Panic disorder in adults: Epidemiology, clinical manifestations, and diagnosis

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Literature review current through: **Oct 2023.**
This topic last updated: **Feb 09, 2022.**

INTRODUCTION AND DEFINITIONS

Panic attacks and panic disorder are common problems in both primary and psychiatric specialty care [1].

- A panic attack is a discrete episode of intense fear that begins abruptly and lasts for several minutes to an hour. Panic attacks may be present in many different psychiatric and medical disorders.
- In panic disorder, patients experience recurrent untriggered panic attacks with one month or more of worry about future attacks, or a maladaptive change in behavior related to the attacks.

This topic will address the epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis of panic disorder. Treatment of panic disorder is discussed separately. The epidemiology, pathogenesis, clinical manifestations, course, and diagnosis of agoraphobia, a disorder commonly associated with panic disorder are also discussed separately. (See "Management of panic disorder with or without agoraphobia in adults" and "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)

EPIDEMIOLOGY

In a nationally representative study, the 12-month and lifetime prevalence of panic disorder in the United States population (age 15 to 54 years) was 2.7 and 4.7 percent, respectively [2]. A systematic review of 13 European studies reported a 12-month prevalence rate of panic disorder of 1.8 percent [3]. The prevalence of panic disorder among primary care patients is approximately twice as high as in the general population with rates of 4 to 8 percent [4-6].

The disorder has a median age of onset of 24 years [2]. The prevalence decreases after age 60 [2]. The lifetime prevalence is approximately 5 percent in females and 2 percent in males [7].

Panic attacks are more common than panic disorder, occurring in up to one-third of individuals at some point in their lifetime [8-10].

COMORBIDITIES

The causes of panic attacks and the comorbidity and differential diagnosis of panic disorder frequently overlap and may be difficult to distinguish in many cases. (See 'Differential diagnosis' below.)

Psychiatric disorders — Panic disorder is often comorbid with other psychiatric disorders [2,11]. Additionally, many psychiatric disorders can present with panic attacks or symptoms similar to panic disorder such as avoidance of situations or depersonalization. We differentiate these disorders by careful history including symptom onset (eg, triggered versus untriggered), temporal profile (phasic, with abrupt onset, quick peak, and short duration) and associated symptoms such as mood changes or the presence of somatic symptoms. In many cases the order of symptom onset may be helpful in distinguishing these disorders. (See 'Differential diagnosis' below.)

- Mood disorders – Depression appears to be the psychiatric disorder most frequently comorbid with panic disorder [11,12]. In a United States national comorbidity survey of representative adults age 15 to 54, 37 percent of patients with panic disorder had a lifetime history of major depression [2]. Other data suggest that bipolar disorder is commonly comorbid with panic disorder [13].

- Generalized anxiety disorder [2].

- Posttraumatic stress disorder [2].

- Somatic symptom disorder.
- Illness anxiety disorder.
- Social anxiety disorder.
- Alcohol and other substance use disorder [14].
- Agoraphobia. (See 'Agoraphobia' below.)

Medical disorders — Panic disorder appears to be associated with several medical conditions [13,15-25]. In many disorders, the comorbidity appears to be bidirectional [17]. Medical conditions that are comorbid with panic disorder include:

- Asthma or other respiratory disease – Several studies confirm the comorbidity between panic disorder and asthma or chronic obstructive pulmonary disease (COPD) [13,15,16]. In population-based studies, up to 25 percent of individuals with COPD and up to 20 percent of individuals with asthma are diagnosed with comorbid panic disorder [13]. The overall lifetime prevalence of respiratory disease is reported to be as high as 47 percent in individuals with panic disorder [13].
- Cardiovascular disease – Individuals with panic disorder appear to have a greater risk of coronary artery disease than individuals without panic disorder. In a meta-analysis including 12 studies and over 1.1 million individuals, panic disorder was associated with an increased risk of developing coronary heart disease (CHD; adjusted hazard ratio 1.47, 95%CI 1.24-1.74), a major adverse cardiac event such as death due to CHD, myocardial infarction (MI), or cardiac arrest (adjusted hazard ratio 1.4, 95% CI 1.24-1.74), or MI (adjusted hazard ratio 1.36, 95% CI 1.12-1.66) [18].
- Irritable bowel syndrome – Individuals with panic disorder appear to have a rate of irritable bowel syndrome that is over twice that of those without panic disorder [21,22].
- Other disorders that are commonly comorbid with panic disorder include:
  - Diabetes [17]
  - Cancer [26]
  - Hypertension [19]
  - Vestibular dysfunction [13]
  - Thyroid dysfunction [13]
  - Interstitial cystitis [23]
  - Migraine headache [24,25]

