration and improve abstinence rates. Dosage and infusion rates vastly differ between these two indications [238]. Flumazenil requires IV or subcutaneous infusion, because its brief half-life and extensive gastric metabolism prohibit oral use [239].

In a study of flumazenil IV infusion, 29 patients stopped benzodiazepines and began flumazenil 1.6 mg/day and oral clonazepam 2 – 6 mg/day. Antidepressants were started three weeks before the trial or were maintained. Clonazepam was tapered during outpatient follow-up. No patient dropped out, withdrawal severity showed significant linear reduction through the seven-day infusion, and 53% remained free of clonazepam and other benzodiazepines at six-month follow-up [240]. In patients with protracted withdrawal at 47 weeks, IV flumazenil significantly reduced aggression and hostility compared with placebo [241].

In research focused on subcutaneous infusion of flumazenil, patients were switched to oxazepam, began a 48-hour taper, and started flumazenil 16 mg over 96 hours. Subcutaneous infusion significantly reduced psychologic distress and benzodiazepine withdrawal symptoms during treatment. Patients with the highest initial withdrawal severity showed greatest improvement. Patients reported high treatment comfort, willingness to receive the treatment again, and likelihood to recommend it to a friend [239].

Flumazenil attenuates chronic benzodiazepine withdrawal symptoms by up-regulating benzodiazepine receptor binding sites to reverse uncoupling between benzodiazepine and GABA binding sites on the GABA-A complex. This reversal of GABA-A functional alteration helps explain its effect on benzodiazepine withdrawal and reports of positive effects on mood, memory, cognition, and motor performance [229].

CLINICAL ISSUES

Poor Treatment Response or Nonresponse

An estimated 30% to 60% of patients with anxiety disorders do not achieve meaningful symptom reduction or remission with initial therapy [242]. Decades of psychopharmacologic research have yielded safer, more tolerable side-effect profiles, but without improved efficacy in anxiety disorders. With poor or non-response, clinicians and patients then must decide how treatment should proceed, but research that best informs this clinical dilemma is only beginning to emerge. Given the limitations of SSRIs and benzodiazepines, investigators are pursuing novel treatment approaches and molecular targets [136].

With apparent patient nonresponse to treatment, clinicians should explore other factors before deciding the next therapy approach. The two broad causes of treatment resistance are pseudo-resistance and true treatment resistance [28].

Treatment Pseudo-Resistance

Pseudo-resistant patients have not actually received sufficient treatment, because of ineffective treatment matching for the anxiety diagnosis, insufficient medication dose or psychotherapy delivery, or patient non-adherence. Treatment pseudo-resistance may be the result of ineffective drug therapies, such a bupropion, beta-blockers (except in performance anxiety), buspirone and trazodone (except in GAD), and TCAs in SAD. Insufficient dosages and waiting an inadequate period for onset are also factors. The time for treatment onset is often longer for anxiety than depression. Patients may not fully respond until 8 to 12 weeks, and response may further increase in the second 6 months. Waiting an adequate time for response may be difficult for patients and healthcare providers, who may feel a need to change prescriptions or the regimen if a patient is distressed over his or her continued anxiety symptoms [28].

Poor patient adherence may also present as apparent treatment resistance. Only half of patients refill their first prescription, and many patients discontinue their drug in the first six months of treatment [136; 185]. Nonadherence may result from medication intolerance or side effects. Even if patients with troubling side effects do not stop the drug, the inherent distress avoidance and anticipatory anxiety with anxiety disorders can delay achieving adequate dose or taking medication long enough for response. Therapeutic skills can help to gain patient trust and overcome their anxiety of medication; adherence improves with medication counseling [136; 185]. Medication beliefs or attitudes that contribute to poor adherence include [28]:

- Unrealistic expectations
- Negative beliefs of perceived harmful effects
- Stigma
- Not "buying in" to treatment rationale or difficulty believing that treatment will work

- Psychologic conflicts over dependence and fear of becoming "addicted" to the medication
- Preference for psychotherapy over medication (as patients are less likely to adhere to a treatment modality they prefer less)

Following adherence and remission or large improvement, some patients will become non-adherent, and relapse follows. This may be addressed by explaining that the disorder requires ongoing treatment, like diabetes or any other chronic disease.

Overlooked Diagnosis, Comorbid Conditions, or Psychosocial Contributors

When established that adequate treatment was delivered and received, factors contributing to treatment resistance can include misdiagnosis or overlooked comorbidities or psychosocial factors. The following should be revisited [28]:

- Primary diagnosis accuracy
- Presence and contribution of unrecognized substance use disorder, psychiatric comorbidity, and/or complicating medical condition
- Psychosocial or lifestyle factors (e.g., caffeine overuse, sleep deprivation, interpersonal or family conflict)

Necessary Treatment Duration for Evidence of Response or Dose Escalation

With initiation of SSRI/SNRI treatment is the uncertainty over how long treatment should continue without signs of improvement before concluding a response is unlikely. With duloxetine and escitalopram, response is unlikely without clinical effect by four weeks of initiation. With pregabalin, onset of clinical effect within two weeks is associated with a 5.3-fold increased likelihood of treatment response; 25% of patients not showing clinical effect at two weeks will ultimately respond to treatment. A pregabalin dosage of 150 mg/day is suboptimal; a dose-response effect usually requires 300 – 600 mg/day [243].

In clinical trials of venlafaxine XR, therapeutic benefits usually separated from placebo at four to six weeks. However, the percentage remitted from panic disorder in one trial increased from 18% at 6 weeks to 50% at 12 weeks [244].

SSRIs/SNRIs usually take two to six weeks to show an initial "partial" response, often defined as ≥ 25% improvement (i.e., beyond random noise or natural symptom fluctuations). Full benefit may not appear for another four to six weeks or longer. Data from patients with depression, and some uncontrolled data with anxiety, suggest that about 20% of patients may need 10 to 12 weeks or longer before responding. Thus, dose escalation to highest level tolerated is recommended for patients with incomplete response before adequate time has passed [245]. In contrast to depression, antidepressant efficacy in anxiety disorders appears to be lost soon after stopping, with anxiety recurrence being the rule rather than the exception [228].

Patient Education

Successful medication treatment often involves dosage adjustments and/or trials of a different medication at some point in order to maximize response and minimize side effects. Because patient adherence is the essential pre-condition for maximum clinical benefit, the following messages should be communicated to the patient to encourage and support ongoing medication adherence [246]:

- Side effects often precede therapeutic benefit and typically recede over time.
- It is important to expect some discomfort prior to the benefit.
- Successful treatment may involve dose adjustments and/or trials of different medications to maximize response and minimize side effects.
- Most people must be on medication at least 6 to 12 months after adequate response, and patients may show improvement at two weeks but need a longer length of time to really see response and remission.

- It is important to take the medication as prescribed, even after feeling better, because early discontinuation is associated with high rates of relapse/recurrence.
- Do not stop taking the medication without calling the provider.
- Side effects can often be managed by changing the dose or dosage schedule.

A novel approach to improve patient understanding of their anxiety disorder and treatment rationale incorporates anxiety neuroscience. A core concept is that anxiety disorders/symptoms with amygdala origin (e.g., panic disorder, phobias) require different approaches than anxiety of cortical origin (e.g., SAD, GAD). Educating patients of the brain-based source of their anxiety can improve treatment adherence and empower patients to modify these areas of brain function. For example, patients with cortex-related symptoms such as obsessions, perfectionism, and chronic worry benefit from an approach termed "Question Your Cortex." They can be encouraged to identify anxiety-generating thoughts in the cortex and use cognitive restructuring methods to exploit cortical neuroplasticity by modifying their thoughts. However, cortex-based interventions are not effective at reducing or managing anxiety with amygdala-mediated symptoms; for these patients, exposure to feared situations is stressed. Most patients benefit from a combination of cortex- and amygdala-focused interventions, with the rationale and order of interventions differing by disorder and individual patient [247].

Antidepressant Withdrawal

In the SSRI literature, "withdrawal syndrome" has been largely replaced by the term "discontinuation syndrome" with industry support to convey the message that SSRIs do not cause addiction, dependence, or a syndrome similar to that experienced following benzodiazepine cessation. This has been challenged, given the potential seriousness of SSRI post-cessation symptoms, as a false dichotomy that minimizes the vulnerabilities induced by SSRIs. For the purposes of this course, the term "withdrawal syndrome" will be used [248]. Clinicians should be aware of these withdrawal syndromes, as misdiagnosis may result in inappropriate diagnostic tests and treatment and unnecessary patient distress and morbidity [248].

The National Collaborating Centre for Mental Health asserts that all patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug.

(https://www.nice.org.uk/guidance/cg113. Last accessed April 11, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

A 2015 meta-analysis found SSRI withdrawal symptoms can occur with any SSRI but are exceedingly more frequent with paroxetine [248]. Common symptoms include dizziness, nausea, headache, confusion, low energy, weakness, sleep disturbance, flu-like symptoms, restlessness, agitation, anxiety, panic, anger, and irritability. Less common and more severe symptoms include electric-shock sensations, vertigo, paresthesias, intensified suicidal ideation, aggression, derealization, depersonalization, and visual/auditory hallucinations. Symptoms do not greatly differ between patients with anxiety versus mood disorders. The authors concluded that the typical SSRI withdrawal syndrome begins within a few days of cessation and lasts two to three weeks [248]. Variations include late onset and protracted duration up to one-year follow-up. Several cases of persistent postwithdrawal disorders induced by paroxetine have been described.

