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Anxiety Disorders

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Overview

Background

According to the American Psychiatric Association (APA), anxiety disorders are the most common type of psychiatric disorders.[1] Many patients with anxiety disorders experience physical symptoms related to anxiety and subsequently visit their primary care providers. Despite the high prevalence rates of these anxiety disorders, they often are underrecognized and undertreated clinical problems.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR),[2] anxiety disorders include disorders that share features of excessive fear and anxiety and related behavioral disturbances. These disorders include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, and anxiety disorder due to another medical condition. Obsessive-compulsive disorder (included in the obsessive-compulsive and related disorders), acute stress disorder, and posttraumatic stress disorder (included in the trauma and stress-related disorders) are no longer considered anxiety disorders as they were in the previous version of the DSM. However, these disorders are closely related to anxiety disorders and the sequential order of these chapters in the DSM-5-TR reflects this close relationship.

Anxiety disorders appear to be caused by an interaction of biopsychosocial factors, including genetic vulnerability, which interact with situations, stress, or trauma to produce clinically significant syndromes. (See Pathophysiology and Etiology.)

Symptoms vary depending on the specific anxiety disorder. (See Clinical Presentation.)

Treatment usually consists of a combination of pharmacotherapy (see Medication), psychotherapy, and/or healthy lifestyle interventions. (See Treatment Strategies and Management.)

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Anatomy

The brain circuits and regions associated with anxiety disorders are beginning to be understood with the development of functional and structural imaging. The amygdala appears to play a pivotal role in modulating fear of imminent threats and anxiety in anticipation of future threats. Patients with anxiety disorders often show heightened amygdala response to anxiety cues in such imaging studies.[3] The amygdala and other limbic system structures are connected to prefrontal cortex regions. Hyperresponsiveness of the amygdala may relate to reduced activation thresholds when responding to perceived social threat.[4, 5] Abnormal activations in the amygdala appear to be reversible with clinical responses to psychological or pharmacological treatments.[6]

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Pathophysiology

In the central nervous system (CNS), the major mediators of the symptoms of anxiety disorders appear to be norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA). Other neurotransmitters and peptides, such as corticotropin-releasing factor, may be involved in the hypothalamic-pituitary-adrenal (HPA) axis.[7] Peripherally, the autonomic nervous system, especially the sympathetic nervous system, mediates many of the symptoms.[8] Positron emission tomography (PET) scanning has demonstrated increased flow in the right parahippocampal region in those with anxiety disorders that is reversible with treatment.[9] Those with anxiety disorders also appear to have reduced serotonin type 1A receptor binding in the anterior and posterior cingulate and raphe of patients with panic disorder.[10, 11] In patients with panic disorder in particular, MRI has demonstrated smaller temporal lobe volume despite normal hippocampal volume.[12, 13] CSF studies in humans show elevated levels of orexin, also known as hypocretin, which is thought to play an important role in the pathogenesis of panic in rat models.[14]

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Etiology

Anxiety disorders in general

The first consideration is the possibility that anxiety is due to a known or unrecognized medical condition. Substance-induced anxiety disorder (over-the-counter medications, herbal medications, substances of abuse) is a diagnosis that often is missed.

Genetic factors significantly influence risk for many anxiety disorders. Environmental factors such as trauma, neglect, chaos, or Adverse Childhood Experiences (ACEs)[15] can also contribute to risk for later anxiety disorders. The debate whether gene or environment is primary in anxiety disorders has evolved to a better understanding of the important role of the interaction between genes and environment.[16] Some individuals appear resilient to stress, while others are vulnerable to stress, which precipitates an anxiety disorder.

Most presenting anxiety disorders are functional psychiatric disorders. Psychological theories range from explaining anxiety as a displacement of an intrapsychic conflict (psychodynamic models) to conditioning (learned) paradigms (cognitive-behavioral models). Many of these theories capture portions of the disorder.

The psychodynamic theory has explained anxiety as a conflict between the id and ego. Aggressive and impulsive drives may be experienced as unacceptable resulting in repression. These repressed drives may break through repression, producing automatic anxiety. The treatment uses exploration with the goal of understanding the underlying conflict. Cognitive theory has explained anxiety as the tendency to overestimate the potential for danger. Patients with anxiety disorder tend to imagine the worst possible scenario and avoid situations they think are dangerous, such as crowds, heights, or social interaction.

Panic disorder

Panic disorder appears to be a genetically inherited (heritability of 40%[17]) neurochemical dysfunction that may involve autonomic imbalance; decreased GABA-ergic tone;[18] allelic polymorphism of the catechol-O-methyltransferase (COMT) gene; increased adenosine receptor function; increased cortisol;[19] diminished benzodiazepine receptor function; and disturbances in serotonin,[20, 21] serotonin transporter (5-HTTLPR)[22] and promoter (SLC6A4) genes,[23] norepinephrine, dopamine, cholecystokinin, and interleukin-1-beta.[24] Some theorize that panic disorder may represent a state of chronic hyperventilation and carbon dioxide receptor hypersensitivity.[25, 26] Some epileptic patients have panic as a manifestation of their seizures. Genetic studies suggest that the chromosomal regions 13q, 14q, 22q, 4q31-q34, and probably 9q31 may be associated with the heritability of panic disorder phenotype.[17]

The cognitive theory regarding panic is that patients with panic disorder have a heightened sensitivity to internal autonomic cues (eg, tachycardia). Triggers of panic can include the following:

- Injury (eg, accidents, surgery)
- Illness
- Interpersonal conflict or loss
- Use of cannabis (can be associated with panic attacks,[27] perhaps because of breath-holding with a belief it promotes absorption, though it does not[28])
- Use of stimulants, such as caffeine, decongestants, cocaine, and sympathomimetics (eg, amphetamine, MDMA ["ecstasy"])[29]
- Certain settings, such as stores and public transportation (especially in patients with agoraphobia)
- A case report found sertraline can trigger panic attacks in those who were previously symptom-free.[30]
- The SSRI discontinuation syndrome can induce symptoms similar to those experienced by panic patients.[31]

In experimental settings, symptoms can be elicited in people with panic disorder by hyperventilation, inhalation of carbon dioxide, caffeine consumption, or intravenous infusions of hypertonic sodium lactate or hypertonic saline,[32] cholecystokinin, isoproterenol, flumazenil,[33] or naltrexone.[34] The carbon dioxide inhalation challenge is especially provocative of panic symptoms in smokers.[35]

Social anxiety disorder

The term “social phobia” was removed from DSM-5-TR in 2022.

Genetic factors seem to play a role in social anxiety disorder. Based on family and twin studies, the risk for social anxiety disorder appears to be moderately heritable.[36, 37]

Social anxiety disorder can be initiated by traumatic social experience (eg, embarrassment) or by social skills deficits that produce recurring negative experiences. A hypersensitivity to rejection, perhaps related to serotonergic or dopaminergic dysfunction, is present. Current thought is that social anxiety disorder appears to be an interaction between biological and genetic factors and environmental events.

A psychoanalyst would likely conceptualize social anxiety as a symptom of a deeper conflict, for instance, low self-esteem or unresolved conflicts with internal objects. A behaviorist would see phobia as a learned conditioned response resulting from a past association with a situation with negative emotional valence at the time of association (eg, social situations are avoided because intense anxiety was originally experienced in that setting). Even if no danger is posed in most social encounters, an avoidance response has been linked to these situations. Treatment from this perspective aims to weaken and eventually separate the specific response from the stimulus.

Specific phobia

Genetic factors seem to play a role in specific phobia as well (eg, the most common being zoophobia, the fear of animals[38]), and the risk for such phobias also seems to be moderately heritable.[36] In addition, specific phobia can be acquired by conditioning, modeling, or traumatic experience.

Agoraphobia

Agoraphobia may be the result of repeated, unexpected panic attacks, which, in turn, may be linked to cognitive distortions, conditioned responses, and/or abnormalities in noradrenergic, serotonergic, or GABA-related neurotransmission.

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United States statistics

Anxiety disorders are the most common type of psychiatric disorders in the United States. The lifetime prevalence of anxiety disorders among American adults is 28.8%.[39]

While specific phobias are the most common anxiety disorders, social anxiety disorder is the second most common anxiety disorder and presents more commonly for treatment than specific phobias do. Social anxiety disorder has an early age of onset—by age 11 years in about 50% and by age 20 years in about 80% of individuals that have the diagnosis—and it is a risk factor for subsequent depressive illness and substance abuse.[40]

According to the DSM-5-TR,[2] the 12-month community prevalence estimate for specific phobia is approximately 8–12% in the United States. The 12-month prevalence estimate of social anxiety disorder for the United States is approximately 7%. The 12-month prevalence of generalized anxiety disorder is 0.9% among adolescents and 2.9% among adults in the United States. The 12-month prevalence estimate for panic disorder across the United States and several European countries is about 2–3% in adults and adolescents. The prevalence of agoraphobia is approximately 1–1.7% of adolescents and adults worldwide.