- Peptic ulcer disease [20]
- Chronic pain [27]

The previously reported association between mitral valve prolapse and panic disorder [28] has been questioned because of inconsistent results and methodologic limitations in the supporting research, including flawed diagnostic criteria for mitral valve prolapse, which resulted in overdiagnosis of this condition [29] (see "Mitral valve prolapse syndrome"). While mitral valve prolapse may be encountered in patients with panic disorder, it is unlikely to be the cause of the panic symptoms. In such instances, our preference is to treat the panic disorder. (See "Management of panic disorder with or without agoraphobia in adults" and "Psychotherapy for panic disorder with or without agoraphobia in adults".)

PATHOGENESIS

The pathogenesis of panic disorder can be explained using the stress-diathesis model (ie, the combination of one or more vulnerability factors interacting with life stressors precipitating symptoms) [30-32]. Vulnerability factors include genetic and neurobiological factors, childhood adversity, and personality traits, including anxiety sensitivity and neuroticism.

Genetics — Multiple genes and varied gene expressions appear to be associated with the disorder [33-35]. Evidence for a genetic component include:

- First-degree relatives of patients with panic disorder have higher rates of panic disorder than relatives of patients with major depression and relatives of healthy controls [36,37]. The rates are even higher if the panic disorder patient had onset of illness before age 20 [37].

- Twin studies have shown higher concordance for monozygotic compared with dizygotic twins (31 percent and 0 percent, respectively, in one study) [38]. A heritability of approximately 40 percent with contributions of 10 percent from common familial environment and greater than 50 percent from individual-specific environmental effects is reported [39].

Neurobiology — Research into underlying neurobiologic factors has shifted from a focus on the neurotransmitters (serotonin, norepinephrine, and gamma-aminobutyric acid [GABA]) linked with commonly prescribed antipanic medications, to proposed neural circuitry closely linked with basic animal models of fear development (figure 1) [40].

- **Neural circuitry** – The proposed neuroanatomical model for panic disorder focuses on specific areas in the amygdala or hypothalamus which are hyperexcitable and make the individual susceptible to unprovoked panic symptoms [41]. The dorsomedial hypothalamus/perifornical (DMH/PeF) region are hypothesized to coordinate rapid mobilization of behavioral, autonomic, respiratory, and endocrinologic responses to stress [42]. Controlled studies provide support for this model [43].

  In addition, cognitive researchers have suggested that catastrophic thoughts may contribute to this susceptibility via the same neural mechanisms [44]. In this model, the amygdala acts as a way station that integrates sensory information and stored experiences and subsequently generates a panic response via outflow to the locus coeruleus, hypothalamus, and other regions [40,45].

  Other reviews have supported a role for the insula and dorsal anterior cingulate cortex in mediating panic responses [46].

- **Neurotransmitters** – Neurotransmitter-focused studies have largely implicated alterations in the GABA-benzodiazepine receptor [47-50] and serotonin receptor systems [51,52].

Psychosocial factors — Panic attacks often occur at times of significant life stress. Loss of loved one, physical threats, and illness are particularly salient [53]. Studies have shown that childhood adversity such as a history of physical or sexual abuse increases the risk of panic disorder in adult years [54]. Furthermore, smoking in childhood appears to increase the risk of onset of panic disorder in adulthood [55,56].

Anxious temperaments, as measured by high neuroticism (ie, a personality trait associated with poor stress resilience and increased reactivity to stressors) [57], and anxiety sensitivity (ie, a measure of catastrophic cognitions regarding bodily sensations) [58,59], are reported to be risk factors for development of panic disorder. Some hypothesize these symptoms may constitute early manifestations of the disorder [59].

Additionally, behavioral inhibition, a temperamental tendency to exhibit fearfulness, or withdrawal behavior when faced with unfamiliar people or situations may be involved with the development of panic disorder [60-62]. Data support the presence of neuroanatomic changes present in children with behavioral inhibition that are thought to be involved with panic disorder [62]. Additionally, a meta-analysis of 25 studies also showed that children with separation anxiety, a manifestation of behavioral inhibition, are 3.5 times more likely to develop panic disorder as adults [63]. (See "Social anxiety disorder in adults: Epidemiology, clinical

features, assessment, and diagnosis" and "Anxiety disorders in children and adolescents: Epidemiology, pathogenesis, clinical manifestations, and course".)