Gradual tapering is a reasonable strategy but does not prevent the onset of SSRI withdrawal [248]. Patient characteristics that predict increased vulnerability are not known. Recognition of withdrawal symptoms requires careful exploration, as they can be misidentified as signs of impending relapse. Even when withdrawal symptoms are recognized, clinical management is hindered by the lack of research.

SSRI cessation may trigger complex phenomena related or unrelated to the onset of withdrawal, such as hypomania, mania, and persistent postwithdrawal disorders. Iatrogenic comorbidity describes the lasting effects from treatment well beyond their time of administration, such as mood instability and high reactivity to environmental stimuli in persistent postwithdrawal disorders [248].

Among 20 patients with remitted panic disorder with agoraphobia followed over one year after SSRI cessation, nine experienced SSRI withdrawal syndrome that subsided within one month [249]. Exceptions were three patients taking paroxetine, who experienced worsened mood, fatigue, and emotional lability with trouble sleeping, irritability, and hyperactivity. One patient prescribed clonazepam after three months of symptom persistence improved considerably but was later unable to discontinue clonazepam. A second patient did not improve with clonazepam or fluvoxamine, and symptoms subsided only with paroxetine reinstatement. In a third patient, clonazepam had little benefit, paroxetine reinstatement was refused, and symptoms persisted unchanged over one year [249].

Following SSRI/SNRI cessation, the rates of withdrawal syndrome range from 17.2% to as high as 78% (with venlafaxine). Among SSRI/SNRIs, venlafaxine XR may have the worst withdrawal syndrome. In addition to serotonergic withdrawal symptoms, palinopsia (persistent visual images) and sensory disturbances are frequently reported. These symptoms are described as sensations affecting the brain and head that feel like electrical shocks or the sensation of the brain shivering. This sensory disturbance, often accompanied by dizziness, headache, and disorientation, is distressing to patients and has been reported to persist for months after venlafaxine XR cessation [244; 250]. Other unexpected withdrawal symptoms that may emerge include gait difficulties, delirium, suicidal ideation, and hypomania or mania. The onset of withdrawal is usually one to four days post-venlafaxine XR cessation; dose reduction can also trigger withdrawal [251].

The etiology and treatment of these highly distressing sensory symptoms are unknown. However, contribution from noradrenergic dysregulation is suggested theoretically and by reports of positive treatment response to noradrenergic agents. Abrupt cessation of venlafaxine XR 37.5 mg led to a sensation that "felt like the brain was shaking inside the skull," with anhedonia, anxiety, tinnitus, headache, nausea, and increased noise sensitivity. A trial of the norepinephrine transporter inhibitor atomoxetine 40 mg/day led to immediate improvement in "brain shivers" two to three hours from the first dose [250]. Post-venlafaxine XR electric shock-like sensations and dizziness were greatly reduced by low-dose clonidine (0.05 mg twice/day), a central α-2 adrenergic agonist. The positive response suggests an underlying noradrenergic rebound mechanism [244].

Interdose withdrawal symptoms have been reported with venlafaxine XR, probably resulting from the "ultrarapid metabolizer" genetic variant of 2D6, the hepatic cytochrome P450 isoenzyme that metabolizes venlafaxine. Occurring in 3% to 5% of white individuals, this polymorphism accelerates venlafaxine elimination, causing interdose withdrawal [251].

Antidepressant Lethality in Overdose

In some patients with anxiety disorder, and especially those with depressive comorbidity, consideration of overdose fatality is necessary when deciding on therapy options. Lethality rates from intentional overdose involving single medication ingestions of agents commonly prescribed for depression and anxiety were calculated from data obtained during the period 2000–2014 [252]. TCAs remain the most lethal antidepressants, with fatality rates from 31–142 per 10,000 ingestions. Amitriptyline is associated with the greatest lethality in overdose and alone accounted for 37% of all deaths from antidepressants [252]. Lithium, bupropion, venlafaxine, quetiapine, and valproic acid had rates of 6.9–12.0 per 10,000 ingestions, while citalopram and fluvoxamine had rates of 3.9–4.1 per 10,000. Fluoxetine, sertraline, paroxetine, and escitalopram had the lowest overdose lethality rates at 0.79–1.34 per 10,000 ingestions [252].

Substance Use Disorder

Anxious patients often use alcohol or anxiolytics to regulate general anxiety, distressing panic symptoms, or social anxiety and social skills deficits. Substance use disorder is highly prevalent in patients with anxiety disorders and interferes with treatment response and leads to poor outcomes [28]. More than 33% of patients with GAD have an alcohol use disorder, and patients with SAD have a lifetime substance use disorder prevalence of roughly 40%. Nicotine dependence is also disproportionately high among patients with panic disorder [253; 254; 255].

Self-medication of anxiety disorder symptoms has been conclusively identified as a significant predictor for later development of alcohol or drug dependence. This is consistent with the self-medication hypothesis, which posits that the specific substance used for anxiety relief/control tends to be the substance to which the person develops a substance use disorder [256]. Ongoing substance use problems are abundantly linked to worse outcomes in comorbid anxiety disorders. Long-term effects of substance use negatively interact with anxiety symptoms, and quitting substances may improve anxiety in some patients. A trial of abstinence will usually answer this question. The duration must be several months to evaluate the link between anxiety and substance use, and there should be ongoing treatment, preferably in a 12-step program. Twelve-step programs have been shown to have anxiolytic effects themselves due to the support and empowerment they offer. Residual anxiety then should be treated with either medication or CBT [28].

If substance use is suspected, patients should be screened during diagnosis. A motivational interviewing approach is recommended to frame the rationale for substance abuse in a non-judgmental manner and explore patient desire and readiness for change. For patients initiating efforts to decrease substance use, concurrent treatment with an SSRI or venlafaxine is reasonable; benzodiazepines should be avoided due to the abuse liability [257]. Detoxification from alcohol or benzodiazepines is indicated if signs of substance withdrawal appear, and referral to a formal substance abuse treatment is recommended. Recognition and treatment of underlying substance abuse is an essential component in the overall treatment plan [13; 28].

Anxiety Disorder Treatment Effect Sizes

A 2015 meta-analysis of panic disorder, GAD, and SAD assessed treatment efficacy [224]. Studies published through 2012 were used to calculate medication, psychologic, or combination treatment efficacy. Effect sizes were calculated from pre- versus post-treatment and treatment versus control comparisons (***Table 3***) [224]. A significantly higher average pre-post effect size was found for medication outcomes than psychotherapy outcomes. Side effects, contraindications, drug interactions, and efficacy should all guide drug selection. Benzodiazepine abuse, dependence, and withdrawal potential; TCA side effects; and quetiapine metabolic risks make these agents second- to fourth-line options and not first-line options, as suggested by effect sizes alone [224].

EFFECT SIZES OF TREATMENTS FOR PANIC DISORDER, GENERALIZED ANXIETY DISORDER, AND SOCIAL ANXIETY DISORDER	
Treatment Modality	**Effect Size[a]**
Medications	
SNRIs	2.25
Benzodiazepines	2.15
SSRIs	2.09
Tricyclic antidepressants	1.83
Psychotherapy	
Mindfulness therapies	1.56
Relaxation	1.36
Individual CBT/exposure therapy	1.30
Group CBT	1.22
Psychodynamic therapy	1.17
Internet and self-directed therapies	1.11
Eye movement desensitization and reprocessing	1.03
Interpersonal therapy	0.78
Other approaches	
CBT/drug combination therapy	2.12
Exercise	1.23
[a]An effect size greater than 0.80 is considered large, indicating that the treatment is effective. CBT = cognitive-behavioral therapy, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin re-uptake inhibitor.	
Source: [224]	*Table 3*

TREATMENT OF GENERALIZED ANXIETY DISORDER

The primary goals of GAD treatment are reduction of anxiety symptoms and reduction or elimination of disability. Pharmacotherapy and CBT or cognitive therapy are equal as first-line options. CBT/cognitive therapy may be preferred by patients who are pregnant or who cannot tolerate or wish to avoid medication [258]. GAD is associated with specific biases for mood-congruent information. Patients with GAD are vigilant for threatening stimuli and tend to misinterpret ambiguous information as threat. These cognitive biases diminish with successful psychologic or drug treatment [243].

PSYCHOTHERAPY

First-Line Options

CBT

The use of CBT in patients with GAD usually combines psychoeducation, worry exposure, relaxation, applied relaxation, problem solving, cognitive re-structuring, and interpersonal psychotherapy. Meta-analyses clearly demonstrate that CBT significantly reduces GAD symptoms and is markedly more effective than placebo or wait-list control conditions [120]. Sessions should occur at least weekly over 6 to 12 weeks and involve 12 to 20 sessions. While fewer than eight sessions is as effective as eight or more sessions for anxiety symptoms, more intense regimens are more effective in improving worry and depression symptoms [258; 259; 260]. Individual

and group CBT seem equally effective in anxiety symptom reduction, but individual therapy may lead to earlier improvement in worry and depression symptoms [120].

According to the National Collaborating Centre for Mental Health, the recommended high-intensity psychological intervention for persons with generalized anxiety disorder is cognitive-behavioral therapy (CBT) or applied relaxation.