International statistics

The prevalence of specific anxiety disorders appears to vary between countries and cultures. A systematic review of the current prevalence of anxiety disorders in 89 countries found significant variation ranging from 0.9% in China to 28.3% in Afghanistan.[41] As an example, in the United States the prevalence of social anxiety disorder is approximately 7%, while in Europe it is 2.3%.[2]

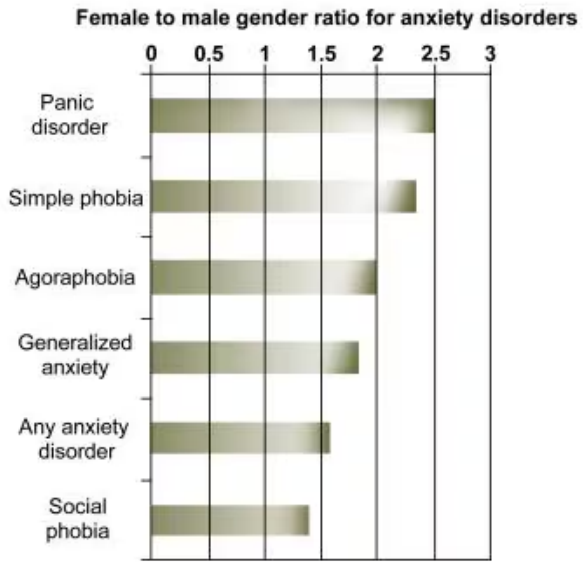
Cross-cultural factors need to be considered. In some Far East cultures, individuals with social anxiety disorder may develop fears of being offensive to others rather than fears of being embarrassed. In Japan and Korea, this syndrome is referred to as taijin kyofusho.[2]

Prevalence of anxiety disorders by race

Respondents who were White, Native American, or Hispanic/Latino were more likely to be diagnosed with an anxiety disorder compared to those who were African American.[42]

Sex ratio for anxiety disorders

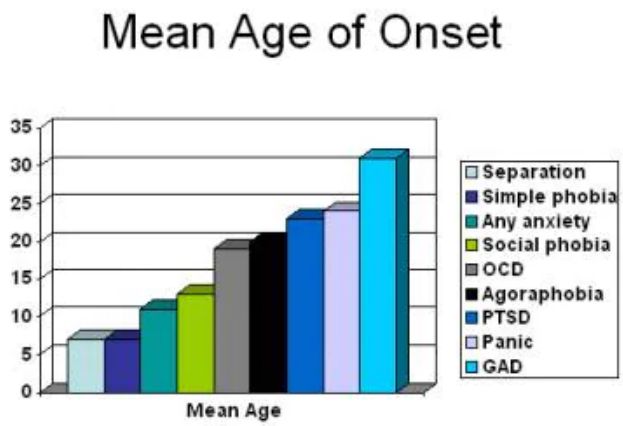
The female-to-male ratio for any lifetime anxiety disorder is 3:2 (see the image below).



Anxiety. Chart showing the female-to-male sex ratio for anxiety disorders. Adapted from Kessler et al, 1994.

Age distribution for anxiety disorders

Most anxiety disorders begin in childhood, adolescence, and early adulthood (see the image below). Separation anxiety is an anxiety disorder that commonly begins in childhood and during adolescence but can uncommonly begin during adulthood.[2] It often includes anxiety related to going to school and may be a precursor for adult anxiety disorders, most commonly panic disorder.



Anxiety. Age of onset for anxiety disorders based on specific anxiety disorder type.

Panic disorder demonstrates a bimodal age of onset in the NCS study[39] in the age groups of 15–24 years and 45–54 years. The age of onset for OCD appears to be in the mid-20s to early 30s.

Most social anxiety disorders begin before age 20 years (median age at illness onset, 16 years[43]).

Agoraphobia usually begins in late adolescence to early adulthood (median age at illness onset, 29 years[43]).

In general, specific phobia appears earlier than social anxiety disorder or agoraphobia. The age of onset depends on the particular phobia. For example, animal phobia is most common at the elementary school level and appears at a mean age of 7 years; blood phobia appears at a mean age of 9 years; dental phobia appears at a mean age of 12 years; and claustrophobia appears at a mean age of 20 years. Most simple (specific) phobias develop during childhood (median age at illness onset, 15 years)[43] and eventually disappear. Those that persist into adulthood rarely go away without treatment.

New-onset anxiety symptoms in older adults should prompt a search for an unrecognized general medical condition, a substance abuse disorder, or major depression with secondary anxiety symptoms.

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Prognosis

Anxiety disorders have high rates of comorbidity with major depression and alcohol and drug abuse. Some of the increased morbidity and mortality associated with anxiety disorders may be related to this high rate of comorbidity. Anxiety disorders may contribute to morbidity and mortality through neuroendocrine and neuroimmune mechanisms or by direct neural stimulation (eg, hypertension or cardiac arrhythmia). Chronic anxiety may be associated with increased risk for cardiovascular morbidity and mortality.

Considerable evidence shows that social anxiety disorder results in significant functional impairment and decreased quality of life.[44, 45]

Severe anxiety disorders may be complicated by suicide, with or without secondary mood disorders (eg, depression). The Epidemiological Catchment Area study found that panic disorder was associated with suicide attempts (odds ratio = 18 compared with populations without psychiatric disorders). How much of the association of panic disorder with suicide is mediated through the association of panic disorder with mood and substance abuse disorders is unclear. Acute stress may play a role in producing suicidal behavior. The presence of any anxiety disorder, phobias included, in combination with a mood disorder appears to increase likelihood of suicide attempts compared with a mood disorder alone.[46] Suicide attempts can be precipitated by adverse life events such as divorce or financial disaster. The effects of acute stress in producing suicidal behavior are increased in those with underlying mood, anxiety, and substance abuse problems.

Phobias are highly comorbid. Most comorbid specific phobias and social anxiety disorders are temporally primary, while most comorbid agoraphobia is temporally secondary. Comorbid phobias are generally more severe than pure phobias. Social anxiety disorder is also frequently comorbid with major depressive disorder and atypical depression, which results in increased disability.[45, 47] Despite evidence of impairment, only a minority of individuals with specific phobia ever seek professional treatment.

Interestingly, in clinical samples, more than 95% of the patients reporting agoraphobia also present with panic disorder, while in epidemiologic samples, simple agoraphobia appears to be more prevalent than panic disorder with agoraphobia.[48]

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Patient Education

Education can be obtained through books, newsletters, support groups, and the Internet. Some useful Web sites are as follows:

- National Institute of Mental Health, Anxiety Disorders
- SAMHSA's National Mental Health Information Center, Anxiety Disorders
- National Alliance on Mental Illness

- eMedicineHealth, Mental Health Center
- eMedicineHealth, Stress, Anxiety Disorders, Panic Attacks, and Hyperventilation
- MentalHelp.net

Family members should receive information about the effect of anxiety disorders on mood, behavior, and relationships. Family members can assist in care by reinforcing the need for medical treatment and supervision. Family members may also assist by providing a collaborative resource for monitoring the severity of the patient's anxiety symptoms and response to treatment interventions.

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Presentation

History

To rule out anxiety disorders secondary to general medical or substance abuse conditions, a detailed history and review of symptoms is essential. Review use of caffeine-containing beverages (coffee, tea, colas, energy drinks), over-the-counter medications (aspirin with caffeine, sympathomimetics), herbal "medications," or street drugs. Ask the patient's sleep partner about apneic episodes or myoclonic limb jerks. Concurrent depressive symptoms are common in all of the anxiety disorders. Of patients with a depressive disorder, 67% also have a current anxiety disorder. Conversely, 63% of those with a current anxiety disorder also have a depressive disorder (about 2/3 in each case).[49] Severe anxiety disorders may produce agitation, suicidal ideation, and increased risk of completed suicide. Always ask about suicidal ideation and suicidal intent.
(See Mental Status Examination)

Screening is essential for diagnosing anxiety disorders. The USPSTF recommended in June 2022 to provide screening for anxiety disorders in the primary care setting,[50] similar to the already established recommendation to do the same for depressive disorders. Standardized examinations may include the GAD-7, Beck Anxiety Inventory (BAI), Primary Care Evaluation of Mental Disorders (PRIME-MD), the Mobility Inventory for Agoraphobia (MIA), the Agoraphobia Cognitions Questionnaire (ACA), and the Body Sensations Questionnaire (BSQ).

Panic disorder

Patients with panic disorder frequently present to the emergency department (ED) with chest pain or dyspnea, fearing that they are dying of myocardial infarction. They commonly report a sudden unexpected and spontaneous onset of fear or discomfort, typically reaching a peak within 10 minutes. DSM-5-TR criteria for panic disorder include experiencing recurrent panic attacks, with one or more attacks followed by at least one month of fear of another panic attack or significant maladaptive behavior related to the attacks.[2] A panic attack is an abrupt period of intense fear or discomfort accompanied by four or more of the following 13 systemic symptoms:

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

Patients tend to appreciate opening up the DSM-5-TR and going through symptoms of disorders with them.

During the panic episode, patients have the urge to flee or escape and have a sense of impending doom (as though they are dying from a heart attack or suffocation). Other symptoms may include headache, cold hands, diarrhea, insomnia, fatigue, intrusive thoughts, and ruminations.

Patients with panic disorder have recurring episodes of panic, with the fear of recurrent attack resulting in significant behavior changes (eg, avoiding situations or locations) and worry about the implications of the attack or its consequences (eg, losing control, going "crazy," dying).

Panic disorder may result in changes in personality traits, characterized by the patient becoming more passive, dependent, or withdrawn.

Assess precipitating events, suicidal ideation or plan, phobias, agoraphobia, and obsessive-compulsive behavior. Exclude involvement of alcohol, illicit drugs (eg, cocaine, amphetamine, phencyclidine, amyl nitrate, lysergic acid diethylamide [LSD], yohimbine, 3,4-methylenedioxymethamphetamine [MDMA, or ecstasy]), cannabis, and medications (eg, caffeine, theophylline, sympathomimetics, anticholinergics).

Consider symptomatology of other medical disorders, which may manifest with anxiety as a primary symptom.