CLINICAL MANIFESTATIONS

The hallmark symptom of panic disorder is recurrent unexpected panic attacks. In panic disorder, at least one of the attacks is followed by one month or more of worry about future attacks or their consequences, or a significant maladaptive change in behavior in an attempt to avoid having attacks (ie, avoidance of unfamiliar situations).

Panic attacks — A panic attack is a symptom, not a diagnosable mental disorder. Panic attacks may be seen in the context of many different psychiatric or medical disorders (eg, posttraumatic stress disorder, mood disorder, anxiety disorders, cardiovascular disorders, pulmonary disorders). (See 'Assessment' below and 'Differential diagnosis' below.)

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria define a panic attack as an abrupt surge of intense fear or discomfort that occurs from a calm or anxious state. The symptoms typically reach a peak within minutes and resolve within an hour. Panic attacks may be triggered or untriggered; however, for a diagnosis of panic disorder, some of the attacks must be untriggered or unexpected. During the attack, an individual manifests at least four of the following 13 symptoms [1]:

- 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

Less commonly, individuals may present with “nonfearful” panic attacks [64]. In these cases, the individual presents with other symptoms of a panic attack but do not endorse intense fear. The absence of subjectively experienced fear in some patients may make recognition of panic more difficult.

Associated features — Panic disorder is frequently associated with agoraphobic avoidance, substance use, increased utilization of medical services, and reduced quality of life.

Agoraphobia — Individuals with panic disorder can develop agoraphobia (ie, fear, anxiety, or avoidance of situations where escape might be difficult in the event of developing panic-like or other embarrassing symptoms) [1].

In a large community study, the lifetime prevalence rate of panic disorder with agoraphobia is reported to be 1.1 percent [10]. The lifetime prevalence rate of panic disorder without agoraphobia was reported to be 3.7 percent.

The presence of agoraphobia is associated with significant impairment in functioning, degree of disability, and level of unemployment [65].

Agoraphobia is classified as a separate disorder in DSM-5 and is diagnosed independently of panic disorder. In cases where both criteria are met, both disorders are diagnosed. The presence of agoraphobia strongly adds to functional impairment because of the life limitations associated with avoidant behavior. The epidemiology, clinical manifestations, course, and diagnosis of agoraphobia are discussed separately [66]. (See "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)

Substance use — Individuals with panic disorder may use alcohol or sedative hypnotics in an attempt to control symptoms of the disorder.

While substance use (eg, alcohol, sedatives) may offer a short-lived anxiolytic effect, it may lead to rebound exacerbation of anxiety and panic symptoms as blood levels decline. Over time, the use of alcohol may have a progressive anxiogenic effect and subsequently lead to worsening of the course of panic disorder [67,68]. (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment" and "Cocaine use disorder: Epidemiology, clinical features, and diagnosis" and "Cannabis (marijuana): Acute intoxication".)

Suicide attempts — Individuals with panic disorder appear to have a higher likelihood of suicide attempts compared with the general population [12,69-71].

For example, in a national comorbidity survey, a lifetime diagnosis of panic disorder was associated with an increased risk of past year suicide attempt (odds ratio 3.9, 95% CI 1.4-10.8) [69]. Additionally, in another longitudinal study, the presence of panic disorder was associated with increased future risk of suicidal ideation (odds ratio 7.85, 95% CI 7.07-10.16) and suicide attempt (odds ratio 7.62, 95% CI 5.2-11.16) [12]. The study also found that individuals with co-occurring anxiety and mood disorders have a higher likelihood of suicide attempt than those with mood disorders alone [12]. (See "Suicidal ideation and behavior in adults".)

Utilization of medical services — Individuals with panic disorder often seek health care from a general medical clinician rather than mental health clinician [72]. Individuals with unexplained or ongoing symptoms of panic disorder are often unsatisfied following a negative general medical work-up and repeatedly seek medical care [73]. This results in high medical utilization including frequent medical evaluations and emergency department visits, use of multiple medications, and frequent tests to rule out medical illness [74,75]. Examples of tests commonly done include cardiac testing for unexplained chest pain, pulmonary function testing for unexplained dyspnea, endoscopy for unexplained abdominal pain, and magnetic resonance imaging (MRI) scanning for unexplained dizziness.