(https://www.nice.org.uk/guidance/cg113. Last accessed April 11, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Cognitive Therapy

Cognitive therapy teaches patients to evaluate their anxious thoughts objectively. Variants include pure cognitive therapy, cognitive restructuring, metacognitive therapy, and uncertainty intolerance therapy. Cognitive therapy typically involves 15 to 20 individual sessions [261].

As discussed, effective cognitive therapy/CBT treatment helps patients develop new, alternative strategies to manage worries and habits and cope with life stressors, which reduces the symptoms of anxiety. Cognitive therapy/CBT helps patients to understand [261]:

- They cannot control their fears, but can control their worrying behavior as a fear response.
- Worrying has no protective value, reinforces negative thinking, and increases the risk of escalating anxiety levels in the future.
- Worrying does not assist in managing negative future scenarios, and patients are equipped to handle whatever future challenges appear.

Cognitive therapy/CBT techniques may be especially helpful for generalized anxiety in later life [120].

Internet-Based CBT

Internet-based CBT is delivered by patient-administered media interventions. Components include cognitive restructuring, exposure, problem solving, and applied relaxation, usually over six to eight sessions [261; 262]. Efficacy is demonstrated, with benefits maintained at long-term follow-up. A peer-to-peer cognitive self-therapy program has been found as effective as treatment-as-usual, with a decreased need for therapist contact [120].

Applied Relaxation

Applied relaxation teaches the patient a coping skill that will enable him or her to relax rapidly, in order to counteract and eventually abort the anxiety reactions. This therapy is different from simple relaxation alone, which is not helpful. Applied relaxation entails having patients relax in actual anxiety-provoking situations. Effective applied relaxation involves around 15 individual sessions [261].

Second-Line Options

Acceptance and commitment therapy and mindfulness are CBT variants with promising initial results. They teach patients to focus on the present moment and follow actions guided by their values rather than by emotions and anxiety. Effective acceptance and commitment therapy usually involves 10 to 15 individual sessions [261].

Short- and long-term psychodynamic psychotherapy has shown efficacy and may be used with unavailability of CBT/cognitive therapy. Specific psychotherapy targets in GAD include intolerance of uncertainty, poor problem-solving confidence, and positive and negative metacognitive beliefs concerning the value or utility of worry [263].

Adjunctive Approaches

Additional modalities can be added to psychotherapy and/or drug therapy. Exercise is not widely studied in GAD, but available data have shown reduction in anxiety symptoms [264]. Meditation training is an option for patients unable or unwilling to receive psychotherapy [265]. Applied relaxation is effective as adjunctive therapy and uses relaxation techniques that are self-monitoring without the use of in-depth psychotherapy [266]. In addition, physical activity has been noted as a cost-effective treatment for GAD [121].

Sleep disturbances are highly prevalent in patients with GAD. Sleep hygiene education can be a useful tool in primary care, used with CBT in GAD to ensure the best possible sleep efficiency and quality. Patients can be counseled to improve sleep hygiene by going to bed and waking up at the same time each day, eliminating alcohol after 6 p.m., avoiding caffeine after 3 p.m., and getting out of bed if unable to fall asleep to avoid development of negative associations with the bed environment [267; 268]. Long-term follow-up data from a meta-analysis and randomized controlled trials suggest that benefits of psychologic treatments are maintained one to three years following treatment [120].

PHARMACOTHERAPY

In addition to efficacy, selection of initial drug therapy for GAD is based on illness severity and degree of distress, medical and psychiatric comorbidities, substance abuse profile, patient preference, and side effect profile.

First-Line Options

The ADAC and the Anxiety and Depression Association of America (ADAA) have created guidelines for the selection of appropriate pharmacotherapy in the treatment of GAD with differing recommendations regarding first- and second-line medications [120; 261]. The ADAC recommends agomelatine, pregabalin, venlafaxine XR, duloxetine, escitalopram, paroxetine, or sertraline as first-line options, while the ADAA suggests venlafaxine XR, duloxetine, paroxetine, escitalopram, sertraline, or fluoxetine [120; 261].

Pregabalin

Two randomized, placebo- and active comparator-controlled, double-blind studies evaluated the efficacy of pregabalin versus lorazepam for the treatment of GAD. The pregabalin and lorazepam groups experienced greater reductions in Hamilton Anxiety Rating Scale (HAM-A) score by week 4 compared with placebo, with no observed statistically significant differences among the active-treatment groups. Relative to placebo, pregabalin 600 mg significantly reduced psychic and somatic anxiety, while lorazepam significantly reduced somatic anxiety symptoms only. Anxiety reduction with pregabalin and lorazepam was evident within one week [185].

A four-week trial randomized 451 patients with GAD to alprazolam 1.5 mg/day; pregabalin 300, 450, or 600 mg/day; or placebo. As measured by HAM-A scores, psychic anxiety symptoms were significantly reduced (vs. placebo) with all pregabalin doses and alprazolam by weeks 1 and 4. Somatic anxiety symptoms were significantly reduced by 300 and 600 mg pregabalin, but not by 450 mg pregabalin or 1.5 mg alprazolam (vs. placebo). Pregabalin produced an early onset (≤1 week) of clinically relevant anxiety reduction comparable to alprazolam and anxiety reduction over a broader range of GAD symptoms than alprazolam by four weeks [269].

Data was combined from six placebo-controlled trials of patients with GAD randomized to pregabalin 150 mg, 300 – 450 mg, or 600 mg; lorazepam 6 mg/day; alprazolam 1.5 mg/day; or placebo. Pregabalin 300 – 600 mg significantly improved HAM-A psychic and somatic anxiety factor scores, but pregabalin 150 mg showed significance in psychic anxiety only. Of the 14 HAM-A items, significant improvement was shown on 13 with pregabalin 300 – 450 mg, 10 with pregabalin 600 mg, and 5 with benzodiazepines. A dose-response effect was evident for pregabalin [270].

Along with SSRIs/SNRIs, pregabalin is considered a first-line agent for long-term GAD treatment by the World Federation of Societies of Biological Psychiatry. Head-to-head studies with SSRIs/SNRIs are lacking, but pregabalin augmentation of SSRI/SNRI therapy has been found more effective than SSRI/SNRI alone [205].

Sleep dynamics were evaluated in healthy volunteers randomized to pregabalin (150 mg three times per day), alprazolam (1 mg three times per day), or placebo for three days. Pregabalin and alprazolam modestly but significantly reduced sleep-onset latency (compared with placebo). Pregabalin significantly increased the proportion of slow-wave sleep to total sleep period, and the slow-wave sleep duration of stage 4 sleep. Alprazolam significantly reduced slow-wave sleep. Rapid eye movement (REM) sleep latency with pregabalin did not differ from placebo and was significantly shorter than with alprazolam. Pregabalin and alprazolam similarly reduced the REM sleep proportion to total sleep (vs. placebo), while pregabalin significantly reduced the number of awakenings longer than one minute. Ease in getting to sleep and sleep quality were subjectively rated as improved with both active treatments. Pregabalin effects on sleep and sleep architecture were distinct from benzodiazepines. Enhancement of slow-wave sleep was relevant to frequent reports of reductions in slow-wave sleep in patients with fibromyalgia or GAD [271].

Clinical trials have reported euphoria, which emphasizes the need for careful and continuing evaluation of any potential for abuse. Reports of pregabalin abuse have appeared, usually involving individuals with a history of psychotropic medication abuse [243]. Discontinuation symptoms were reported after abruptly stopping pregabalin and were more prominent with higher daily doses. However, significantly fewer withdrawal symptoms were found after stopping pregabalin compared with lorazepam, and when tapered over one week, pregabalin withdrawal symptoms are minimal. Tentative evidence suggests pregabalin may be beneficial in withdrawal from benzodiazepines and related compounds [243].

Agomelatine

Agomelatine studies have mostly investigated its efficacy in GAD. Three randomized controlled trials have been performed. One trial with an escitalopram arm found that agomelatine led to comparable efficacy in GAD and significantly improved sleep restoration with fewer side effects and no discontinuation symptoms compared with escitalopram [202]. The low discontinuation rate reflected good tolerability, and laboratory results showed a low incidence of transient elevations in liver enzymes. Another trial that measured therapeutic response as 50% or greater reduction in HAM-A score found response rates of 66.7% with agomelatine, compared with 46.6% with placebo. Agomelatine was noted to improve sleep quality, with a lack of sexual side effects or discontinuation syndrome. Dizziness (8%) and nausea (5%) were more frequent than placebo [202; 272]. Agomelatine was superior to placebo in symptom reduction beginning at six weeks and in relapse prevention at six-month follow-up [203].

Second-Line Options

In patients for whom SSRIs/SNRIs are ineffective or intolerable, alternative agents with demonstrable efficacy include the TCA imipramine, the second-generation antipsychotic agent quetiapine, and pregabalin. Pregabalin is also effective for augmenting other first- and second-line agents in patients showing partial response. Internationally, pregabalin is regarded as a first-line option for GAD, but U.S. guidelines have not yet integrated this agent into the first-line tier [185].

Several options as second-line agents have efficacy in GAD comparable to first-line agents but possess potential side effects or other risks that preclude first-line use [120]. Benzodiazepines would be considered first in most cases, except where there is a risk of substance abuse, while bupropion XL would likely be reserved for later. Quetiapine XR remains a good choice in terms of efficacy, but given the metabolic concerns associated with this atypical antipsychotic, it should be reserved for patients who lack response or cannot tolerate antidepressants or

benzodiazepines [120]. It is important to note that drugs such as beta-blockers (e.g., propranolol) prescribed to address the physical symptoms of anxiety are ineffective in the treatment of GAD [243].