- Angina and myocardial infarction (eg, dyspnea, chest pain, palpitations, diaphoresis)
- Cardiac dysrhythmias (eg, palpitations, syncope)
- Mitral valve prolapse
- Pulmonary embolus (eg, dyspnea, hyperpnea, chest pain)
- Asthma (eg, dyspnea, wheezing)
- Hyperthyroidism (eg, palpitations, diaphoresis, tachycardia, heat intolerance)
- Hypoglycemia
- Pheochromocytoma (eg, headache, diaphoresis, hypertension)
- Hypoparathyroidism (eg, muscle cramps, paresthesias)
- Transient ischemic attacks (TIAs)
- Seizure disorders

Anticipatory anxiety may be helpful in distinguishing panic disorder from other etiologies. Consider other mental illnesses that may result in panic attacks, including schizophrenia, mania, depressive disorder, posttraumatic stress disorder, phobic disorders, and somatic symptom disorders. Assess family history of panic or other psychiatric illness.

Generalized anxiety disorder

This disorder is characterized by excessive anxiety and worry about a number of events and activities. Worrying is difficult to control. Anxiety and worry are associated with at least 3 of the following 6 symptoms occurring more days than not for at least 6 months:

- Restlessness or feeling keyed-up or on edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance

Although not a diagnostic feature, suicidal ideation and completed suicide have been associated with generalized anxiety disorder.[51]

Social anxiety disorder

A person with social anxiety disorder will typically report a marked and persistent fear of social or performance situations in which the individual is exposed to possible scrutiny by others, to the extent that their ability to function at work or in school is impaired. The individual fears that they may act in a way that will show their anxiety symptoms and result in humiliation or embarrassment. Exposure to social or performance situations almost always produces fear or anxiety. These situations are avoided or endured with intense anxiety. Avoidance behavior, anticipation, or distress in the feared social or performance setting produces significant impairment in functioning.

Ask the patient about any difficulties in social situations, such as speaking in public, eating in a restaurant, or using public washrooms. Fear of scrutiny by others or of being embarrassed or humiliated is described commonly by people with social phobia.

Agoraphobia

Inquire about any intense anxiety reactions that occur when the patient is exposed to specific situations such as heights, animals, small spaces, or storms. Other areas of inquiry should include fear of being trapped without escape (eg, being outside the home and alone; in a crowd of unfamiliar people; on a bridge, in a tunnel, in a moving vehicle).

Specific phobia

If specific phobias are suspected, specific questions need to be asked about irrational and out-of-proportion fear to specific situations (eg, animals, insects, blood, needles, flying, heights). Phobias can be disabling and cause severe emotional distress, leading to other anxiety disorders, depression, suicidal ideation, and substance-related disorders, especially alcohol abuse or dependence. The physician must inquire about these areas as well.

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Mental Status Examination

A complete mental status examination should be obtained for each patient with anxiety symptoms, assessing appearance, behavior, ability to cooperate with the exam, level of activity, speech, mood and affect, thought processes and content, insight, and judgment. Patients may exhibit

physical signs of anxiety such as sweaty palms, restlessness, and distractibility. Patients are generally oriented x 4 (person, place, time, and situation) and cooperative. Mood may be normal or depressed. Affect is often constricted in the anxious or nervous range. Psychotic symptoms are not typical of uncomplicated anxiety disorders. Suicidal ideation should be assessed by asking about passive thoughts of death, desires to be dead, thoughts of harming self, or plans or acts to harm self. Homicidal ideation is uncommon. Cognition is typically intact with no impairment in memory, language, or speech. Insight and judgment are typically intact.

Generalized anxiety disorder

Two main elements of the mental status examination should be assessed in generalized anxiety disorder. The first involves asking about suicidal/homicidal ideation or plan, such as the following:

- Have you ever wished you were never born, thought you would be better off dead, wish you would be “hit by a bus,” wish to harm yourself or others, have a plan to harm yourself or others, or ever tried to kill yourself or seriously injure yourself or others?

The second involves formal testing of orientation/recall, such as the following:

- Does the patient respond when you call them by name (oriented to person)?
- Is the patient oriented to place, time, and situation? When you ask what place, season, day, month, or year it is, does the patient respond appropriately? Do they understand the setting in which they are being treated?
- Does the patient have intact short- or long-term recall? Ask the patient to spell the word WORLD forward and backward, count backward from 100 by 7s, recall what they did to celebrate their birthday last year, and the name of their first-grade teacher.

Panic disorder

No signs on mental status examination are specific for panic disorder. While the patient may or may not appear anxious at the time of interview, their Mini-Mental State Examination, including cognitive performance, memory, serial-7s, and proverb interpretation, should appear intact and consistent with the patient’s educational level and apparent baseline intellectual functioning.

The mental status examination may reveal an anxious-appearing person, although this is not required for diagnosis. Speech may reflect anxiety or urgency, or it may sound normal. Mood may be described as similar to “anxious,” with congruent affect. Incongruent affect should raise consideration for other diagnostic possibilities. Thought processes should be logical, linear, and goal-directed. Thought content is particularly important to specifically assess in order to ensure a patient has no suicidal or homicidal thoughts. Acute anxiety, as a form of acute mental anguish, can lead to unsafe or self-injurious behavior. Abnormalities in thought process or thought content (aside from impulsive suicidal thoughts) should prompt reconsideration of other etiologies. Insight and judgment are usually present and intact.

Phobic disorders (including social anxiety disorder, specific phobia, and agoraphobia)

In a situation where the patient is acutely confronted with the object of their phobia, the patient’s mental status examination is significant for an anxious affect, with a restricted range. Neurovegetative signs (such as tremor or diaphoresis) might be present. The patient also reports feeling anxious (mood) and can clearly identify the reason for their anxiety (thought content). The thought content is significant for phobic ideation (unrealistic and out-of-proportion fears). Insight might be impaired, especially during exposure, but most times the patient has preserved insight and while reporting that they cannot control their feelings, they also acknowledge that the severity of their fears is not justified.

At any other time, a patient with phobic disorder has a mental status within normal limits, with the exception of thought content positive for phobic ideation. Of note, phobic ideas usually remain undisclosed unless questions about phobias are specifically asked. Phobias generally do not present with suicidal or homicidal ideation, but comorbid conditions commonly associated with phobias, including depression and other anxiety disorders, may present with suicidal or homicidal ideation. If comorbid conditions exist, a specific assessment of the suicidal and homicidal risk should also be completed.

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Physical Examination

Because anxiety manifests with a number of physical symptoms, any patient who presents with a de novo complaint of physical symptoms suggesting an anxiety disorder should have a physical examination and basic laboratory workup to rule out medical conditions that might present with anxiety-like symptoms (see Differentials).

For a patient who presents for a repeat visit with similar complaints, after medical contributors have been ruled out, a careful mental status examination might be better suited than repeat physical examination and laboratory investigations (see Mental Status Examination). While considering anxiety as the primary suspect, the physician should always remember that, over time, patients with anxiety do develop medical conditions at the same or higher rate as other patients.[52] In other words, a diagnosis of anxiety, while changing the threshold for investigation of physical symptoms, should not deprive the patient of regular primary care follow-up examinations as otherwise indicated.

Panic disorder

No signs on physical examination are specific for panic disorder, unless the patient is in the throes of a panic attack. The diagnosis is made primarily by history.

The patient may or may not have an anxious appearance. A patient presenting in an acute state of panic can physically manifest any anticipated sign of an increased sympathetic state. Tachycardia and tachypnea are common; blood pressure and temperature may be within the reference range, though hypertension typically occurs as well. Tremors may be noted. Cool, clammy skin may be observed. Hyperventilation may be difficult to detect by observing breathing because respiratory rate and tidal volume may appear normal. Patients may have frequent sighs or difficulty with breath-holding. Reproduction of symptoms with overbreathing is unreliable. Chvostek sign (percussion-induced twitching of facial muscles),

Trousseau sign (carpopedal spasm following blood pressure cuff inflation), or overt carpopedal spasm may be present related to hyperventilation-induced hypocalcemia.

The remaining examination findings are typically normal in panic disorder. However, remember that panic disorder is largely a diagnosis of exclusion, and attention should be focused on ruling out other disorders.

A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes,[2] typically lasting 5–30 minutes.[53] Somatic concerns of death from cardiac or respiratory problems may be a major focus of patients during an attack. Anecdotally, some physicians tell patients, “100% of panic patients believe they are going to die from their panic attack with 0% actually doing so.” Patients very often end up in the ED with their panic attacks receiving a “million-dollar” workup.

Generalized anxiety disorder

Common physical signs of generalized anxiety disorder include tremor, tachycardia, tachypnea, sweaty palms, and restlessness. Typically, children and adults with generalized anxiety disorder also experience uncomfortable physical symptoms including rapid heartbeat, feeling short of breath, increased sweating, stomach cramping, a feeling of a “lump in the throat” or inability to swallow, frequent need to urinate, dry mouth, nausea, diarrhea, cold and/or clammy hands, headaches, and/or neck/back aches. A feeling of nervous tension is often accompanied by a feeling of shaking, trembling, twitching, or body aches. Often, children especially are not diagnosed or receive incorrect treatment and they may undergo unnecessarily invasive and potentially dangerous medical testing. Inappropriate medication treatment for supposed presence of physical illnesses can cause an increase in the intensity of fear and worry about their health status as well as adverse, unnecessary side effects.[54, 55, 56]

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Diagnostic Considerations

Prior to pharmacological treatment for anxiety, order testing for drugs of abuse, pregnancy, and broad-based medical screening tests to include ruling out diabetes mellitus and thyroid disorders.

Anxiety disorders have one of the longest differential diagnosis lists of all psychiatric disorders. Anxiety is a nonspecific syndrome and can be due to a variety of medical or psychiatric syndromes. For example, a 2018 study found that about 30% of those with anxiety also have autoimmune thyroiditis (AIT).[57] Additionally, a variety of anxiety symptoms, such as panic, worry, rumination, and obsessions, can present in a variety of psychiatric illnesses, including mood disorders, psychotic disorders, personality disorders, somatoform disorders, and cognitive impairment disorders (eg, delirium). Anxiety also can be observed as part of a drug withdrawal or drug intoxication effect.