This extensive use of resources often precedes the diagnosis of panic disorder by as long as 10 years [76].

Quality of life — Panic disorder reduces the quality of life and function in affected patients and their families. Decrements in familial, social, and vocational functioning occur to a degree comparable with that seen with major depression [77,78]. In one study, the number of disability days taken by patients with anxiety disorders was significantly greater than in those with diabetes, cardiac disease, or renal disease [79].

Course — Panic disorder is typically a chronic, recurrent disease. Many individuals show improvement of symptoms with treatment; however, few show lasting complete remission [78,80]. Recurrence is common [80].

In a large community-based study of panic disorder, individuals were monitored over a two-year period [81]. While remission was reached in 64 percent of subjects with a mean time to remission of 5.7 months, recurrence occurred in 21 percent of those individuals over the follow-up period.

Comorbid disorders such as major depression, agoraphobia, or the presence of a personality disorder predict a poorer outcome in individuals with panic disorder [80]. Factors found to predict remission include female gender, absence of life stressors, low initial frequency of attacks, and subthreshold panic symptoms [81].

ASSESSMENT

In individuals with panic attacks, medical, psychiatric, and substance-related causes must be ruled out to accurately diagnose panic disorder. Our assessment includes:

Interview — We establish a detailed description of the panic symptoms including:

- **Symptom characteristics** – Type of symptoms, location, quality, and intensity. If not spontaneously reported, we ask about the following symptoms to accurately diagnose a panic attack and gauge the severity of the symptoms:

  - Heart racing or pounding
  - Sweating
  - Shortness of breath or difficulty breathing
  - Chest pain or discomfort
  - Dizziness
  - Paresthesias
  - Abdominal pain, nausea
  - Feeling of unreality or being detached (depersonalization, derealization)
  - Fear of death, losing control, or "going crazy"

  We also ask about:

  - Rate of onset
  - Description of symptom trajectory (eg, rapid escalation/surge in symptoms reaching peak within minutes)
  - Duration of symptoms

- **Precipitating factors** – To diagnosis panic disorder, at least one panic attack must be untriggered or unexpected.

- **Response to the symptoms** – We ask the individual how the symptoms are affecting their daily functioning and behavior. To diagnose panic disorder, there must be one of the following:

  - Persistent worry or concern about having additional attacks or their consequences

  - Changes in behavior in response to the symptoms (avoidance of situations, increase in medical utilization such as emergency department visits)

- **Past medical history** – We pay particular attention to disorders that can present with panic attacks and other possible factors. These include (see 'Differential diagnosis' below):

  - Cardiac/cardiovascular history – History of angina or chest pain, abnormal electrocardiogram, hypertension
  - Thyroid disorder – History of hyperthyroidism or related symptoms such as unexplained weight loss, restlessness or irritability
  - Pulmonary disorders – History of smoking, asthma, or COPD
  - Neurologic disorder – Seizure disorder (eg, temporal lobe epilepsy), migraine
  - Vestibular disorders – Dizziness, imbalance, prior diagnosis of Meniere disease
  - Emergency department visits – History of prior emergency department visits, or prior evaluations for similar or other symptoms
  - Medication changes – Recent changes in medication dose or addition of a new medication such as theophylline, amphetamines, antihistamines, steroids

- **Past psychiatric history** – We evaluate for disorders that can present with panic attacks or other similar symptoms, or are comorbid with panic disorder. We establish a timeline of current and past psychiatric symptoms, diagnoses, and treatment to differentiate them from panic disorder. (See 'Differential diagnosis' below.)

  We ask about the following:

  - Mood changes – Presence of low mood or sadness, excessive sleep or insomnia, hedonic capacity or ability to enjoy activities, and energy level (eg, higher than normal, lower than normal, normal) to assess for depression. (See "Comorbid anxiety and depression in adults: Epidemiology, clinical manifestations, and diagnosis".)
  - Anxiety
    - Excessive worry about events, activities or other stressors that are present. We review the frequency, intensity and the individual's ability to control this worry to assess for a generalized anxiety disorder. (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis", section on 'Screening, assessment, and diagnosis'.)

- Fear or discomfort in social or other specific situations or fear/avoidance of specific objects to assess for social anxiety disorder or specific phobia. (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)

- Persistent worry about having acquired a serious illness to diagnosis illness anxiety disorder. (See "Illness anxiety disorder: Epidemiology, clinical presentation, assessment, and diagnosis".)