Quetiapine

In three 10-week randomized controlled trials of patients with GAD, quetiapine monotherapy showed clinically and statistically significant improvements in anxiety reduction and remission rates versus placebo [185]. Meaningful separation from placebo in anxiety reduction began as early as four to seven days after initiation of treatment. Somnolence, dizziness, and fatigue were more frequent with quetiapine, and sexual function improved slightly in quetiapine groups. Quetiapine has shown decreased symptom recurrence and improved sleep quality during maintenance treatment. However, quetiapine is not recommended for patients with nonresponding GAD because efficacy is inconsistent [185]. One literature review included three studies that evaluated the use of quetiapine extended-release (XR) as monotherapy for acute GAD treatment, one study that evaluated quetiapine XR monotherapy for maintenance treatment of GAD, and five studies that evaluated quetiapine (2 XR, 3 immediate release) as adjunct therapy for acute GAD treatment [273]. Quetiapine displayed both efficacy and tolerability in all monotherapy trials evaluating its use for acute and long-term treatment of GAD. Despite limitations to and heterogeneity among the five adjunct therapy studies, three studies showed that quetiapine resulted in statistically significant changes in the HAM-A scores [273].

Imipramine

While TCA use has become disfavored because of tolerability and safety issues, compelling support of imipramine efficacy in GAD came from a landmark study comparing the anxiolytic effects of imipramine, trazodone, diazepam, and placebo in nondepressed patients with GAD. Imipramine resulted in moderate-to-marked improvement between weeks 2 and 8 of therapy in 73% of patients, compared with 69% for trazodone, 66% for diazepam, and 44% for placebo [274].

Vortioxetine

Multiple randomized controlled trials involving patients with GAD found clinical improvement and symptom reduction with vortioxetine marginally greater or similar to placebo. With vortioxetine, discontinuation from side effects was modestly greater than placebo, with incidence of sexual dysfunction comparable. Patients with severe baseline GAD did show significantly greater benefit from vortioxetine [186; 275; 276].

Comorbid Major Depression

With a few caveats, treatment of GAD is generally the same whether comorbid major depression is present or absent. Use of buspirone and pregabalin is not recommended, while duloxetine has shown efficacy in comorbid anxiety disorder and major depressive disorder [277]. Patients with comorbid major depression and GAD prescribed benzodiazepines, sedating medications, or TCAs should be monitored for suicide risk; those with severe depression and suicidal ideation may require hospitalization while therapy is initiated [278].

Relapse Prevention

Relapse-prevention studies randomized patients showing response to acute treatment to placebo or the same medication/dose. Results in GAD showed significant advantages with continuing the active medications agomelatine, duloxetine, escitalopram, paroxetine, quetiapine, venlafaxine, or vortioxetine versus switching to placebo for periods of 6 to 18 months [243].

TREATMENT OF PANIC DISORDER

A meta-analysis found sufficient evidence that combined treatment is superior in panic disorder, with effects of combined psycho- and pharmacotherapy treatment versus placebo about twice as large as pharmacotherapy alone versus placebo [279]. The results also suggest that the effects of pharmacotherapy and psychotherapy are largely independent from each other and roughly equal in contribution to the effects of combined treatment. The effects remain strong and significant up to two years post-treatment. As such, monotherapy may not constitute optimal care [279].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Mental Health asserts that people who have panic disorder and their families and carers need comprehensive information, presented in clear and understandable language, about the nature of their condition and the treatment options available.

(https://www.nice.org.uk/guidance/cg113. Last accessed April 11, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

PSYCHOTHERAPY

Behavior Therapy

With panic disorder, behavior therapy consists of graded exposure to the body sensations that accompany panic (interoceptive exposure), to situations perceived as threatening (in vivo exposure, imagery exposure, virtual reality exposure), or both, in order to progressively reduce apprehensive reaction toward them by the patient. Although exposure strategies alone can be effective in the treatment of panic disorder, they do not appear to be a valid alternative to CBT as a first-line treatment [151].

Cognitive Therapy

In cognitive therapy for panic disorder, panic attacks are thought to result from the catastrophic misinterpretation of certain bodily sensations. The patient perceives the sensations of normal anxiety response as much more dangerous than they are, such as palpitations viewed as evidence of impending heart attack. Cognitive therapy identifies these negative interpretations of the bodily sensations experienced in panic attacks, suggests alternative non-catastrophic interpretations, and helps the patient test the validity of these alternative interpretations. While cognitive therapy is often combined with behavioral techniques, there is some evidence that training in cognitive procedures in isolation from exposure and behavioral procedures is efficacious in reducing some aspects of panic [151; 280; 281; 282; 283].

CBT

CBT assumes that cognitions, behaviors, and emotions are interrelated and combines behavior therapy and cognitive therapy to reduce emotional distress and psychologic symptoms. CBT usually includes psychoeducation, breathing retraining, progressive muscle relaxation, cognitive restructuring, behavioral experiments, interoceptive exposure, and in vivo exposure. A fairly consistent body of evidence supports the efficacy of CBT for panic disorder in individual or group sessions. There is also growing evidence that supports CBT efficacy when therapist-supported and self-administered via the Internet [151; 284; 285]. A network meta-analysis found that the most effective combination of CBT components for treatment of panic disorder were face-to-face and interoceptive exposure components, while muscle relaxation and virtual-reality exposure were the least effective components [286].

Patient Education

An essential step after diagnosis of panic disorder is to review with patients their fears of medical illness and expectations of medical testing and treatment. More than 80% of patients with panic disorder present with a medical symptom, and most are fearful of having a serious condition, such as a stroke. Clinical experience suggests that patients benefit from education about panic disorder as the cause of their symptoms and the mechanism by which a mental disorder may provoke physical symptoms. Educational materials for patients may be obtained from the ADAA (at https://adaa.org) and the National Institute of Mental Health (https://www.nimh.nih.gov) [129].

PHARMACOTHERAPY

The first-line drugs recommended for the treatment of panic disorder are SSRIs or venlafaxine XR [120]. Research suggests that the largest effect size is found with clonazepam, followed by venlafaxine and fluoxetine [224]. Despite a sizeable number of pharmacologic options, less than 50% of patients with panic disorder experience full and sustained remission to first-line medication therapy [287].

SSRI/SNRI

The SSRI safety/side effect profile relative to TCAs, MAOIs, and benzodiazepines led to their recommendation as first-line drug options for patients with panic disorder. SSRI side effects occur early in treatment before the therapeutic effects. Many patients with panic disorder are highly sensitive to side effects, and SSRIs should be started at low doses, with dose titration every five to seven days, as tolerated [129].

Following 10 weeks of venlafaxine treatment for panic disorder, patients with few dissociative symptoms during panic attacks showed significantly greater treatment response than patients with greater presence of panic attack-associated dissociative symptoms. These findings suggest that dissociative symptoms accompanying panic disorder negatively impact pharmacologic treatment response. Re-evaluation of dissociative symptoms at the beginning and end of treatment would help in personalizing therapy [288].

Benzodiazepines

A meta-analysis was performed of randomized controlled trials comparing alprazolam to other benzodiazepines in the treatment of panic disorder with or without agoraphobia [289]. In the pooled results, there were no significant differences in efficacy between alprazolam and comparator benzodiazepines on improvements in panic attack frequency, anxiety rating scores, or proportion of patients panic attack-free at final evaluation. To date, the evidence fails to demonstrate alprazolam superiority to other benzodiazepines for panic disorder treatment [289]. Additionally, while alprazolam is one of the most widely prescribed benzodiazepines for the treatment of panic disorder, its clinical use is contentious due to its potential for misuse [290].

TREATMENT OF AGORAPHOBIA

Almost all agoraphobia studies reported treatment outcomes of patients with co-occurring panic disorder, as they were not separated into distinct diagnostic entities until the DSM-5 was published in 2013.

PSYCHOTHERAPY

CBT is the most empirically supported psychosocial treatment for panic disorder with agoraphobia, with a central focus of repeated exposure to feared situations and sensations and application of skills learned in therapy. These include cognitive skills to control negative thoughts and somatic skills to control dysregulated physiology during exposure. While CBT has clearly been established as an effective treatment for panic disorder with agoraphobia, the effect sizes are smallest among the anxiety disorders and a large percentage of treatment completers are not panic free or do not reach responder status after treatment. The largest randomized controlled trial to date for panic disorder with agoraphobia found only 32% of those assigned to CBT alone demonstrated strong treatment response at 12 months post-treatment [162]. A small 20-year follow-up of patients with panic disorder with agoraphobia found that completion of medication-free, integrated exposure and psychodynamic treatment resulted in excellent very long-term outcomes for these patients [291].

The relevance of process variables in patient response and outcomes with CBT have been studied. Among 301 patients with panic disorder/agoraphobia, changes in panic symptoms were preceded by changes in catastrophic appraisal and agoraphobic avoidance in all treatment phases, anxiety sensitivity during generalization and follow-up, and psychologic flexibility during exposure therapy. Changes in functioning were preceded by changes in agoraphobic avoidance and psychologic flexibility in all treatment phases, fear of bodily symptoms during generalization/follow-up, and anxiety sensitivity during exposure. The effects of process variables on outcomes differed across treatment phases and outcomes. Agoraphobic avoidance and psychologic flexibility should be therapeutically targeted in addition to cognitive variables [292].