Other important causes in the differential include medication-induced anxiety (eg, due to epinephrine or other sympathomimetics, theophylline or other neurostimulant bronchodilators, analgesics containing caffeine, corticosteroids, antivirals, others); migraine, seizure disorders, or other CNS-based disorders; and sleep disorders such as restless legs syndrome, sleep apnea, and periodic limb movement. Sedative abuse as a compensatory strategy should also be considered in the differential.

Differential Diagnoses

- Acute Gastritis
- Acute Respiratory Distress Syndrome (ARDS)
- Addison Disease
- Adrenal Crisis
- Alcohol-Related Psychosis
- Alcoholism
- Amphetamine-Related Psychiatric Disorders
- Anaphylaxis
- Androgen Excess
- Anorexia Nervosa
- Asthma
- Atrial Fibrillation
- Atrial Tachycardia
- Body Dysmorphic Disorder
- Brief Psychotic Disorder
- Bulimia Nervosa
- Caffeine-Related Psychiatric Disorders

- Cannabis-Related Disorders
- Cardiogenic Shock
- Chronic Gastritis
- Conversion Disorders
- Delayed Hypersensitivity Reactions
- Delirium
- Delirium Tremens (DTs)
- Delusional Disorder
- Depression
- Diabetic Ketoacidosis (DKA)
- Diffuse Toxic Goiter (Graves Disease)
- Digitalis Toxicity
- Dissociative Disorders
- Dysthymic Disorder
- Encephalopathy, Dialysis
- Epilepsy Surgery
- Esophageal Motility Disorders
- Esophageal Spasm
- Euthyroid Hyperthyroxinemia
- Factitious Disorder Imposed on Self (Munchausen's Syndrome)
- Folate Deficiency
- Food Poisoning
- Geriatric Sleep Disorder
- Goiter
- Hallucinogen Use
- Hepatic Encephalopathy
- Hypercalcemia
- Hyperparathyroidism
- Hyperprolactinemia
- Hypertensive Encephalopathy
- Immediate Hypersensitivity Reactions
- Inhalant-Related Psychiatric Disorders
- Injection Drug Use
- Insomnia
- Irritable Bowel Syndrome (IBS)
- Lyme Disease
- Malingering
- Meningitis
- Multifocal Atrial Tachycardia
- Obstructive Sleep Apnea (OSA)
- Personality Disorders

- Phobic Disorders
- Premenstrual Dysphoric Disorder
- Primary Aldosteronism
- Primary Hypersomnia
- Primary Insomnia
- Rehabilitation and Fibromyalgia
- Schizoaffective Disorder
- Schizophrenia
- Shared Psychotic Disorder
- Sleep-Wake Disorders
- Somatic Symptom Disorders
- Stimulants
- Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)
- Thyroiditis, Subacute
- Tourette Syndrome
- Type 1 Diabetes Mellitus
- Undifferentiated Connective-Tissue Disease
- Unstable Angina
- Uremic Encephalopathy

Workup

Approach Considerations

When the index of suspicion for anxiety being produced by a medical disorder is low (lack of physical findings, younger age, typical anxiety disorder presentation), initial laboratory studies might be limited to the following:

- Complete blood cell count
- Chemistry profile
- Thyroid function tests
- Urinalysis
- Urine drug screen

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Studies to Exclude Medical Disorders

For presentations with a higher index of suspicion for other medical causes of anxiety (ie, atypical anxiety disorder presentation, older age, specific physical examination abnormalities), more detailed evaluations may be indicated to identify or exclude underlying medical disorders.

Electroencephalography, lumbar puncture, and head/brain imaging

Rule out CNS disorder using electroencephalography (EEG), lumbar puncture, or brain computed tomography (CT) scan, as indicated by history and associated clinical findings. EEG may be used to exclude seizure disorder because these conditions may mimic anxiety.

Imaging studies are limited to presentations in which medical illness, such as a seizure disorder, is suspected. If headache is a prominent feature, an EEG or MRI could be considered along with neurologic consultation to rule out seizures or brain tumor. A head CT scan may be ordered for suspected intracranial abnormality, or an MRI scan for intracranial abnormality.

Functional MRI and PET scanning have shown increases in blood flow and metabolic activity in the orbitofrontal cortex, limbic structures, caudate, and thalamus, with a trend toward right-sided predominance, in patients with obsessive-compulsive disorder. In some studies, these areas of overactivity have been shown to normalize following successful treatment with either SSRIs or CBT.[58] These imaging modalities, however, are of value for research, and not indicated for normal workups.

Electrocardiography

Rule out cardiac disorders (eg, myocardial infarction) using electrocardiography (ECG) or treadmill ECG. ECG may be used to check for mitral valve prolapse or to exclude arrhythmia.

Tests for infection

Rule out infectious causes using rapid plasma reagent test, lumbar puncture (CNS infections), or HIV testing.

Arterial blood gas analysis

Arterial blood gas analysis is useful in confirming hyperventilation (respiratory alkalosis) and excluding hypoxemia or metabolic acidosis. The presence of hypoxemia with hypocapnia or a widened alveolar-arterial (A-a) gradient should increase the suspicion of pulmonary embolus.

Electrolyte analysis

Electrolyte analysis is unnecessary, although several abnormalities may be present in the setting of hyperventilation. Serum phosphorus and ionized calcium may be diminished in patients with hyperventilation and carpopedal spasm, Chvostek sign, or Trousseau sign. The serum calcium level may be within the reference range.

Chest radiography

Chest radiography is useful in excluding other causes of dyspnea with chest pain (eg, pulmonary embolism).

Thyroid function

Hyperthyroidism is one of the most common medical causes for anxiety related to a medical condition. Serum thyroid-stimulating hormone and T4 levels should be considered for excluding a primary thyroid abnormality.

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Treatment

Approach Considerations

Treatment usually consists of a combination of pharmacotherapy (see Medication) and/or psychotherapy.[59] Antidepressant agents are the medications of choice in the treatment of anxiety disorders, particularly the newer selective serotonin reuptake inhibitors (SSRIs). SSRIs have a safer side effect profile (particularly in overdose) and are more easily titrated to effective doses without excessive side effect burden as compared to the older tricyclic antidepressants (TCAs). Antidepressants that are not FDA-approved for the treatment of a given anxiety disorder, such as nefazodone and mirtazapine, still may be beneficial and are standard of care utilized by many practicing psychiatrists. Older antidepressants, such as TCAs and monoamine oxidase inhibitors (MAOIs), also are effective in the treatment of some anxiety disorders.

Behavioral therapy and cognitive-behavioral therapy (CBT) have demonstrated efficacy through controlled studies.[60, 61] Computerized CBT (FearFighter) has been recommended for panic and phobia by the National Institute for Health and Clinical Excellence guidelines (NICE).[62] Psychodynamic therapy (or insight-oriented therapy) is rarely indicated as an exclusive treatment for phobias and is now mostly used for cases of phobic disorders that overlap personality disorders. Interpersonal psychotherapy (IPT) has also shown some efficacy. Eight trials examined the use of IPT for anxiety disorders and found large effects in comparison with control groups. There was no evidence suggesting that IPT is less effective than CBT for anxiety.[63]

In 2019, the FDA approved a cranial electrotherapy stimulator (CES) for treatment of anxiety, depression, and insomnia. The prescription device delivers micro pulses of electrical current across the brain, which in clinical trials led to a reduction in anxiety levels, insomnia, and depressed mood.[64] It is the first CES integrated into noise-cancelling, Bluetooth-enabled headphones and the first CES managed through an app.[65]

Deciding which treatment or combination of treatments to prescribe depends on a careful interview and assessment of the patient's goals and level of pathology. The outcome of treatment is determined by several factors, including the following:

- Specific type of anxiety disorder
- Severity of diagnosis
- level of functioning prior to onset of symptoms
- Degree of motivation for treatment
- Level of support (eg, family, friends, work, school)
- Ability to comply with medication and/or psychotherapeutic regimen

Acute anxiety

Patients with significant discomfort from their anxiety can benefit from emergency anxiolytic treatment, primarily with a benzodiazepine. In addition to ED treatment, patients in an acute anxious state of such severity that they pose a danger to themselves or to others should have a psychiatric consultation.

In the best of circumstances, a calm environment and social support from family, friends, and the emergency staff are ideal. For patients with more severe anxiety, a short course of a fast-acting anxiolytic agent is recommended. Chronic anxiety requires a comprehensive approach; the best pharmacotherapy varies for each individual, and outpatient follow-up with a psychiatrist is recommended. However, these patients can be discharged on a short course of benzodiazepines until they see a psychiatrist. Patients who express suicidal or homicidal thoughts should have an emergent psychiatric evaluation in the ED.