- Somatic preoccupations including the presence of physical symptoms of undiagnosed etiology or of chronic concern to diagnosis somatic symptom disorder. (See "Somatic symptom disorder: Epidemiology and clinical presentation".)

- History of trauma – Including prior traumatic events, recent exposure to trauma, presence of flashbacks, hypervigilance, or depersonalization to assess for posttraumatic stress disorder (PTSD). (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)

- Substance use – Review of complete history of substance use including alcohol, sedatives, stimulants, marijuana to assess for a substance use disorder or other substance-related disorder such as withdrawal. (See "Co-occurring substance use disorder and anxiety-related disorders in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

- **Family history** – We assess for a family history of anxiety disorders (eg, generalized anxiety disorder, somatoform disorder, or panic disorder). (See 'Genetics' above.)

- **Psychosocial history and recent stressors** – We review ongoing or recent psychosocial stressors including work or school difficulties, relationship concerns, recent loss. (See 'Psychosocial factors' above.)

- **Mental status examination** – For individuals with panic disorder we focus on the following:

  - General behavior and demeanor – Including hygiene, level of awareness, cooperation with interviewer, eye contact

  - Assessment of mood and affect – Presence of low mood, hedonic capacity, psychomotor slowing, lability of mood

- Thoughts of self-harm or harm to others
- Thought content – Including paranoia, delusions, preoccupations, hallucinations

Medical screening — Panic attacks may be seen in many medical conditions. In all individuals with new onset or undiagnosed panic attacks of unclear etiology, we screen for underlying medical causes of panic attacks. This is done through general physical examination and laboratory screening. For all patients with new onset panic attacks or in panic attacks of unclear etiology we suggest the following testing:

- Vital signs and general physical examination – To evaluate for hypertension, tachycardia, diaphoresis, dyspnea
- Electrocardiogram – To evaluate for arrhythmia, evidence of coronary artery disease
- Chemistry panel including calcium – To evaluate for disturbance in fluid or electrolytes
- Complete blood count with differential
- Thyroid panel – To evaluate for thyroid disorder or dysfunction
- Urine pregnancy testing individuals of childbearing age
- Toxicology screen – To assess for substances such as stimulants, opioids, sedatives (ie, benzodiazepines), or marijuana

Additionally, in individuals with panic attacks associated with symptoms that may suggest other etiologies, we obtain further testing to rule out those causes. As examples:

- For individuals with sustained hypertension, tachycardia, headaches, or a family history of pheochromocytoma, we measure 24-hour urinary and plasma fractionated metanephrines and catecholamines. (See "Clinical presentation and diagnosis of pheochromocytoma".)
- For individuals with fluctuating or a change in level of consciousness, arousal, or awareness, we order an electroencephalogram. (See "Focal epilepsy: Causes and clinical features".)
- For individuals with suspected underlying or contributing pulmonary disease, we obtain consultation with the individuals primary care or other specialist. (See "Chronic obstructive pulmonary disease: Diagnosis and staging" and "Asthma in adolescents and adults: Evaluation and diagnosis".)

- For individuals with suspected sleep apnea, particularly patients with panic attacks that awaken them from sleep, we obtain consultation with a pulmonary or sleep specialist [82].

- For individuals with possible toxic or other effects of prescribed medications (ie, theophylline, low blood sugar due to treatment of diabetes) we order blood levels of the suspect agent.

Further discussion of differentiating these disorders from panic disorder is discussed below. (See 'Differential diagnosis' below.)

Rating scales — We often use clinician-administered and patient self-assessment instruments as diagnostic tools and to monitor response to treatment. The gold standard instrument for the disorder is the Panic Disorder Severity Scale [83]. This is a seven-item scale that covers key clinical aspects of the syndrome (attack frequency, attack intensity, anticipatory anxiety, phobic avoidance, avoidance of internal bodily sensations, relationship impairment, work impairment). The scale has excellent reliability and validity and has been widely used [84,85].

DIAGNOSIS

Diagnostic criteria — DSM-5 diagnostic criteria for panic disorder are described below [1].

- A. Recurrent unexpected panic attacks

- B. At least one of the attacks has been followed by a month or more of one or both of the following:

  - 1. Persistent concern or worry about additional panic attacks or their consequences (eg, losing control, having a heart attack, "going crazy").

  - 2. A significant maladaptive change in behavior related to the attacks (eg, behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

- C. The disturbance is not attributable to the physiological effects of a substance (eg, medication or illicit drug) or another medical condition (eg, hyperthyroidism, cardiopulmonary disorders).