Low remission rates in patients with panic disorder/agoraphobia following CBT-based therapies has led to the development and evaluation of novel psychotherapies, adjunctive drug therapies, and cognitive enhancer drugs to improve exposure therapy response and remission rates.

Novel Psychotherapies

The intervention for patients with panic disorder/agoraphobia who are nonresponsive to CBT has generally been pharmacotherapy, with few studies evaluating a switch to psychotherapy. In one study, patients with previous unsuccessful state-of-the-art treatment were randomized to immediate acceptance and commitment therapy or four-week waiting list with delayed acceptance and commitment therapy; they were then followed for up to six months. Significantly greater changes in functioning and symptomatology were found in patients who received immediate acceptance and commitment therapy versus those on the waiting list, and medium-to-large effect sizes were maintained for six or more months. Acceptance and commitment therapy may be a viable treatment option for treatment-resistant panic disorder with agoraphobia [293].

A long-term study of patients with panic disorder and agoraphobia found catastrophic beliefs to be an important mediator of change. Of 46 patients with panic disorder/agoraphobia randomized to cognitive or guided mastery therapy, 31 (67.4%) medication-free patients who completed treatment were followed up to 18 years post-treatment. Both groups showed a large effect size for avoidance of situations when alone, and 56.5% no longer met diagnostic criteria for panic disorder or panic disorder with agoraphobia. Patient outcomes between the two treatments were comparable, although guided mastery was associated with greater beneficial changes in catastrophic beliefs and self-efficacy. Greater reduction in panic-related beliefs about physical and mental catastrophes predicted lower anxiety level at follow-up [294].

Combination Therapy

Following paroxetine plus CBT (once weekly for 12 weeks), paroxetine plus CBT and virtual reality exposure (four sessions), or paroxetine only, the six-month follow-up of 99 patients with panic disorder/agoraphobia showed reduced anxiety levels in all three groups and greatest reduction in both CBT groups. The virtual reality exposure group showed greater improvement in confronting agoraphobic stimuli, although medication cessation and dropout were high [295].

The one-year follow-up of patients with panic disorder with and without agoraphobia treated with CBT, SSRI, or CBT and SSRI found that panic attack frequency significantly declined in all groups and both SSRI groups improved significantly faster than CBT [296]. The SSRI gains were maintained after tapering. Panic frequency in patients with moderate-to-severe agoraphobia decreased more rapidly with CBT plus SSRI than either sole treatment. With CBT alone, improvement was slower than with SSRI or CBT plus SSRI. SSRI monotherapy was concluded sufficient for patients with panic disorder with no or mild agoraphobia, while patients with panic disorder and moderate-to-severe agoraphobia should receive CBT plus SSRI [296].

PHARMACOTHERAPY

An efficacy analysis of drug therapy trials in the treatment of panic disorder with agoraphobia was published in 2011 [86]. It concluded that panic attack recurrence worsens agoraphobic behaviors in panic disorder with agoraphobia and disrupts agoraphobia remission. This suggests that using panic attack-blocking medication in patients with panic disorder/agoraphobia at risk of panic attack recurrence is more appropriate than CBT alone.

The meta-analysis also found that paroxetine displayed high efficacy in panic and phobic symptoms and agoraphobia severity reduction. This efficacy was similar to CBT in reducing agoraphobic behaviors and superior to CBT in reducing panic attacks during acute treatment phase [86]. Adding paroxetine to CBT in patients with poor CBT response is significantly more effective in improving agoraphobic behaviors than adding placebo, so it is strongly suggested to add paroxetine for patients lacking adequate response or panic attack reduction with CBT [86]. Sertraline, citalopram, and escitalopram are also effective in the treatment of panic disorder/agoraphobia.

A randomized controlled trial compared treatment with an SSRI (paroxetine or citalopram) to continued treatment with CBT in a sample of 68 individuals with panic disorder (with or without agoraphobia) who had not responded to an initial course of CBT [297]. Participants were randomized to three months of treatment and then followed for an additional nine months. Those who responded to treatment after 3 months were maintained on the treatment until 12-month follow-up. Participants receiving an SSRI showed significantly lower panic disorder symptoms compared with continued CBT at three months, suggesting a greater improvement in panic disorder symptoms when patients are switched to an SSRI after failure to respond to an initial course of CBT [297].

The TCA clomipramine has similar panic/phobic efficacy to paroxetine and sertraline. Imipramine is more effective than placebo in long-term maintenance, but less effective than sertraline in short-term outcomes. Venlafaxine is effective in reducing panic and phobic symptoms [86]. Reboxetine is more effective in the treatment of panic/phobia than placebo. It has similar efficacy to paroxetine in phobic avoidance and anticipatory anxiety, but lower efficacy in reducing panic attacks.

Fluvoxamine has only inconsistent efficacy in the treatment of panic disorder/agoraphobia, and while fluoxetine may be used to address panic attacks, it has limited efficacy for panic disorder/agoraphobia [86].

These results suggest noradrenergic system involvement in modulating panic disorder with agoraphobia avoidance behaviors, but serotonergic system targeting is important to decrease panic attacks. Re-analysis of prior pharmacologic randomized controlled trial data found higher efficacy with sertraline and clomipramine in reducing agoraphobic symptoms than paroxetine, fluvoxamine, or citalopram. This may reflect the added dopaminergic modulation of these agents beyond their primary serotonergic activity [86].

A novel treatment approach is based on multiple findings of balance system dysfunction in patients with panic disorder/agoraphobia. An open study found citalopram influenced the balance system in these patients by improving postural stability, as measured by static posturography. Compared with baseline scores, most patients whose balance system function improved were no longer agoraphobic, while those whose posturography scores remained abnormal continued to be agoraphobic. These findings suggest the involvement of balance system dysfunction in panic disorder with agoraphobia and serotonergic system relevance in mediating the connection between balance and agoraphobia [298]. The authors suggest that real abnormal body

functioning (primarily involving cardiorespiratory and balance systems), which leads to reduced overall physical fitness, may be a primary cause of panic disorder and that the anxiety and fear it induces is sustained by repeated signals of impaired body functioning [299].

In one study, patients with panic disorder/agoraphobia received alprazolam plus exposure, alprazolam plus progressive muscle relaxation, placebo plus exposure, or placebo plus progressive muscle relaxation. The highest rate of improvement at follow-up was observed in the placebo/exposure (71%) and alprazolam/exposure (71%) groups; alprazolam/progressive muscle relaxation (51%) and progressive muscle relaxation/placebo (25%) groups were less improved [300]. Alprazolam showed no benefit over placebo when added to exposure therapy as treatment for panic disorder/agoraphobia [300].

CONTRIBUTING FACTORS TO PANIC DISORDER WITH AGORAPHOBIA TREATMENT RESPONSE

Pronounced safety behaviors during exposure therapy, but not at baseline, have been associated with poor treatment response in patients with panic disorder/agoraphobia. This underscores the importance of rigorous safety behavior assessment during therapy [301].

During 13 to 21 years post-treatment follow-up, major depression at baseline predicted worse improvement in agoraphobic avoidance in the first year. Employment and marriage/cohabitation at baseline predicted greater improvement at 1-year, 2-year, and 13- to 21-year follow-up [302].

A substantial number of patients with panic disorder/agoraphobia fail to improve following CBT. Agoraphobic avoidance is the most consistent predictor of decreased improvement, followed by low expectancy for change, high levels of functional impairment, and Cluster C personality pathology [303].

TREATMENT OF SOCIAL ANXIETY DISORDER

PSYCHOTHERAPY

CBT is the criterion-standard psychologic treatment for SAD. Cognitive techniques that address SAD include restructuring and challenging maladaptive thoughts, and the behavioral component typically involves exposure therapy. The efficacy of CBT is supported by many randomized controlled trials, with outcomes that vary but are typically similar to pharmacotherapy. Some reports suggest that, after treatment discontinuation, gains achieved with CBT may persist longer than those achieved with pharmacotherapy. CBT for SAD can be administered in group or individual formats. Although some studies have reported that individual CBT is superior to group CBT, meta-analyses have failed to find significant differences in efficacy between the two modalities. There is evidence to support the effectiveness of exposure therapy alone, but efficacy compared with CBT is equivocal [120].

Several CBT variants have been examined. Videotaped feedback was not shown to enhance the effects of exposure-based treatment. However, CBT with virtual reality exposure was found more effective than wait-list control and as effective as CBT with imaginal or in vivo exposure according to two meta-analyses [120].

A form of CBT focused on interpersonal behavior found similar improvements in social anxiety compared to standard CBT and also increased relationship satisfaction and social approach behaviors. Evidence to support interpersonal therapy in SAD is conflicting; while some results are negative, interpersonal therapy is probably more effective than wait-list control, but less effective than traditional CBT [120].

With Internet CBT for SAD, patients with an avoidance and depression profile showed lower remission after treatment, higher levels of social anxiety at follow-up assessments, and typically remained highly symptomatic. In patients with SAD, high levels of social avoidance and depressive symptoms constitute a risk profile for poor treatment response [304].

PHARMACOTHERAPY

Pharmacotherapy of SAD is effective but varies considerably, with room for further improvement [305]. The ADAC recommends escitalopram, fluvoxamine (immediate- or controlled-release), paroxetine (immediate- or controlled-release), pregabalin, sertraline, or venlafaxine XR for first-line treatment of SAD [120]. Citalopram has less evidence but is likely as effective as other SSRIs. Phenelzine efficacy is established in multiple randomized controlled trials but is recommended as a second-line option due to concerns over dietary and medication restrictions that, if not strictly adhered to, can lead to hypertensive crisis [120].