Generalized anxiety disorder

Successful treatment approaches generally involve medication combined with psychotherapy. However, CBT has been proven superior in placebo-controlled trials. CBT generally includes self-reward as well as problem solving and can be as effective as medications, especially for children with mild generalized anxiety disorder.[66]

Combining CBT with medications is extremely helpful in resistant cases.[67, 68] Other psychotherapies, such as relaxation therapy, supportive psychotherapy, or mindfulness therapy, have been used if CBT is not appropriate.[69]

Indications for hospitalization include the following

- Severe functional impairment (cannot meet own daily needs)
- Suicide or homicide risk
- Social skills deficits (eg, the person is so preoccupied that he or she is unaware that his or her actions and behaviors have the potential to provoke others to cause harm)

Emotional intelligence is a protective factor for suicidal behavior; thus, this should be assessed as part of the decision regarding need for a psychiatric hospitalization.[55]

Panic disorder

Pharmacotherapy, cognitive and behavioral psychotherapy, and other psychological treatment modalities are all used to treat panic disorder. The 2011 American Psychiatric Association practice guideline for the treatment of patients with panic disorder strongly recommends SSRIs, other pharmacotherapy, or CBT as initial treatment. According to the guideline, there is insufficient evidence to recommend any of these pharmacological or psychosocial approaches as superior to the others, or to routinely prescribe a combination of treatments over monotherapy. Patient preference, and the availability of pharmacotherapy and specialized psychosocial treatments should be taken into consideration when choosing initial therapy for panic disorder.[70]

Reassure and calm the patient. Untreated panic attacks can subside spontaneously within 20–30 minutes, especially with reassurance and a calming environment. Transport the patient to a medical treatment facility to exclude medical causes for the first attack or when suspected on subsequent attacks. The 2011 APA guidelines support this recommendation.[70]

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Pharmacotherapy for Anxiety and Panic Disorders

Selective serotonin reuptake inhibitors (SSRIs) are generally used as first-line agents, followed remotely by tricyclic antidepressants (TCAs).

Fluoxetine (Prozac) can be used (especially if panic disorder occurs with depression); however, patients may poorly tolerate it initially because it may increase anxiety at first, except at very low starting doses. Fluoxetine has a long half-life, making it a good choice in marginally compliant patients. It alters metabolism of cytochrome P-450 2D6-cleared agents (25% of medications in common clinic use[71]); this fact should be considered.

Paroxetine (Paxil) represents a partially sedating SSRI option that is also available in a controlled-release preparation (Paxil CR), which may improve tolerability, but paroxetine still inhibits P450 2D6. Paroxetine has a short half-life, which may be a limitation in marginally adherent patients secondary to its well-known harsh discontinuation syndrome.[72, 73] Paroxetine is the only SSRI that has anticholinergic properties.

Citalopram (Celexa) carries a risk of dose-dependent QT prolongation. Because of the risk for QT prolongation, citalopram is contraindicated in individuals with congenital long QT syndrome and the dose should not exceed 40 mg/day. Do not exceed a dose of 20 mg/day when coadministered with CYP2C19 inhibitors (eg, cimetidine, fluconazole, omeprazole).[74, 75]

Escitalopram (Lexapro) is likely to cause fewer hepatic enzyme interactions and may be appropriate initial choices for patients with complicated medical regimens or those who are concerned about drug interactions. Escitalopram also appears to be particularly well tolerated in preliminary studies.

Sertraline (Zoloft) represents a similar SSRI option with a slightly different pharmacodynamic profile, including sigma receptor effects, although it has some P450 3A4 interactions.

Mirtazapine (Remeron)[76] has a much more sedating effect, generally reducing its potential to aggravate initial anxiety. Mirtazapine acts distinctly as an alpha-2 antagonist, consequently increasing synaptic norepinephrine and serotonin, while also blocking some postsynaptic serotonergic receptors that conceptually mediate excessive anxiety when stimulated with serotonin.

Mirtazapine may cause residual morning sedation that often improves with continued therapy and may cause an increase in appetite or weight gain. A study by Kim et al suggests among patients with major depressive disorder who have high anxiety symptoms, mirtazapine (15–30 mg/d) administered in the early weeks of treatment may have an earlier-onset action for anxiety symptoms.[77]

Sedating antidepressants such as paroxetine, mirtazapine, and other TCAs/TeCAs are usually prescribed only at night before bed to help improve sleep but should include a warning not to operate a motor vehicle or machinery if feeling sedated or directly after the dose.

Initiation of antidepressant agents are thought to cause early worsening of anxiety, agitation, and irritability, particularly when used to treat anxiety. Sinclair et al use the term jitteriness/anxiety syndrome to describe these effects and completed a systematic search of articles that describe these effects.[78]

No validated rating scales for jitteriness/anxiety syndrome were identified among 107 articles included in the review. No evidence indicated a difference in incidence of jitteriness/anxiety syndrome between SSRIs and TCAs, and a higher incidence was not observed in anxiety disorders. Incidence rates of jitteriness/anxiety syndrome varied widely in the published literature (4–65%).

The authors concluded that jitteriness/anxiety syndrome is poorly characterized, but perception of this syndrome influences clinician prescribing. They recommend more evaluation of adverse effects at early points during antidepressant trials to more comprehensively describe this syndrome.

Intravenous or oral acute sedation with benzodiazepines may be used. Alprazolam (Xanax) has been widely used for panic disorder, but it is currently discouraged because of its higher dependence potential; alprazolam has a short half-life, which makes it particularly prone to rebound anxiety and psychological dependence. Clonazepam (Klonopin) has become a favored replacement because it has a longer half-life and empirically elicits fewer withdrawal reactions upon discontinuation.

Prompt use of benzodiazepines can ease the uncomfortable anxiety associated with the attack and can provide the patient with definitive confidence that treatment can control the symptoms. This is particularly helpful for preventing subsequent visits to emergency services while longer-term therapy is helping the patient gain control.

Benzodiazepines act quickly but carry the liability of physiologic and psychologic dependence. They can be reasonably used as an initial adjunct while SSRIs are titrated to an effective dose, and they can then be tapered over 4–12 weeks while the SSRI is continued. This approach can improve short-term tolerability, although it may increase the risk of sedation and requires warnings not to operate motor vehicles after taking benzodiazepines or if feeling sedated. If possible, avoid long-term benzodiazepines for chronic anxiety disorders. Benzodiazepines can achieve long-term control but should be reserved for patients with refractory panic disorder and should generate a psychiatric referral for pharmacologic management review and potentially a psychotherapist for any additional nonpharmacologic treatment options.

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Psychotherapy for Anxiety and Panic Disorders

Cognitive and behavioral psychotherapy can be used alone or in addition to pharmacotherapy. The combination approach yields superior results for most patients compared to either single modality.

Cognitive therapy helps patients understand how automatic thoughts and false beliefs/distortions lead to exaggerated emotional responses, such as anxiety, and can lead to secondary behavioral consequences. Specific patterns of cognitive distortions (twisted thoughts) tend to respond best to specific techniques described in cognitive behavior therapy books (eg, The Feeling Good Handbook by David Burns, MD). While intended for use in conjunction with therapy, patients can purchase these books and complete the course themselves.

Behavioral therapy involves sequentially greater exposure of the patient to anxiety-provoking stimuli; over time, the patient becomes desensitized to the experience. Relaxation techniques also help control patients' levels of anxiety. Respiratory training can help control hyperventilation during panic attacks and help patients control anxiety with controlled breathing. Other forms of psychological treatment, including psychodynamic psychotherapy for specific issues, are available but exceed the scope of this article.

Consultation with a psychiatrist is helpful to initiate longer-term therapy and to provide follow-up planning. Longer-term therapy currently consists of SSRIs, often with additional psychotherapeutic techniques.

The 2011 APA guidelines state the importance of monitoring changes in key symptoms such as frequency and intensity of panic attacks after treatment has been started. Treatment is effective if it produces a decrease in panic symptoms, although some symptoms may respond more quickly than others. For those individuals who do not respond, or respond incompletely, to initial treatments for panic disorder, treatment modalities should be reassessed.[70]

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Phobic Disorders

Social phobia (social anxiety disorder)

Both psychotherapy and pharmacotherapy are useful in treating social anxiety disorder. Self-exposure monotherapy is recommended for this phobia, as it has been shown to work as well as computerized-based exposure training, clinician-led exposure, or combinations therapies of self-exposure and cognitive-behavioral therapy (CBT)/self-help manual.[79]

A systematic review of self-help interventions for psychiatric disorders suggests this appears to be an effective way of treating individuals diagnosed with social anxiety disorder and panic disorder. The addition of clinician support and the presentation of multimedia or web-based self-help materials improved treatment outcome. Further research is needed to determine the cost-effectiveness and acceptability of these methods.[80]

Social anxiety disorder typically responds to either a selective serotonin reuptake inhibitors (SSRI) or a monoamine oxidase inhibitor (MAOI).[81, 82, 83] Initiate treatment with an SSRI and titrate to the minimum effective dose. SSRIs approved for social phobia include paroxetine[84] (including SR form) and sertraline, but other SSRIs have also been shown to be effective (eg, fluvoxamine[85]). The SSRI dose can be increased if response is partial or nonexistent at 6 weeks—doses can be increased every 2 weeks until maximum dose is reached.

Failing this, patients sometimes respond to high-potency benzodiazepines. Long-term treatment data from clinical studies of clonazepam are limited but support the drug's efficacy.[86] Beta-blockers, clonidine, and buspirone are usually not helpful for long-term treatment, although a beta-blocker such as atenolol, nadolol, or propranolol may be useful for the circumscribed treatment of situational/performance anxiety on an as-needed basis.

Consider tapering medications slowly after 6–12 months of full response. If symptoms reoccur following taper, restart therapy and continue indefinitely.[86]

Specific (simple) phobia

Specific phobias respond well to CBT. Gradual desensitization is the most commonly used treatment. Randomized, controlled clinical trials indicate that specific (simple) phobias also respond to exposure therapy.[87] A small, randomized, controlled clinical trial showed that virtual reality exposure (VRE) therapy is as effective as standard exposure (SE) therapy for fear of flying, with gains maintained up to 1 year following the treatment.[88]

Other treatments include cognitive approaches, relaxation, and breathing control techniques. To date, no controlled studies demonstrate the efficacy of psychopharmacologic intervention for specific phobias.