- D. The disturbance is not better explained by another mental disorder. As examples, the panic attacks do not occur only in response to:

  - Feared social situations, as in social anxiety disorder

- Circumscribed phobic objects or situations, as in specific phobia
- Obsessions, as in obsessive-compulsive disorder
- Reminders of traumatic events, as in posttraumatic stress disorder (PTSD)
- Separation from attachment figures, as in separation anxiety disorder

Differential diagnosis — We differentiate panic disorder from other causes of panic attacks and severe anxiety primarily by the course of symptoms, presence of precipitating factors, and review of prior medical and psychiatric history. (See 'Clinical Manifestations' above and 'Assessment' above.)

Conditions or disorders that may present with panic attacks — The following medical and psychiatric conditions can present with panic attacks and should be ruled out in diagnosing panic disorder.

- **Psychiatric conditions or disorders** – If the individual meets criteria for one or more disorders in addition to panic disorder, then both may be diagnosed. (See 'Psychiatric disorders' above and 'Interview' above.)
  - **Posttraumatic stress disorder** – Both panic disorder and PTSD may present with panic attacks. However, panic attacks in PTSD are precipitated by exposure to or recollection of a traumatic event. In panic disorder, the attacks are untriggered. Additionally, other features of PTSD such as intrusions, depersonalization, or other dissociative episodes are less commonly seen in panic disorder. (See "Posttraumatic stress disorder in adults: Epidemiology, pathophysiology, clinical features, assessment, and diagnosis".)
  - **Specific phobia and social anxiety disorder** – Specific phobia, social anxiety disorder, and panic disorder may be accompanied by panic attacks. We differentiate these disorders by the presence of attacks triggered by exposure to a feared social situation or specific object (in social anxiety disorder or specific phobia, respectively) while in panic disorder the attacks are paroxysmal or untriggered. (See "Social anxiety disorder in adults: Epidemiology, clinical features, assessment, and diagnosis" and "Specific phobia in adults: Epidemiology, clinical manifestations, course, and diagnosis".)
  - **Substance use disorder or withdrawal, prescription drug misuse** – Substance intoxication or withdrawal can present with sudden onset of anxiety or panic symptoms. Stimulant drugs such as cocaine and amphetamines can precipitate panic attacks as can prescribed medications such as theophylline or stimulants. In addition, withdrawal from sedative hypnotics, alcohol, and opiates can also precipitate panic

attacks. These can be differentiated by a temporal association between the substance use/withdrawal and the onset of symptoms. (See "Cocaine use disorder: Epidemiology, clinical features, and diagnosis", section on 'Acute intoxication' and "Cocaine use disorder: Epidemiology, clinical features, and diagnosis", section on 'Psychiatric effects' and "Prescription drug misuse: Epidemiology, prevention, identification, and management", section on 'Stimulants' and "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)

- **General medical conditions** (see 'Medical screening' above)

  - **Cardiovascular disease/arrhythmia** – We differentiate panic attacks or severe anxiety due to angina or other cardiac etiology (eg, arrhythmia) from panic disorder by reviewing the time course of the panic attack and by reviewing an electrocardiogram. Individuals with panic disorder have untriggered panic attacks while panic or anxiety secondary to angina is temporally related to the angina. Cardiac causes of severe anxiety or presyncope may include cardiac arrhythmia, structural heart disease, or prior history of myocardial infarction. (See "Outpatient evaluation of the adult with chest pain", section on 'Psychiatric' and "Evaluation of palpitations in adults".)

  - **Thyroid disorder** – Hyperthyroidism can present with agitation, anxiety, restlessness, and irritability. We use thyroid function tests to rule out thyroid disorder. (See "Overview of the clinical manifestations of hyperthyroidism in adults", section on 'Neuropsychiatric'.)

  - **Pheochromocytoma** – Pheochromocytoma can present with episodic bursts of tremulousness, flushing and hypertension that may often but not always resemble nonfearful panic attacks [86,87]. We use 24-hour urine for catecholamine metabolites to differentiate them in suspected cases (eg, those with sustained hypertension and/or family history). (See "Clinical presentation and diagnosis of pheochromocytoma".)