Abnormalities in brain GABA and glutamate systems have been studied in patients with SAD, including whether these changed following eight weeks of levetiracetam. Compared to healthy controls, patients with SAD at baseline showed significantly higher whole brain levels of glutamate and glutamine (but not GABA) and significantly higher thalamic glutamine and lower GABA levels. Following treatment, these patients showed significant reduction in thalamic glutamine. These findings support the role of impaired GABAergic and overactive glutamatergic function in SAD and may explain the anxiolytic effects of levetiracetam [306].

TREATMENT OF SPECIFIC PHOBIA

Patients with specific phobias generally do not consult medical professionals when able to avoid the specific feared situations or objects. Exposure therapy is effective in treating specific phobia and is the favored approach.

PSYCHOTHERAPY

Exposure-based therapies are the treatments of choice and show a high degree of successful remission for all phobias. In vivo exposure and virtual reality exposure can be effective, with in vivo exposure superior to imaginal and virtual reality exposure at post-treatment but not at follow-up [307]. The effectiveness of exposure-based therapy is enhanced when exposure sessions are grouped closely together; when exposure is prolonged, real (not imagined), and provided in different settings; and when there is some degree of therapist involvement instead of being entirely self-directed. A greater number of sessions have been shown to predict more favorable outcomes. There is no evidence that flooding is more effective, and patients usually find graded, progressive exposures more tolerable [307].

A variety of psychotherapeutic options have been found effective for the treatment of specific phobias, with some approaches recommended for particular phobias (***Table 4***) [120]. For blood-injection-injury phobias, an effective approach is combining exposure therapy with muscle tension exercises (applied tension) designed to prevent fainting. Using stress-reducing medical devices, such as decorated butterfly needles and syringes, has significantly reduced needle phobia and stress in pediatric and adult patients. With dental phobias, use of CBT can reduce avoidance of oral injections and decrease patient anxiety [120; 307].

PSYCHOLOGIC TREATMENTS EFFECTIVE IN SPECIFIC PHOBIA	
Treatment Approach	**Phobia(s)**
Exposure-based treatments	All specific phobias
Virtual reality exposure	Heights, flying, spiders, claustrophobia
Computer-based self-help programs	Spiders, flying, small animals
Applied muscle tension (i.e., exposure with muscle tension exercises)	Blood-injection-injury type
Cognitive therapy and exposure	Dental, flying
Source: [120]	*Table 4*

Long-term treatment of specific phobia is rare. CBT and exposure therapies show sustained benefits at long-term follow-up assessments following a time-limited course of treatment [120].

The National Collaborating Centre for Mental Health recommends against routinely offering computerized CBT to treat specific phobias in adults. (https://www.nice.org.uk/guidance/cg159/resources/social-anxiety-disorder-recognition-assessment-and-treatment-pdf-35109639699397. Last accessed April 11, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

PHARMACOTHERAPY

Pharmacotherapy has a minimal role in specific phobia treatment, largely from the lack of drug therapy research and the success of exposure therapies. Alprazolam benefit was studied in 28 women with flying phobia during two air travel exposures, one week apart. Compared with subjects given pre-flight placebo for both flights, those receiving alprazolam before the first flight had less anxiety and symptoms but greater heart and respiratory rates. Those given alprazolam had a substantial increase in panic attacks during the second flight compared with the first flight (71% vs. 7%), greater overall anxiety, and further elevation in heart rate. Alprazolam increased physiologic activation under acute stress conditions and hindered the therapeutic effects of exposure therapy for flying phobia [120; 308]. These findings require replication to determine clinical utility.

Some benefit is suggested by small trials of paroxetine or escitalopram. However, there is too little evidence to recommend any drug treatment of specific phobias [224].

A NOVEL APPROACH COMBINING MEDICATION AND EXPOSURE THERAPY

In 2015, a potential landmark study of 45 subjects with spider phobia was published. A pre-treatment two-minute tarantula exposure was followed four days later by randomization to propranolol without exposure or to exposure and then propranolol 40 mg or placebo (within 10 minutes). All three groups went through tarantula exposure 9 days, 16 days, 90 days, and one year later [309].

After nine days, all exposure/propranolol subjects touched the tarantula, while the other two groups barely touched its container. By 16 days, all exposure/propranolol subjects further progressed in approach, while the two other groups did not progress. Approach behavior remained stable for all three groups throughout one year. Most interestingly, significant reduction in self-reported spider fear lagged several months behind the instant behavioral transformation in the exposure/propranolol group [309].

This study is the first to identify optimal drug and timing for durable remission of phobic anxiety and avoidance. The results challenge the fundamental tenet of CBT that changes in cognition are necessary for behavioral change. Such a novel approach is clearly needed, and similar trials enrolling subjects with agoraphobia and social phobia are expected in the future [309].

TREATMENT OF SEPARATION ANXIETY DISORDER

PSYCHOTHERAPY

As mentioned, the presence of pathologic separation anxiety has a pervasive negative influence on treatment response in patients with diverse anxiety and mood disorders receiving standard therapies. Patients with SEPAD show poor response to standard CBT and exposure-based therapies. This poorer treatment response may reflect the difficulties these patients experience forming and maintaining attachments, including therapeutic relationships. Growing evidence points to the incompatibility in applying the prevailing fear extinction model of anxiety to patients with SEPAD. This pathophysiologic model emphasizes desensitization to threatening stimuli. While theoretically and empirically supported in other anxiety disorders, this model does not consider the role of earlier childhood SEPAD in adult panic disorder and other anxiety disorders [98].

The unmet need for SEPAD-specific treatment has led to psychotherapies that focus on relationships and separation anxiety. These approaches use the therapist-patient relationship to recapture and better understand important elements of earlier pathologic parent-child relationships. Panic-focused psychodynamic psychotherapy is an affect-focused therapy that specifically targets separation anxiety as a core component of panic disorder. Preliminary efficacy is shown in patients with prominent separation anxiety symptoms across different anxiety and mood disorders. High separation anxiety levels constitute a central organizing element in patient self-perception as incompetent and unable to manage developmentally normative tasks without the presence of their central attachment figures. Panic-focused psychodynamic psychotherapy emphasizes free association, centrality of transference, unconscious thoughts that underlie physical sensations of panic, and difficulty with separation and autonomy. The therapist focuses on these processes as they relate to panic symptoms. Common themes of difficulty with separations and unconscious rage inform interpretive interventions. The pre-determined 24-session, 12-week time limit enhances the opportunity to work with separation anxiety and permits the re-experiencing and better understanding [98].

PHARMACOTHERAPY

With adult SEPAD becoming formalized in 2013 as a distinct diagnostic entity and anxiety disorder, little pharmacotherapy research has been performed specifically addressing this condition.

EMERGING THERAPIES AND NOVEL TREATMENT APPROACHES

NEUROENHANCING AGENTS TO AUGMENT EXPOSURE THERAPY

Some neuroenhancers, especially D-cycloserine (DCS), are promising for treating anxiety disorders because these agents improve extinction learning efficacy, integral in exposure therapy. They facilitate learning new memories through habituation and extinction, and these safe memories will over-ride the previous fear memories. Use of neuroenhancers to augment CBT represents a promising translational effort—taking neuroscience discovery into clinical practice. In contrast, use of anxiolytics and CBT in anxiety disorders did not originate from a theoretical basis for the mechanism of action, and overall effectiveness leaves substantial room for improvement [164].

D-Cycloserine

The most extensively studied exposure augmentation agent is DCS, an *N*-methyl-D-aspartate (NMDA) receptor partial agonist. Findings that extinction learning is modulated, in part, by the glutamatergic NMDA receptor complex prompted interest in the role of glutamatergic transmission in anxiety disorders. Clinical trials began to study the potential efficacy of low-dose DCS for enhancing memory consolidation and effectiveness of exposure therapies for anxiety disorders [165]. DCS studies of patients with specific phobia (e.g., heights, snakes), OCD, panic disorder with agoraphobia, PTSD, or SAD have been published. Following promising early findings, more recent studies have reported inconsistent results, including findings that DCS resulted in faster rates of improvement but not higher response or remission rates in SAD and even more symptoms at post-treatment in PTSD. These inconsistent trials have informed the understanding of limitations and indications of DCS augmentation of exposure therapy [310; 311; 312; 313].

Dosing and dose timing of DCS is essential. Most trials reporting positive results used low-dose DCS (50–250 mg) one to two hours before three to five exposure sessions. Studies with negative results often used higher doses (≥250 mg), chronically (before 12 exposures), and more than one to two hours before an exposure. Higher-dose DCS shows weaker NMDA partial agonist or antagonist effects. Key extinction learning processes occur hours following exposure, and DCS blood concentration peaking at four to six hours makes it more effective taken within one to two hours before exposure for peak activity to coincide with key extinction processes. Repeated DCS use can desensitize the NMDA receptor complex, leading DCS to effectively work as an NMDA antagonist. Long-term antidepressants can induce neurochemical changes at the glycine binding site of the NMDA receptor complex, which alters the action of DCS. Therefore, use of DCS should consider the narrow therapeutic window and the need to be administered without concomitant medication, acutely, and at low doses one to two hours pre-exposure [310].