Agoraphobia

Agoraphobia (specifically, the panic symptoms) most often responds to treatment with an SSRI.[89, 90, 91] Treatment should be started at a low dose then titrated to the minimum effective dose for controlling the patient's panic. Benzodiazepines can be used either as an adjunct or as primary treatment; however, benzodiazepines are usually not chosen as a first-line treatment because of the potential for abuse.[92] If the patient has frequent panic attacks and no history of substance abuse, a benzodiazepine can be considered until the SSRI takes effect. Long-acting benzodiazepines (eg, diazepam, clonazepam) prescribed on a standing rather than on an as-needed basis are preferred due to a lower addictive potential; dose can be increased every 2–3 days until panic symptoms are controlled or the maximum dose is reached.

Consider using the short-acting alprazolam for short-term use to control acute symptoms of panic. If response is minimal or nonexistent after 6 weeks, the SSRI dose can be further increased every 2 weeks until response or maximal dose is reached. Partial or no response at the highest SSRI dose warrants consideration of the following alternatives: change to a different SSRI; change to a different class (venlafaxine, duloxetine); change to TCAs/TeCAs or MAOIs (both TCAs/TeCAs and MAOIs have demonstrated efficacy in controlled trials for agoraphobia).

For a patient with good response, treatment should be continued for 9–12 months before considering slowly tapering the medications. With symptom recurrence following taper, treatment should be resumed and continued indefinitely.

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Diet

Caffeine-containing products, such as coffee, tea, and colas, should be discontinued (or decreased to a low reasonable level). Over-the-counter preparations and herbal remedies should be reviewed with special caution because ephedrine and other herbal compounds may precipitate or exacerbate anxiety symptoms. The use of some gentle herbal preparations may be considered in persons who do not have allergies or sensitivities to those agents.[93]

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Other Healthy Lifestyle Interventions

Research shows that meditation has a small to moderate effect (SMD confidence interval of .22 to .56) on anxiety.[94] Other meta-analyses support this,[95] and an American Academy of Family Physicians position paper suggested mindfulness-based meditation has a positive effect on anxiety disorders but that limited evidence exists for use as monotherapy.[96] Exercise[97] and spiritual interventions may reduce anxiety symptoms,[98] which can be helpful given their low risk and potential beneficial social connection found in a weekly gathering of worshippers. Indeed, social connection seems to be inversely related with measures of anxiety.[99] Prosocial acts of kindness may even increase the idea that your life is valuable and reduce anxiety, which may be further avenues of discussion.[100, 101]

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Consultations

Most often, psychiatrists are consulted. Psychological consultation and testing is indicated if cognitive impairment is of concern or if the patient may be a candidate for cognitive-behavioral therapy (CBT). Social work consultation may be helpful if coping skills are markedly impaired.

In anxiety disorders secondary to a general medical condition, specialty consultation may be indicated. Cardiology consultation is indicated when symptoms include heart rate irregularity or abnormal blood pressure. Neurology consultation is indicated when symptoms include headaches or visual field abnormalities, balance abnormalities, or mental status changes. Endocrinology consultation is indicated when symptoms include heat or cold intolerance, problems with fluid balance, or mood swings due to cortisol abnormalities.

To reduce muscle tension, manual manipulation or massage therapy can be helpful in nonpharmacologic approaches. Treatment with a licensed practitioner is important, as there have been cases of sexual abuse or battery with nonlicensed nonprofessionals.

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Guidelines

Guidelines Summary

American Psychiatric Association

The 2011 American Psychiatric Association practice guideline for the treatment of patients with panic disorder strongly recommends SSRIs, other pharmacotherapy, or CBT as initial treatment. According to the guideline, there is insufficient evidence to recommend any of these pharmacological or psychosocial approaches as superior to the others, or to routinely prescribe a combination of treatments over monotherapy. Patient preference, and the availability of pharmacotherapy and specialized psychosocial treatments should be taken into consideration when choosing initial therapy for panic disorder.[70]

The guidelines state the importance of monitoring changes in key symptoms such as frequency and intensity of panic attacks after treatment has been started. Treatment is effective if it produces a decrease in panic symptoms, although some symptoms may respond more quickly than others. For those individuals who do not respond, or respond incompletely, to initial treatments for panic disorder, treatment modalities should be reassessed.[70]

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Medication

Medication Summary

Antidepressant agents are the drugs of choice in the treatment of anxiety disorders, particularly the newer agents that have a safer adverse effect profile and greater ease of use than the older tricyclic antidepressants (TCAs), such as selective serotonin reuptake inhibitors (SSRIs). Antidepressants that are not FDA-approved for the treatment of a given anxiety disorder, such as nefazodone and mirtazapine, still may be beneficial. Older antidepressants, such as TCAs and monoamine oxidase inhibitors (MAOIs), also are effective in the treatment of some anxiety disorders but have a significant adverse effect burden.

A Cochrane review of second-generation antipsychotic drugs found that quetiapine and risperidone were effective when combined with antidepressants; however, adverse side effects were also reported.[102] Of antipsychotic medications, the most evidence exists for quetiapine augmenting treatment of anxiety.

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Selective Serotonin Reuptake Inhibitors

Class Summary

The SSRIs include paroxetine (Paxil), escitalopram (Lexapro), sertraline (Zoloft), fluoxetine (Prozac), fluvoxamine (Luvox), and citalopram (Celexa). SSRIs are first-line agents for long-term management of anxiety disorders, with control gradually achieved over a 2- to 4-wk course, depending on required dosage increases. In general, SSRIs need to be dosed at higher ranges for anxiety than for depressive disorders.[103]

SSRIs are helpful for generalized anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), and social phobia. All SSRIs may be equal in the treatment of anxiety disorders; however, higher doses may be necessary in the treatment of OCD.

All commonly used SSRIs appear to have a role in the treatment of panic disorder. However, patients with panic disorder may be more sensitive to treatment with antidepressants and frequently need lower initial doses and slower titration to accomplish successful therapy without prompting panic attacks.[104]

Fluoxetine has a very long half-life, making it well-suited for patients who have difficulty remembering to take all of their medications each day. The longer half-life also minimizes the risk and severity of SSRI withdrawal that can occur when patients abruptly discontinue their medication.

Paroxetine (Paxil)

Potentially sedating and anticholinergic SSRI. Potent selective inhibitor of neuronal serotonin reuptake. Also has weak effect on norepinephrine and dopamine neuronal reuptake. For maintenance dosing, make dosage adjustments to maintain patient on lowest effective dosage, and periodically reassess patient to determine need for continued treatment. With abrupt cessation, Paxil is well known for its harsh discontinuation syndrome.

Escitalopram (Lexapro)

The FDA has approved escitalopram for generalized anxiety disorder in patients aged 7 years and older. Escitalopram is the S-enantiomer of racemic citalopram. It inhibits the reuptake of serotonin, with little or no effect on norepinephrine or dopamine reuptake.

Sertraline (Zoloft)

Sertraline selectively inhibits presynaptic serotonin reuptake with minimal or no effect on the reuptake of norepinephrine or dopamine. FDA-approved for panic disorder, PTSD, social phobia, and OCD. May be helpful for other anxiety disorders.

Fluoxetine (Prozac)

Fluoxetine selectively inhibits presynaptic serotonin reuptake but has minimal or no effect on reuptake of norepinephrine or dopamine. A common side effect is sexual dysfunction, which may impact long-term compliance. FDA-approved for OCD and panic disorder. May be helpful for other anxiety disorders.

Fluvoxamine (Luvox)

Fluvoxamine enhances serotonin activity through selective reuptake inhibition at the neuronal membrane. Because this drug does not significantly bind to alpha-adrenergic, histamine, or cholinergic receptors, it has fewer side effects than TCAs do. FDA-approved for OCD in children (8–17 y) and adults. May be helpful for other anxiety disorders.

Citalopram (Celexa)

Enhances serotonin activity through selective reuptake inhibition at the neuronal membrane. Citalopram is a 50:50 racemate of r- and s-citalopram. Reports of dose-dependent QT interval limit dose escalation and coadministration with CYP2C19 inhibitors.

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Serotonin and Norepinephrine Reuptake Inhibitors

Class Summary

Pharmacologic agents with reuptake inhibition of serotonin and norepinephrine such as venlafaxine (Effexor and Effexor XR) and duloxetine (Cymbalta) may be helpful in a variety of mood and anxiety disorders.

Venlafaxine (Effexor XR)

A reuptake inhibitor of both serotonin and norepinephrine. FDA-approved for generalized anxiety disorder, panic disorder, and social anxiety disorder in adults. May be helpful for other anxiety disorders.

Duloxetine (Cymbalta)

Potent inhibitor of neuronal serotonin and norepinephrine reuptake. Its antidepressive action is theorized to be due to serotonergic and noradrenergic potentiation in the CNS. It is indicated for generalized anxiety disorder in patients aged 7 years and older.

Levomilnacipran (Fetzima)

SNRI with preferential inhibition of norepinephrine reuptake (Montgomery et al, 2013) that was FDA-approved in 2013 (Roman et al., 2014) for the treatment of depression. In one study, it reduced anxiety rating scales in those with moderate or severe depression (Montgomery et al, 2013). Current cost can make this medication burdensome.

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Atypical Antidepressants

Class Summary

Antidepressants that are not FDA-approved for the treatment of a given anxiety disorder, such as nefazodone and mirtazapine, still may be beneficial for the treatment of anxiety disorders.

Nefazodone

Antagonist at the 5-HT2 receptor and inhibits the reuptake of 5-HT. Also has negligible affinity for cholinergic and histaminergic receptors.

Trazodone

Useful in the treatment of panic disorders. Antagonist at the 5-HT2 receptor and inhibits the reuptake of 5-HT. Also has negligible affinity for cholinergic and histaminergic receptors.

In animals, selectively inhibits serotonin uptake by brain synaptosomes and potentiates the behavioral changes induced by the serotonin precursor 5-HTP.