  - **Medication effect/side effects** – We differentiate side effects of medication or other treatment effects by obtaining serum concentrations of the suspected agent (eg, hypoglycemia in patients with diabetes, toxic serum aminophylline concentrations in patients with asthma. Excessive or initial caffeine intake or nicotine intake can cause severe anxiety and panic attacks. Additionally, a trial off of caffeine or nicotine can aid in the diagnosis. (See "Hypoglycemia in adults without diabetes mellitus: Clinical manifestations, causes, and diagnosis" and "Theophylline use in asthma" and "Evaluation of palpitations in adults", section on 'Caffeine, nicotine, and other substance use'.)

Conditions with other symptoms that overlap with panic disorder — We rule out the following medical and psychiatric conditions by careful assessment including psychiatric interview and medical screening.

- **Psychiatric conditions or disorders** – If the individual meets criteria for one or more disorders in addition to panic disorder, then both may be diagnosed. (See 'Psychiatric disorders' above and 'Interview' above.)

  - **Depressive disorder** – Depressive symptoms and severe anxiety or panic attacks may be present in both depressive disorders such as major depression and panic disorder. Individuals with depression often have pervasive symptoms such as affective blunting, anhedonia, early morning awakening, and appetite changes in addition to severe anxiety or panic attacks. In individuals with panic disorder, depressive symptoms are typically less pervasive and may be a response to untreated panic attacks and the limitations they incur. Additionally, order of onset of the prominent symptoms may help to distinguish them.

  - **Bipolar disorder** – In bipolar disorder, panic attacks may be a prominent feature of mixed states and divert attention from the bipolar diagnosis. Panic attacks, often accompanied by marked anxiety, may be admixed with dysphoric symptoms thereby giving the impression of a simple anxious depression rather than bipolar disorder with panic attacks [88,89]. (See "Unipolar depression in adults: Assessment and diagnosis" and "Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis".)

  - **Generalized anxiety disorder** – Individuals with generalized anxiety disorder have persistent worry about real-life concerns such as work or school performance. Panic disorder typically presents with recurrent, unexpected periods of intense fear or discomfort that reaches a peak within minutes. (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis".)

  - **Somatic symptom disorder** – Individuals with either somatic symptom disorder or panic disorder may present with intense anxiety and somatic preoccupations. However, somatic symptoms and preoccupation is more enduring with somatic symptom disorder and is often present since adolescence. In panic disorder somatic symptoms are episodic, typically occurring with panic attacks. (See "Somatic symptom disorder: Epidemiology and clinical presentation" and "Somatic symptom disorder: Assessment and diagnosis".)

- **Illness anxiety disorder** – Individuals with both illness anxiety disorder and panic disorder may have worries about acquiring a serious illness. In both cases, the individual may perform excessive health-related behaviors such as checking their body for signs of illness or having tests to identify illness. However, individuals with panic disorder have a surge of acute somatic symptoms including tachycardia, dyspnea, or chest pain, while acute anxiety with multiple somatic symptoms is less common in illness anxiety disorder. (See "Illness anxiety disorder: Epidemiology, clinical presentation, assessment, and diagnosis".)

- **Agoraphobia** – Individuals with agoraphobia experience marked fear or avoidance of two or more situations (using public transportation, being in open spaces, being in enclosed places, being outside the home, standing in a crowd) from which escape would be difficult in the event of experiencing panic like symptoms. In individuals that meet criteria for panic disorder and agoraphobia, both diagnoses are assigned. (See 'Agoraphobia' above and "Agoraphobia in adults: Epidemiology, pathogenesis, clinical manifestations, course, and diagnosis".)

- **General medical conditions** (see 'Medical screening' above)

  - **Chronic obstructive pulmonary disease and asthma** – We differentiate anxiety, shortness of breath, and other symptoms of respiratory illness from those of panic disorder by temporal history of symptoms.

    In panic disorder, symptoms are paroxysmal, recurrent, and increase in intensity over several minutes while in primary respiratory disease the symptoms are more pervasive. (See "Chronic obstructive pulmonary disease: Diagnosis and staging", section on 'Symptoms and pattern of onset' and "Asthma in adolescents and adults: Evaluation and diagnosis".)

  - **Temporal lobe epilepsy** – We differentiate symptoms of temporal lobe epilepsy from panic disorder; a change in level of awareness or consciousness or the presence of other sensory or psychic phenomena (eg, déjà vu, jamais vu) suggests temporal lobe epilepsy. Additionally, symptoms caused by temporal lobe epilepsy are typically brief and stereotyped. Electroencephalogram findings may also differentiate them. (See "Focal epilepsy: Causes and clinical features", section on 'Neuropsychiatric symptoms'.)