DCS is associated with serious risks. DCS not only enhances cognitive processes during fear extinction learning but also during fear memory reconsolidation, thus improving good exposures and worsening bad exposures. If fear-inducing stimulus re-exposure during fear memory reactivation is too brief relative to the strength of fear conditioning or if fear decrease during exposure is inadequate, little extinction is induced and DCS can augment the process of fear memory reconsolidation to worsen symptoms [310].

These findings led to DCS administered post-exposure, contingent on the level of fear reduced (i.e., extinction learning achieved) by the end of the exposure session. Preliminary evidence shows that this approach may be effective in capitalizing on the benefits while minimizing the risks of DCS use to augment exposure therapy [310].

Yohimbine Hydrochloride

Yohimbine hydrochloride (YOH) is a selective competitive alpha2-adrenergic receptor antagonist currently only approved for veterinary use. This compound increases extracellular norepinephrine in humans by blocking autoreceptor inhibition of norepinephrine release. This mechanism potentially facilitates extinction learning in exposure therapies. Placebo-controlled trials have been performed in specific phobia and SAD. Subjects with claustrophobia given YOH 10.8 mg before two 60-minute exposures of sitting in a closed, dark chamber showed more robust reductions in claustrophobia symptoms. Patients with SAD given YOH 10.8 mg before four exposure sessions showed accelerated treatment improvement and lower levels of social anxiety symptoms. More research is needed, but these results suggest YOH may have a role in augmenting exposure therapy [164].

Glucocorticoids

Glucocorticoids have shown enhancement of virtual reality-based exposure therapy for fear of heights and were investigated for possible outcome enhancement in exposure-based group therapy for spider phobia. In one randomized controlled trial, cortisol 20 mg or placebo was orally administered one hour before each therapy session and patients were assessed at one-month post-therapy follow-up. Compared to placebo, cortisol led to significantly greater reduction in fear of spiders at follow-up but not immediately post-treatment, as measured psychometrically and by exposure to live spiders. Groups did not differ in phobia-unrelated state-anxiety before and after exposure sessions and at follow-up [314].

Another randomized controlled trial investigated the role of hydrocortisone as an adjunct to brief CBT for specific (spider) fear [315]. Spider-fearful participants were randomized to receive either 20 mg hydrocortisone or placebo one hour prior to single-session, predominantly computerized, exposure-based CBT. Participants' fear of spiders was assessed using self-report and approach behaviors measured at baseline and at one-day and one-month follow-up. Threat processing was assessed at baseline and at one-day follow-up. Cortisol and cortisone levels from hair and saliva samples were analyzed at baseline. All measures improved following CBT. Augmentation with hydrocortisone resulted in greater improvement in self-reported fear and approach behavior but not threat bias. Neither threat bias nor endogenous glucocorticoids predicted symptom change. Evidence indicates that higher hair cortisone predicts a stronger threat bias reduction [315].

Methylene Blue

Methylene blue is a nitric oxide synthase inhibitor, central MAO inhibitor, and cerebral metabolic enhancer. A placebo-controlled trial of subjects with severe claustrophobic fear found that participants displaying low fear at the end of extinction training showed significantly less fear at follow-up if they received methylene blue post-training relative to placebo. In contrast, participants displaying moderate-to-high levels of post-training fear tended to fare worse at follow-up with methylene blue compared with placebo. Similar to the profile of DCS, methylene blue enhanced memory and retention of fear extinction when administered after a successful exposure session, but it may have deleterious effects on extinction when administered after an unsuccessful session [316].

CAPNOMETRY-ASSISTED RESPIRATORY TRAINING

Panic disorder and sensitivity to increased carbon dioxide (CO_2) levels common in patients with panic disorder may represent pathologically amplified survival mechanisms. Panic disorder reflects a "fight-or-flight" response, and CO_2 hypersensitivity is an evolutionary carry-over from when alarm response to dwindling oxygen helped ensure survival. Panic attacks that awaken people at night only occur during non-REM sleep, when deep relaxation and slowed breathing lead to rising CO_2 levels that trigger a false suffocation alarm [317].

Capnometry-assisted respiratory training (CART) is an intervention that addresses CO_2 fluctuation and its role in panic attacks for some people. CART targets respiratory dysregulation and hypocapnia through a four-week training using immediate feedback of end-tidal CO_2 pressure (PCO_2). Patients are taught how to raise subnormal PCO_2 levels (caused by hyperventilation) to control dysfunctional respiratory patterns and related panic symptoms of shortness of breath and dizziness. CART uses novel technologies that allow precise assessment and monitoring of core respiratory variables. A portable capnometer offers breath-by-breath feedback of expired CO_2 and breathing rate, as measured via nasal cannula.

In one study, four weeks of CART led to reductions in panic symptom severity and frequency comparable to standard CBT, maintained at 12-month follow-up. Patients with panic disorder/agoraphobia randomized to four weeks of CART or cognitive therapy showed significant and comparable reductions in panic symptom severity and panic-related cognitions [281]. Across studies in patients with panic disorder with agoraphobia and asthma, compliance with the 17-minute, twice-daily exercises was high, and compliance correlated with the extent of panic symptom reduction [281; 318]. Changes in PCO_2 mediated and preceded changes in fear of panic sensations, cognitive reappraisal of symptoms, and perceived control. Reductions in respiration rate were unrelated to outcome [281; 319]. These findings strengthen the idea that panic symptom reduction can be achieved through different mechanisms [162].

NEUROMODULATION THERAPIES

Brain stimulation (also referred to as neuromodulation, neurostimulation, or somatic therapy) for the treatment of neuropsychiatric disorders was developed as an option for patients with severe disorders refractory to multiple treatments. Electroconvulsive therapy, introduced more than 75 years ago, has been historically the only widely used somatic treatment of psychiatric disorders. This was changed by the development and FDA approval of several minimally or non-invasive brain stimulation modalities with much greater specificity than electroconvulsive therapy. Other modalities are undergoing evaluation and possible market entry [320]. This approach shifts the treatment focus from altering synaptic neurotransmission to altering or modulating the function of entire neural circuits, the dysfunction of which underlies anxiety disorders [120].

Repetitive Transcranial Magnetic Stimulation

The most studied neurostimulation approach in the United States is repetitive transcranial magnetic stimulation (rTMS). As discussed, patients with panic disorder often lack response or only partially respond to drug or psychologic treatments, which increases the risk of the disorder becoming chronic and disabling. Transcranial magnetic stimulation delivers non-invasive stimulation to the cerebral cortex, with currents induced by powerful, extremely brief magnetic fields. Administration in a rhythmic, repetitive form is rTMS. Modulation of cortical excitability uses high-frequency rTMS to increase cortical excitability or low-frequency rTMS to inhibit cortical excitability of targeted areas. rTMS can also affect remote brain areas connected to the stimulated site [321].

Early studies of rTMS in anxiety disorders often found no difference between active vs. sham rTMS, reflecting the inability to stimulate brain regions deeper than superficial cortical layers and inadequate treatment duration or post-treatment follow-up [322]. Subsequent technical refinements show treatment efficacy.

A randomized controlled trial treated 28 patients with panic disorder and major depression with active or sham rTMS to the right dorsolateral prefrontal cortex. Response was defined as reduction by ≥40% in panic disorder severity and ≥50% in depression ratings. After four weeks, panic disorder response rate was 50% with active and 8% with sham rTMS, with no difference in depression. After eight weeks of active rTMS, response rates were 67% for panic and 50% for depressive symptoms. Significant improvements occurred in panic disorder, major depression, clinical global impression, and social adjustment. Clinical improvements were maintained at six months post-treatment. While four weeks of rTMS was sufficient to significantly reduce panic symptoms, a longer course led to better outcomes for both panic disorder and major depression. These data suggest that inhibitory rTMS to the right dorsolateral prefrontal cortex affects symptom expression in comorbid anxiety and depressive disorder [323]. Another study found that inhibitory rTMS to the left dorsolateral prefrontal cortex showed therapeutic effects in patients with major depressive disorder [324].

NEW OR NOVEL ANXIOLYTIC AGENTS

Cannabidiol

Cannabidiol is the second most abundant cannabinoid in *Cannabis* plants and lacks the consciousness-altering effects of delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound in *Cannabis*. Cannabidiol is a pharmacologically broad-spectrum drug that has drawn increasing interest as a treatment for a range of neuropsychiatric conditions, including anxiety disorders. Preclinical evidence supports cannabidiol as a treatment for GAD, panic disorder, SAD, OCD, and PTSD when administered acutely, but few studies have investigated chronic cannabidiol dosing. Randomized controlled trials showed that, relative to placebo, cannabidiol significantly reduced anxiety in patients with SAD and GAD [136; 325].

In a series of randomized controlled trials using fear-conditioning paradigms, subjects who received cannabidiol (vs. placebo) all showed successful conditioning, extinction, and recall. When given after resolution of symptoms, cannabidiol enhanced consolidation of extinction learning. Cannabidiol administered pre- or post-extinction reduced the reinstatement of autonomic contextual responding. No acute effects of cannabidiol were found on extinction. These results are the first evidence that cannabidiol may enhance consolidation of extinction learning in humans, suggesting cannabidiol may have potential as an adjunct to extinction therapies for anxiety disorders [326].