Mirtazapine

Mirtazapine has a much more sedating effect, generally reducing its potential to aggravate initial anxiety. Mirtazapine acts distinctly as an alpha-2 antagonist, consequently increasing synaptic norepinephrine and serotonin while also blocking some postsynaptic serotonergic receptors that conceptually mediate excessive anxiety when stimulated with serotonin.

Vortioxetine (Trintellix)

A serotonergic modulator (reuptake inhibition, agonism of 5-HT1 receptor, antagonism of 5-HT3 and 5-HT7 receptors) (De Deigo-Adeliño et al., 2022) that was FDA-approved in 2013 (Roman et al., 2014) for the treatment of depression, but there is also evidence for the treatment of anxiety as well. First antidepressant with beneficial effects on depression and cognitive symptoms (De Deigo-Adeliño et al., 2022). The side-effect profile is similar to that of SSRIs (Sanchez et al., 2015). Current cost can make this medication burdensome.

Vilazodone (Viibryd)

A serotonin modulator and stimulator (reuptake inhibitor and 5-HT1A receptor partial agonist) (Wang et al., 2015) like vortioxetine. There is some evidence that this medication is helpful for anxiety treatment (Thase et al., 2014), though more evidence is needed (Stuivenga et al., 2019). Current cost can make this medication burdensome.

Tricyclic Antidepressants

Class Summary

The tricyclic antidepressants are a complex group of drugs that have central and peripheral anticholinergic effects, as well as sedative effects. They include imipramine and clomipramine (Anafranil). Caution is warranted in the use of TCAs because of their higher toxicity and potential lethality in overdose. Their use should be limited to cases in which SSRIs are ineffective. Clomipramine, a nonselective serotonin reuptake inhibitor in contrast to a selective serotonin receptor inhibitor, has an FDA indication in the treatment of OCD and is the only TCA effective in the treatment of this condition. Indeed, it can be effective in cases of OCD refractory to treatment with SSRI agents.

Imipramine

Tricyclic antidepressant that has norepinephrine and serotonin reuptake-inhibition properties. One of the oldest agents available for the treatment of depression and has established efficacy in the treatment of panic disorder. Elderly and adolescent patients may need lower dosing or slower titration.

Amitriptyline

First TCA discovered and has very strong anticholinergic side effects. Tricyclic antidepressant that has norepinephrine and serotonin reuptake-inhibition properties.

Desipramine (Norpramin)

Tricyclic antidepressant that has norepinephrine and serotonin reuptake-inhibition properties. One of the oldest agents available for the treatment of depression and has established efficacy in the treatment of panic disorder. Elderly and adolescent patients may need lower dosing or slower titration.

Clomipramine (Anafranil)

Dibenzazepine compound belonging to family of tricyclic antidepressants. Inhibits membrane pump mechanism responsible for uptake of norepinephrine and serotonin in adrenergic and serotonergic neurons. Clomipramine is the most serotonin-specific of the TCAs, affecting serotonin uptake while it affects norepinephrine uptake when converted into its metabolite desmethylclomipramine. It is believed that these actions are responsible for its antidepressant activity. It is typically a second line or augmenting medication for the treatment of SSRI-resistant OCD.

Nortriptyline (Pamelor)

Has demonstrated effectiveness in the treatment of chronic pain. By inhibiting the reuptake of serotonin and/or norepinephrine by the presynaptic neuronal membrane, this drug increases the synaptic concentration of these neurotransmitters in the central nervous system. Pharmacodynamic effects such as the desensitization of adenyl cyclase and down-regulation of beta-adrenergic receptors and serotonin receptors also appear to play a role in its mechanisms of action. This medication is distinctive by having a curvilinear relationship to its effectiveness, a therapeutic window, not working below 50 ng/ml or above 150 ng/ml (Murphy et al., 1985).

Protriptyline

Increases synaptic concentration of serotonin and/or norepinephrine in CNS by inhibiting their reuptake by the presynaptic neuronal membrane. It has been used in central sleep to stimulate a respiratory drive.

Doxepin (Silenor)

Increases concentration of serotonin and norepinephrine in the CNS by inhibiting their reuptake by presynaptic neuronal membrane. These effects are associated with a decrease in symptoms of depression. It is low in anticholinergic effects (Aaltonen et al., 1985) and may be used in the elderly.

Amoxapine

Inhibits reuptake of norepinephrine or serotonin (5-hydroxytryptamine, 5-HT) at presynaptic neuron. Metabolite (7-hydroxyamoxapine) has significant dopamine receptor blocking activity similar to haloperidol and therefore can cause acute and chronic extrapyramidal symptoms. Elicits strong anticholinergic effects.

Trimipramine

Inhibits reuptake of norepinephrine or serotonin (5-hydroxytryptamine, 5-HT) at presynaptic neuron. Elicits strong anticholinergic effects.

Benzodiazepines

Class Summary

Benzodiazepines often are used with antidepressants as adjunct treatment. They are especially useful in the management of acute situational anxiety and adjustment disorder where the duration of pharmacotherapy is anticipated to be six weeks or less and for the rapid control of panic attacks. They include lorazepam (Ativan), alprazolam (Xanax) clonazepam (Klonopin), diazepam (Valium), chlordiazepoxide, and oxazepam among others.

If long-term use of benzodiazepines seems necessary, obtaining a confirmatory opinion from a second clinician may be helpful because chronic benzodiazepine use may be associated with tolerance, withdrawal, and treatment-emergent anxiety with rapid cessation of the medication. The risk of addiction with benzodiazepines should be carefully considered before their use in the anxiety disorders (approximately 2.2% of the general population abuses benzodiazepines).[105] Avoid use in patients with a prior history of alcohol or other drug abuse. Closely monitor for evidence of unauthorized dose escalation or obtaining benzodiazepine prescriptions from multiple sources.

Alprazolam (Xanax, Xanax XR)

For management of anxiety attacks. Binds receptors at several sites within the central nervous system, including the limbic system and reticular formation. Effects may be mediated through GABA receptor system. Has a very rapid onset with short half-life leading to rapid withdrawal symptoms upon cessation. This medication, like Valium, is less commonly used to treat anxiety because of euphoria.

Lorazepam (Ativan, Loreev XR)

Sedative hypnotic in the benzodiazepine class that has a short onset of effect and a relatively long half-life. By increasing action of gamma-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter in the brain, may depress all levels of the CNS, including limbic and reticular formation. Available for PO, IV, or IM use.

Clonazepam (Klonopin)

Long-acting benzodiazepine that increases the presynaptic GABA inhibition and reduces the monosynaptic and polysynaptic reflexes. Suppresses muscle contractions by facilitating inhibitory GABA neurotransmission and other inhibitory transmitters. Has multiple indications, including suppression of myoclonic, akinetic, or petit mal seizure activity and focal or generalized dystonias (eg, tardive dystonia). Reaches peak plasma concentration at 2-4 h after oral or rectal administration.

Diazepam (Valium)

Modulates postsynaptic effects of GABA-A transmission, resulting in an increase in presynaptic inhibition. Appears to act on part of the limbic system, the thalamus, and hypothalamus, to induce a calming effect. Also has been found to be an effective adjunct for the relief of skeletal muscle spasm caused by upper motor neuron disorders.

Rapidly distributes to other body fat stores. Twenty minutes after initial IV infusion, serum concentration drops to 20% of Cmax.

Individualize dosage and increase cautiously to avoid adverse effects. This medication, like Xanax, is less commonly used to treat anxiety because of euphoria.

Chlordiazepoxide

Depresses all levels of CNS, including limbic and reticular formation, possibly by increasing gamma-aminobutyric acid (GABA) activity, a major inhibitory neurotransmitter. Provides rapid onset and efficacy in sedating aggressive patients and is commonly used in alcohol withdraw.

Oxazepam

Depresses all levels of CNS (eg, limbic and reticular formation), possibly by increasing activity of GABA.

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Antianxiety Agents

Class Summary

Buspirone is a nonsedating antianxiety medication unrelated to benzodiazepines, barbiturates, and other sedative-hypnotics. It has been found to be comparable with benzodiazepines in reducing symptoms of anxiety in double-blind placebo-controlled clinical trials and has fewer sedative effects with non-lethal withdrawal effects compared to benzodiazepines (lethal). Buspirone also has fewer cognitive and psychomotor adverse effects, which makes its use preferable in elderly patients or those operating potentially dangerous heavy vehicles. Major limitations include lack of antipanic activity and reduced anxiolytic effects in patients recently withdrawn from benzodiazepines. Also has a longer onset of action (comparable to antidepressants) and, thus, is of fairly limited use as a sole agent in the treatment of acute anxiety in the ED.

Buspirone is a specific antianxiety agent with no other members in its class.

Buspirone

Partial 5-HT1A agonist affecting serotonergic neurotransmission in CNS. Has some dopaminergic activity as well (Lechin et al., 1998). In addition, has demonstrated anxiolytic effect but can take up to 2-3 wks for full efficacy. Also has a low abuse potential and does not mitigate panic attacks. Not useful in benzodiazepine withdrawal and has a low adverse-effect profile. Requires twice a day dosing.

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Anticonvulsant

Class Summary

The drug of choice in this category is the gamma-aminobutyric acid derivative pregabalin (Lyrica). However, caution is necessary when prescribing (prescribe the smallest amount with fewest refills), as it is a Schedule V medication due to the possibility of drug diversion and drug dependence and has a “street value” to drug addicts. Some anticonvulsant medications, such as divalproex (Depakote), pregabalin (Lyrica), and gabapentin (Neurontin), may have a role in the treatment of anxiety disorders,[106, 107, 108] especially in patients with high potential for abusing benzodiazepines after exhausting antidepressant trials which are the treatment of choice for anxiety disorders.