  - **Vestibular dysfunction** – Both vestibular disease and panic disorder can present with nonspecific transient dizziness. In some cases, physical examination will detect the presence of nystagmus which may help differentiate dizziness from anxiety or

hyperventilation from vestibular dysfunction. (See "Approach to the patient with dizziness".)

- **Pulmonary embolus** – Individuals with pulmonary embolus can present with dyspnea or chest pain. We consider the diagnosis of pulmonary embolus in all individuals who present with acute onset of panic attack symptoms with associated chest pain and dyspnea of unclear etiology. This diagnosis is often missed in young women on oral contraceptives. Discussion of the evaluation of pulmonary embolism is found elsewhere. (See "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism".)

- **Syncope (vasovagal, cardiogenic, orthostatic)** – Individuals with syncope can present with a prodrome of lightheadedness, sweating, and nausea. These can be distinguished from panic disorder by recent history (ie, response to a procedure in vasovagal syncope), presence of arrythmia (cardiogenic syncope), or orthostatic changes (orthostatic hypotension).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anxiety and anxiety disorders in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Panic disorder (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Presentation** – The hallmark symptom of panic disorder is recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or discomfort that reaches a peak in minutes and is associated with four or more somatic symptoms or fears. (See 'Clinical Manifestations' above and 'Diagnostic criteria' above.)

- **Comorbidity** – The causes of panic attacks and the comorbidity and differential diagnosis of panic disorder frequently overlap and may be difficult to distinguish in many cases. Medical comorbidities include asthma, chronic obstructive pulmonary disease, arrhythmias, vestibular dysfunction, and gastrointestinal disorders such as irritable bowel syndrome. Psychiatric comorbidities include mood disorders, general anxiety disorder, posttraumatic stress disorder, and alcohol and other substance use disorders. (See 'Comorbidities' above.)

- **Pathogenesis** – The pathogenesis of panic disorder is not fully known. Genetic factors, alterations in neural circuitry, psychological factors (eg, temperament, anxiety sensitivity), and social factors (eg, stressors) are thought to contribute to the etiology of panic disorder. The stress-diathesis model has also been used to explain the underlying pathogenesis. (See 'Pathogenesis' above.)

- **Course –** Panic disorder is typically a chronic, recurrent disease. While most individuals with panic disorder show improvement of symptoms, even in individuals who achieve remission, recurrence is common. (See 'Course' above.)

- **Associated features** – Individuals with panic disorder often have agoraphobic avoidance, increased risk of suicide, increased utilization of medical services, and reduced overall quality of life. (See 'Associated features' above.)

  Individuals with panic disorder may use substances such as alcohol or sedatives in an attempt to control symptoms. While substance use may offer a short-lived anxiolytic effect, it may lead to rebound exacerbation of anxiety and panic symptoms as blood levels decline. (See 'Substance use' above.)

- **Assessment** – We rule out underlying medical or psychiatric causes of panic attacks in all individuals that present with new onset panic or in individuals with panic attacks of unclear etiology. (See 'Assessment' above.)

- **Interview** – We establish a detailed history of panic symptoms including their characteristics, precipitating factors or triggers, timeline, and the response to them including persistent worry or maladaptive behavior changes related to the attack.

  Review of current and past medical and psychiatric history paying particular attention to disorders than can present with panic attacks or severe anxiety.

  Review past history of trauma, recent exposure to trauma, or other recent stressors. (See 'Interview' above.)

- **Medical screening** – We complete a general physical examination and pertinent laboratory tests in all individuals with panic attacks of undiagnosed etiology. In some cases, further testing such as electrocardiogram, electroencephalogram, or 24-hour urine testing is needed. (See 'Medical screening' above.)

- **Diagnosis** – The diagnosis of panic disorder is made based on diagnostic criteria that include the presence of unexpected panic attacks followed by one month or more of worry about the attack or their consequences. We rule out other causes of panic attacks or other conditions that may present with overlapping symptoms prior to making a diagnosis of panic disorder. (See 'Diagnostic criteria' above and 'Differential diagnosis' above.)

ACKNOWLEDGMENTS

The UpToDate editorial staff acknowledges Wayne Katon, MD, now deceased, who contributed to an earlier version of this topic review. The UpToDate editorial staff also acknowledges Paul Ciechanowski, who contributed to an earlier version of this topic review.

Topic 14628 Version 35.0

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