Brain imaging cannabidiol trials in patients with GAD or SAD consistently showed changes in functional activity in limbic and paralimbic cortical areas implicated in anxiety pathophysiology, with effects in the left para-hippocampal gyrus, the hippocampus, and the right posterior cingulate gyrus. Cannabidiol was found safe and tolerable, with few side effects and without major side effects during acute treatment. Cannabidiol administered chronically in oral doses of 10–1,280 mg/day to healthy volunteers and patients with schizophrenia, bipolar affective disorder, Parkinson disease, or Huntington disease did not find significant side effects or induction of any new neurologic, psychiatric, or general clinical conditions [136; 327]. Overall, evidence indicates cannabidiol has considerable potential as a treatment for several anxiety disorders, with further study of chronic and therapeutic effects in relevant clinical populations needed [325; 328].

Etifoxine

Etifoxine (also known as etafenoxine) is a non-benzodiazepine anxiolytic and anticonvulsant not yet approved in the United States. Clinical effects are mediated by GABA-Aα2 receptors, similar to benzodiazepines, and etifoxine appears to produce anxiolytic effects directly by binding to β2 or β3 subunits of the GABA-A receptor complex. The effects of etifoxine are not completely reversed by the benzodiazepine antagonist flumazenil. Etifoxine also stimulates neurosteroid production, which contributes to anxiolytic and neuroprotective effects. Several randomized controlled trials comparing etifoxine to lorazepam found vigilance, psychomotor performance, and free recall significantly impaired by lorazepam but not etifoxine. Superior anxiolytic effect and memory recall were noted with etifoxine, with fewer withdrawal symptoms than with lorazepam. Etifoxine appears promising as a non-benzodiazepine anxiolytic agent that lacks many shortcomings with benzodiazepines and SSRIs, although acute liver toxicity has been reported [329; 330].

Asenapine

Asenapine is a newer atypical antipsychotic drug. Its dominant mechanism of action is mediated through 5HT2A and D2 receptor antagonism and also by antagonism of 5HT2B, 5HT2C, 5HT6, and 5HT7 serotoninergic; α1A, α2A, α2B and α2C adrenergic; and D3/D4 dopaminergic receptors [178]. Clinical efficacy in anxiety and mood disorders is predicted by its serotoninergic profile. This agent lacks affinity for muscarinic receptors and induces fewer anticholinergic side effects than other second-generation antipsychotics [331]. Asenapine is FDA-approved for schizophrenia and bipolar disorder; its use for anxiety disorders is off-label [178].

Tandospirone

Closely related to buspirone, tandospirone (also known as metanopirone) is a 5-HT1A receptor partial agonist used in China and Japan. Its efficacy was compared to sertraline in an eight-week randomized controlled trial in adolescents with SAD. Both drugs significantly improved anxiety scores from baseline, showed similar overall response and anxiety symptom-specific response rates (≥50% reduction), and resulted in significant and comparable improvements in social phobia symptoms. Tandospirone appeared non-inferior to sertraline treatment of SAD in adolescents. The drug is not FDA-approved [332].

COMPLEMENTARY/ ALTERNATIVE THERAPIES

HERBAL PRODUCTS AND SUPPLEMENTS

Myo-Inositol

Myo-inositol is a glucose isomer and essential component of the phosphatidylinositol second messenger system critically linked to several CNS receptor-signaling systems [333]. Myo-inositol anxiolytic and antidepressant activity is mediated by a serotoninergic 5-HT2A/5-HT2C receptor-signaling pathway [334].

Several randomized controlled trials have been conducted using placebo or active controls. In 21 patients with panic disorder with or without agoraphobia given inositol 12 g/day or placebo for four weeks, significant decreases were found in the frequency and severity of panic attacks and agoraphobia severity with inositol relative to placebo [335]. Another randomized controlled trial compared myo-inositol 18 g/day with fluvoxamine 150 mg/day in patients with panic disorder with or without agoraphobia. Both drugs led to significant but comparable improvements in anxiety symptoms/severity, agoraphobia symptoms/severity, and global impression. In the first month, reduction in the number of panic attacks per week was significantly greater with inositol than fluvoxamine (4.0 vs. 2.4). Nausea and fatigue were significantly more common with fluvoxamine [336].

Other randomized controlled trials found that myo-inositol 12 g/day in 28 patients with major depression significantly reduced Hamilton Depression Rating Scale scores (vs. placebo) after four weeks; and 18 g/day given to patients with OCD for six weeks led to significant reductions in OCD symptom scores (vs. placebo) [335]. A review of supplements and herbal therapies with purported anxiolytic efficacy concluded myo-inositol was one of very few with demonstrated effectiveness [337]. The published research needs larger trials but is intriguing in light of a study in which patients with severe depression receiving treatment with rTMS showed significantly elevated prefrontal cortex myo-inositol levels, and this elevation correlated with extent of clinical improvement [338]. A meta-analysis of inositol for depression and anxiety disorders found that the agent may be particularly beneficial for treatment of depression [339].

The effective dose is 12–18 g per day, and inositol is free of side effects other than loose stools and drowsiness [335]. A drawback is the large amount required for therapeutic benefit, necessary to compensate for poor blood-brain barrier penetration.

An Italian pharmaceutical company has developed a more concentrated myo-inositol formulation, with dose comparability to standard myo-inositol at 25% the dose level [338].

Overall, inositol is a natural compound with few side effects and may be an attractive option for patients with panic disorder who are ambivalent about taking psychiatric medication [336]. Myo-inositol is one of nine inositol isomers, but unless another inositol isomer is specified, inositol sold at retail is almost always myo-inositol.

Kava

Kava (*Piper methysticum*) extract has been used for anxiolytic effects, mediated through GABA channel modulation and weak GABA binding, β-adrenergic downregulation, and MAO-B inhibition. Efficacy studies in GAD showed superiority to placebo and comparability to buspirone. However, distribution and use of kava dropped off when reports of liver toxicity surfaced in the early 2000s [340; 341; 342].

Lavender Oil

A six-week randomized controlled trial compared silexan, a lavender oil capsule preparation, with lorazepam in GAD treatment efficacy. Both treatment groups showed similar reductions on the primary anxiety measure (HAM-A) and similar and comparable reductions on measures of somatic anxiety, psychic anxiety, anxiety self-rating, impression of illness severity, sleep quality, and other scales. Silexan appears to be an effective and well-tolerated alternative to benzodiazepines for GAD treatment [343]. A 10-week randomized controlled trial compared silexan with paroxetine and placebo in GAD treatment efficacy. Participants received 80 mg or 160 mg silexan, 20 mg paroxetine, or placebo once daily for 10 weeks [344]. The primary outcome measured was HAM-A total score reduction between baseline and treatment end. A total of 60.3% of participants in the silexan 160 mg group showed a HAM-A total score reduction greater than 50% of the baseline value compared with 51.9% in the silexan 80 mg group, 34.1% in the paroxetine group and 37.8% in the placebo group. Silexan additionally showed a pronounced antidepressant effect and improved general mental health and health-related quality of life. Rates of adverse effects were comparable among the silexan and placebo groups and lower for the paroxetine group [344].

EXERCISE THERAPY

Resistance exercise (i.e., strength training) includes a broad group of activities that evoke repeated muscle action against resistances above those encountered in daily life. A growing body of literature has identified anxiolytic effects of resistance exercise after both single sessions and long-term training. This research has shown that resistance training at a low-to-moderate intensity produces the most reliable and robust decreases in anxiety. Higher intensity has shown either no change or increased anxiety from baseline. One caveat is most of this research involved participants with state (not trait) anxiety [345].

YOGA

Yoga is an ancient mind/body practice that involves different techniques in physical postures, controlled breathing, deep relaxation, and meditation that have positive and specific influences. Research on yoga has demonstrated significant improvements in emotional self-regulation with consequent reductions in depression, stress, and anxiety levels and improvements in mood, quality of life, and well-being [346]. Several studies have found significant anxiolytic effects with yoga in patients with GAD or panic disorder, and it is considered the complementary therapy with strongest evidence of safety and efficacy in anxiety disorders.

One randomized controlled trial compared patients with panic disorder who received yoga or CBT plus yoga weekly over two months. Both treatment groups showed significant decreases from baseline in anxiety levels associated with panic disorder, panic-related beliefs, and panic-related body sensations, although the CBT/yoga combination group led to greater reductions over yoga alone [346].

A group of patients with GAD lacking response to pharmacotherapy received a five-day, 22-hour yoga course. Compared with baseline, follow-up at four weeks found a 73% response rate and 41% remission rate and significant reductions in HAM-A total score and psychic subscale score. Attrition was 25% [347].

Combining yoga with CBT integrates yoga and meditation with traditional and alternative CBT methods to enhance restructuring of the destructive cognitive and emotional patterns associated with physical and psychologic anxiety symptoms. Given in 90-minute sessions once per week for six weeks, CBT/yoga consisted of yoga/meditation, instruction and experiential cognitive restructuring using traditional and alternative CBT interventions, and group discussion with processing. In a group of patients with GAD receiving CBT/yoga, post-treatment scores were compared to baseline. The patients showed significant improvements on measures of state and trait anxiety, depression, panic, suicidality, sleep disturbance, sexual function, and quality of life [348].

CONCLUSION

In the primary care setting, anxiety disorders are often under-recognized and undertreated because many patients present with and report distress from the physical symptoms of anxiety. The prevalence, patient distress and impairment, potential comorbidity, and treatment complexity associated with anxiety disorders underscore the importance of greater understanding of the signs and symptoms, differential diagnosis, and appropriate treatment selection in these patients.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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