Pregabalin (Lyrica, Lyrica CR)

Structural derivative of GABA. Mechanism of action unknown. Binds with high affinity to alpha2-delta site (a calcium channel subunit). In vitro, reduces calcium-dependent release of several neurotransmitters, possibly by modulating calcium channel function. FDA approved for neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia and as adjunctive therapy in partial-onset seizures.

Gabapentin (Neurontin)

Membrane stabilizer, a structural analogue of inhibitory neurotransmitter gamma-amino butyric acid (GABA), which paradoxically is thought not to exert effect on GABA receptors. Appears to exert action via the alpha(2)delta1 and alpha(2)delta2 auxiliary subunits of voltage-gaited calcium channels

Has apparent anxiolytic properties. Gabapentin is now prevalent as a drug of abuse (Smith et al., 2012).

Divalproex (Depakote, Depakote ER)

Has proven effectiveness in treating and preventing mania. Classified as a mood stabilizer and can be used alone or in combination with lithium. Useful in treating patients with rapid-cycling bipolar disorders and has been used to treat aggressive or behavioral disorders. A combination of valproic acid and valproate has been effective in treating persons in manic phase, with a success rate of 49%.

Valproate is not a first-line agent for anxiety. There is some evidence it can be helpful with anxiety states (Aliyev et al., 2008).

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Antihypertensive Agent

Class Summary

Agents in this class may have a positive effect on the physiological symptoms of anxiety. Beta-blockers such as atenolol, nadolol, or propranolol may be useful for the circumscribed treatment of situational/performance anxiety on an as-needed basis.

Clonidine (Catapres)

Investigational agent. Central alpha-adrenergic agonist that stimulates alpha2-adrenoreceptors in brain stem and activates an inhibitory neuron, resulting in a decrease in vasomotor tone and heart rate. Available in tab or transdermal skin patches. Frequently given to children. Affects alpha1-, alpha2-, and alpha3-adrenergic receptors.

Propranolol (Inderal LA, Hemangeol, InnoPran XL)

Investigational agent. Blocks the physiological symptoms of anxiety and may be helpful for decreasing the severity of the somatic symptoms of anxiety. May cause unpleasant cardiovascular and GI adverse effects and is not the DOC especially as hypotension and/or cardiac block can occur. Initiation of therapy should be performed with close monitoring of blood pressure to prevent hypotensive crisis. Do not discontinue abruptly as this may precipitate hypertensive crisis. Available as tablets, sustained release, and liquid preparations. Great caution should be taken when administering in patients with asthma and diabetes.

Nadolol (Corgard)

Competitively blocks beta1 and beta2-receptors. Does not exhibit membrane stabilizing activity or intrinsic sympathomimetic activity.

Atenolol (Tenormin)

Used to treat hypertension. Selectively blocks beta-1 receptors with little or no effect on beta-2 types. Beta-adrenergic blocking agents affect blood pressure via multiple mechanisms. Actions include negative chronotropic effect that decreases heart rate at rest and after exercise, negative inotropic effect that decreases cardiac output, reduction of sympathetic outflow from the CNS, and suppression of renin release from the kidneys. Used to improve and preserve hemodynamic status by acting on myocardial contractility, reducing congestion, and decreasing myocardial energy expenditure.

Beta-adrenergic blockers reduce inotropic state of left ventricle, decrease diastolic dysfunction, and increase LV compliance, thereby reducing pressure gradient across LV outflow tract. Decreases myocardial oxygen consumption, thereby reducing myocardial ischemia potential. Decreases heart rate, thus reducing myocardial oxygen consumption and reducing myocardial ischemia potential. During IV administration, carefully monitor blood pressure, heart rate, and ECG.

Monoamine Oxidase Inhibitor (MAOI)

Class Summary

MAOIs are most commonly prescribed for patients with social phobia. They include the agents phenelzine (Nardil), selegiline (Emsam), tranylcypromine (Parnate), and isocarboxazid (Marplan).

Advantages of MAOIs are low risk of dependence and less anticholinergic effect than TCAs. Disadvantages are the higher number of adverse effects, including sexual difficulty, hypotension, weight gain, and potential lethality in overdose. A diet low in tyramine must be followed to avoid a hypertensive crisis. Over-the-counter medications, especially sympathomimetics, should be used with great caution.

The use of MAOIs should be limited to cases in which SSRIs are ineffective. MAOIs may be especially indicated in treatment-refractory panic disorder and social anxiety disorder. MAOIs also may have a role in the treatment of certain subtypes of OCD refractory to conventional treatment, such as patients with symmetry obsessions or associated panic attacks.

Phenelzine (Nardil)

Has demonstrated clear superiority over placebo in double-blind trials for treating specific symptoms of panic disorders. Usually reserved for patients who do not tolerate or respond to newer antidepressants.

Selegiline (Emsam, Zelapar)

Irreversible MAOI. Has greater affinity for MAO-B compared with MAO-A; however, at antidepressant doses, inhibits both isoenzymes. MAO-A and MAO-B catabolize neurotransmitter amines in CNS (eg, norepinephrine, dopamine, serotonin). Indicated for treating major depressive disorder. At lowest strength (eg, 6 mg delivered over 24 h), may be used without the dietary restrictions required for oral MAOIs used to treat depression

Tranylcypromine (Parnate)

Treats major depression. Binds irreversibly to MAO, thereby reducing monoamine breakdown and enhancing synaptic availability.

Isocarboxazid (Marplan)

Nonselective hydrazine MAOI demonstrated to inhibit MAO in the brain, heart, and liver. Mechanism by which MAOIs act as antidepressants is not fully understood but is thought to involve elevation of brain levels of biogenic amines. However, MAO is a complex enzyme system widely distributed throughout body, and drugs that inhibit MAO cause a number of clinical effects. Thus, it is unknown whether MAO inhibition, other pharmacologic actions, or interaction of both is responsible for the antidepressant effects observed.
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Antipsychotic Agent

Class Summary

Atypical and typical antipsychotic medications are generally used more as augmentation strategies and are second-line treatment options in Generalized Anxiety Disorder.[109] Mechanisms of action generally include a combination of neuroreceptor blockade (generally dopaminergic blockade) as well as up- and downregulation of receptor sensitivity.

All medications in this class may increase risk of life-threatening neuroleptic malignant syndrome, acute dystonias, tardive dyskinesia, weight gain, metabolic syndrome, and potential to cause diabetic ketoacidosis, as well as stroke, hypertension, hypotension, or sudden death from cardiac conduction or cardiac electrophysiological abnormalities. Quetiapine was not FDA-approved for monotherapy in Generalized Anxiety Disorder as well as Major Depressive Disorder because of a potential excessive side effect burden.[110] It seems that low doses (50-300 mg range) of quetiapine may not be associated with the risk of hyperglycemia and metabolic syndrome that potentially can occur in higher dosage ranges or with other antipsychotic medications.

Risperidone (Risperdal)

Binds to dopamine D2 receptor with a 20-times lower affinity than for the 5-HT2 receptor. Improves negative symptoms of psychoses and reduces incidence of extrapyramidal adverse effects.

Response to antipsychotics is less dramatic than in true psychotic Axis I disorders, but symptoms such as anxiety, hostility, and sensitivity to rejection may be reduced. Antipsychotics are typically used for a short time while the symptoms are active.

Aripiprazole (Abilify)

Improves positive and negative schizophrenic symptoms. The mechanism of action is unknown but is hypothesized to work differently than other antipsychotics. Aripiprazole is thought to be a partial dopamine (D2) and serotonin 5HT1A agonist and serotonin 5HT2A antagonist. Additionally, no QTc interval prolongation was noted in clinical trials. Available as tab, orally disintegrating tab, or oral solution.

Quetiapine (Seroquel, Seroquel XR)

May act by antagonizing dopamine and serotonin effects.

Newer antipsychotic used for long-term management. Improvements over earlier antipsychotics include fewer anticholinergic effects and less dystonia, parkinsonism, and tardive dyskinesia. Immediate- and extended-release formulations available.

Haloperidol (Haldol)

DOC for patients with acute psychosis when no contraindications exist. Haloperidol and droperidol (below) are of butyrophenone class, and are noted for high potency and low potential for causing orthostasis. However, the potential for EPS/dystonia is high.

Parenteral dosage form may be admixed in same syringe with 2-mg lorazepam for better anxiolytic effects.

Clozapine (Clozaril, Verzacloz)

Demonstrates weak D2-receptor and D1-receptor blocking activity, but noradrenolytic, anticholinergic, antihistaminic, and arousal reaction inhibiting effects are significant. Also possesses antiserotonergic (5-HT1c, 5-HT2, 5-HT3) properties. Affinity for mesolimbic D4 dopamine receptor accounts for striking effects in control of behavioral and psychiatric symptoms with low incidence of extrapyramidal symptoms. Histamine receptor blockade accounts for increased incidence of sleep disturbances. Associated with a risk of agranulocytosis when used at doses required for treatment of patients with schizophrenia whose symptoms are refractory to standard neuroleptics. In the U.S., weekly dosing and weekly CBCs are required for clozapine to be dispensed; discontinuing therapy at first sign of leukopenia decreases but does not eliminate risk of agranulocytosis; whether agranulocytosis is associated with low doses in treating elderly patients and those with dementia is not clear.

Olanzapine (Zyprexa)

May inhibit serotonin, muscarinic, and dopamine effects. Response to antipsychotics is less dramatic than in true psychotic Axis I disorders, but symptoms such as anxiety, hostility, and sensitivity to rejection may be reduced. Antipsychotics are typically used for a short time while the symptoms are active.

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Questions & Answers

Overview

Presentation

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